Calixarenes

An Introduction

2nd Edition

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An Introduction
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RSC Publishing

ISBN: 978-0-85404-258-6

A catalogue record for this book is available from the British Library

Published by The Royal Society of Chemistry,
Thomas Graham House, Science Park, Milton Road,
Cambridge CB4 0WF, UK

Registered Charity Number 207890

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Preface

In the preface to the 1989 volume which bore the simple title of "Calixarenes", I wrote that "science comprises a marvelous mosaic of individual pieces – some large, some small, some of cosmic importance, some of minor consequence. Each has a shape, color, structure, and set of characteristics that distinguish it from all others and make it unique". I went on to say that the book dealt with one such piece which fits somewhere in the middle between these boundaries, being medium in size and modest in importance but a piece that boasts a more than humdrum history that is acquiring an interesting patina with the passage of time. I commented that "one important purpose of the book was to provide a timely survey of the chemistry of the molecular baskets called "calixarenes", a survey that might serve as a springboard for researchers interested in expanding this domain of supramolecular chemistry".

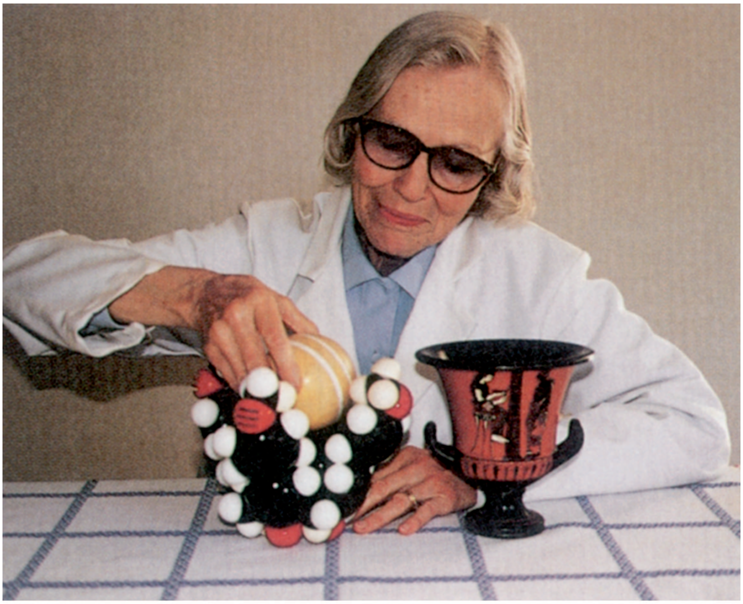
Little did I realize in 1989, when there were relatively few workers in the field, that only nine years later it would be necessary to write a sequel to this first volume to bring things up to date. From the outset of writing that second volume, however, it was clear that it was fruitless to try to include in a relatively short book all of the new information coming from the publications of the dozens of research groups that had entered the field in the interim. Consequently, "Calixarenes Revisited", published in 1998, represented a judicious selection from the literature but in no way a complete and definitive compendium. Today, the pace of publication continues unabated, further compounding the problem of writing a concise overview of the field. What has happened instead is that books and long reviews are being published that provide complete and definitive treatments of various individual segments of calixarene chemistry. To take advantage of these scholarly efforts, the present book contains frequent references to appendices A–D which list these contributions (abbreviated in the text as "*Apndx*" followed by the specification of the particular appendix and the item number within that appendix – *e.g. A-2, p. 89; C-9*; *etc.*). To read and assimilate all the information in this long list of reviews is a daunting task for a young investigator not yet familiar with calixarene chemistry and might deter him/her from entering the field. The aim of this third volume, therefore, reiterates that of the first volume, *viz.* to provide a survey of calixarene chemistry to serve as an introduction to the longer and more in-depth coverage provided by these other sources.

In 2002 I retired from active research after a career spanning more than half a century. Living now in Tucson, Arizona, where I have a relaxed affiliation with the University of Arizona as a Visiting Scholar, I thought that calixarene chemistry would become a passive activity, merely a pleasant memory of former days. However, when prevailed upon by The Royal Society of Chemistry to bring the earlier editions of "Calixarenes" up to date the passive life suddenly became an active and daunting life. Were it not for the availibility of the tools of internet access to library collections of chemistry journals it would have been an impossibly daunting task for this octogenarian. I want to pay homage, therefore, to the University of Arizona libraries and to the incredible services that modern technology provides.

The first edition of "Calixarenes" in 1989 was written in a rather leisurely style, for it was possible at that time to include in a short book most of the research in the field. By 1998 this was no longer feasible and now in 2008 it has become truly impossible. Unhappily, the result is that the leisurely style has given way to a more pedantic and dry style. Furthermore, it has required draconian decisions to be made as to what to include and what not to include in trying to cover every facet of calixarene chemistry at least to some extent. To those authors whose work has not been included or which has been inappropriately truncated I express my sincere regrets.

The progress that has been made in modern calixarene chemistry, starting over 30 years ago, can be attributed to the conscientious and often inspired work of many scientists. In Tolstoy's War and Peace an incident is described in which the generals have given up the battle and the regiment is facing defeat when a young soldier seizes the fallen flag and rushes toward the enemy, inspiring the others of the regiment to follow suit and turn defeat into victory. In like fashion, members of my research group and, no doubt those of many other research groups around the world, often seized the calixarene flag and carried it forward. It is to this army of often under-recognized research associates that the chemical community owes a great debt of gratitude, for without them we generals might well have nothing to show for our clever ideas and glorious schemes. Included in this tribute to all of my former research associates is a special one to my wife Alice, who spent countless hours in past years in the library collecting references, who continues to offer accurate and careful editorial advice and whose untiring abilities as homemaker and spouse have contributed inestimably to all three volumes of this triptych on calixarene chemistry.

C. David Gutsche
Tucson, Arizona



Alice Gutsche with molecular model and calix crater

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CHAPTER 1

From Resinous Tar to Molecular Baskets

"A man is wise with the wisdom of his time only and ignorant with its ignorance. Observe how the greatest minds yield in some degree to the superstitions of their age"

Henry David Thoreau, Journal, 1951

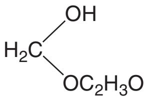
1.1 The Resinous Tar

The path of scientific research is seldom straight, often taking twists and turns quite unexpected at the outset of an odyssey. Such is the case with phenol-formaldehyde chemistry, which began over a century ago in the laboratories of Adolph von Baeyer. It has developed in ways that could not have been foreseen by this eminent scientist but which would certainly provide him with amusement and delight were he still alive to enjoy the passing scene of twenty-first-century chemistry.

Adolph von Baeyer

Johann Friedrich Wilhelm Adolph von Baeyer was one of the great organic chemists of the nineteenth century and received the Nobel Prize in Chemistry in 1905.[1] Born in Berlin in 1835, he received his training in chemistry from Bunsen and Kekulé in Heidelberg. His first professional appointment was at the University of Ghent with Kekulé, but his career as an independent investigator really began in 1860 when, at the age of 25, he joined the staff of the Technical Institute at Berlin. Twelve years later he moved to Strasbourg as director of the chemical laboratories of the university where his talents as a teacher and researcher blossomed, leading in 1875 to an appointment as successor to the great Justin Liebig at the University of Munich. He held this position until his retirement many years later. Although Baeyer was best known for his elucidation of the structure and synthesis of the naturally occurring dye indigo as well as his work on carbocyclic ring compounds, he also delved into many other areas of organic chemistry. Among these was a brief foray into the reaction of phenols with formaldehyde. Two short papers[2,3] were published from Berlin in 1872 followed by a somewhat longer one[4] later that year after he had moved to Strasbourg. These appeared in *Chemische Berichte* and describe the results of mixing aldehydes and phenol in the presence of strong acids.

In the first of the three papers Baeyer simply reported that a thickening of the reaction mixture of aldehydes and phenols occurs with the formation of a "kittartige Substanz" ("a cement-like substance"). Specific examples of these reactions were discussed in more detail in the second paper, including the reaction of benzaldehyde and pyrogallol (benzene-1,2,3-triol), which gave a red-brown, resin-like product. Not until the third paper, however, was the reaction with formaldehyde introduced, heralding the beginning of the field of phenol-formaldehyde chemistry. This delay can probably be attributed to the fact that in 1872 formaldehyde was a rare chemical not easily available. Baeyer had to prepare it by reducing iodoform (CHI_3) with HI and red phosphorus to methylene diiodide (CH_2I_2) and then replacing the iodine atoms with oxygen moieties by treatment with silver acetate in acetic acid. This yielded the liquid which Baeyer formulated as



(*i.e.* the adduct of HCHO and CH_3CO_2H), recognizing with great insight the proclivity of the C=O group of formaldehyde to add proteated nucleophiles. Thus, acquiring formaldehyde in sufficient quantity for use in reactions was a major undertaking, in marked contrast to today where it is one of the world's cheapest and most readily available chemicals (current production exceeds 2.5 million tons per year).

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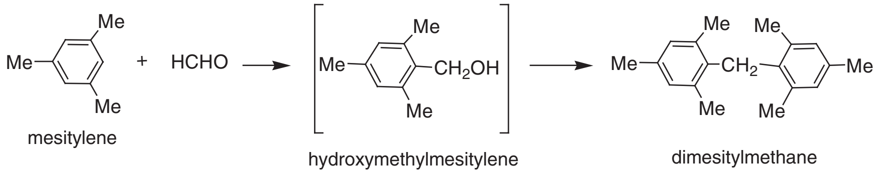
[1] For excellent biographies of Baeyer *cf. J. Chem. Educ.* **1930**, 7, 1231; *ibid.* **1929**, 6, 1381; R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 297.

[2] A. Baeyer, *Ber.* **1872**, 5, 25.

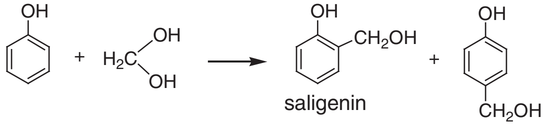
[3] A. Baeyer, *Ber.* **1872**, 5, 280.

[4] A. Baeyer, *Ber.* **1872**, 5, 1094.

Using formaldehyde synthesized as described above, Baeyer showed that it reacts with phenol in a fashion similar to that of the larger aldehydes to produce a resinous material. However, he was unable to isolate pure substances from any of these reactions and, therefore, could not obtain elemental analyses which might have allowed him to propose possible structures. In retrospect we can appreciate how formidable a problem he faced, for even today with our impressive array of analytical techniques the structure of the phenol-formaldehyde product is not known in complete detail. However, Baeyer did manage to provide some structural insights by proposing a dimesitylmethane structure for the more tractable product obtained from mesitylene and formaldehyde. So, even though he was unsuccessful in characterizing the phenol-formaldehyde product, Baeyer had, nevertheless, given birth to phenol-formaldehyde chemistry.



The next chapter in this nascent field occurred in 1894 when two German chemists, L. Lederer[5] and O. Manasse,[6] independently studied the base-induced reaction of formaldehyde with phenol and succeeded in isolating *o*-hydroxymethylphenol and *p*-hydroxymethylphenol as well-defined crystalline solids, viewing the reaction as a dehydration process in which formaldehyde reacts in its hydrated form, *viz*.



o-Hydroxymethylphenol was of particular interest, because it had already been isolated a half century earlier as a naturally occurring compound present in nature as a glucoside. The success of the Lederer–Manasse reaction, as it came to be called, depended on the use of mild and well-controlled conditions. Under more strenuous conditions the base-induced reaction, like its acid-catalyzed counterpart, yields a resinous tar of ill-defined structure.

At the dawn of the twentieth century phenol-formaldehyde chemistry, introduced a quarter of a century earlier, remained a rather intransigent and largely unattended area of investigation that seemed to hold little reward for explorers intrepid enough to set foot within its confines. But, explorers there were, such as Blumer,[7] Storey,[8] Luft[9] and others, all of whom tried to tame

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[5] L. Lederer, *J. Prakt. Chemie*, **1894**, 50, 223.

[6] O. Manasse, *Ber*. **1894**, 27, 2409.

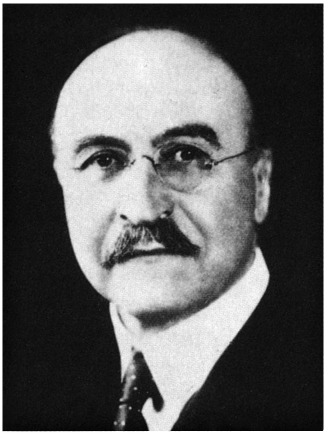
[7] L. Blumer, British Patents 6,823 and 23,880.

[8] W. H. Storey, British Patent 8875.

[9] A. Luft, British Patent 10,218.

these resinous tars and find practical applications for them. For one reason or another, however, all failed to produce materials with marketable qualities.[10]

Success was to go to another explorer, Leo Hendrik Baekeland, who was born in 1863 in Ghent, Belgium.[11] From early childhood Baekeland's brilliance as a scholar was evident, and by 1884 at the youthful age of 21 he had already acquired a Doctor of Science degree. After several years of restless associations with chemistry departments at Ghent and Bruges in Belgium, Cambridge and Oxford in England, and Edinburgh in Scotland, Baekeland and his young wife sailed to America in 1889, there to continue his research on photographic papers.



Leo Baekeland

This eventually led to a commercially successful material that he called "Velox", a name still known to an older generation of pre-digital photographers. So successful was this product that the Velox process was purchased by George Eastman in 1900 for one million dollars, making Baekeland a wealthy man at the age of 37. Constrained by the terms of the sale from continuing to carry on his photographic experiments, yet not wanting to abandon his passion for research, Baekeland set up a laboratory in his home, hired a number of assistants, and proceeded to explore an amazing diversity of projects. Among these was an investigation starting in 1902 that dealt with the reaction of phenol and formaldehyde. Although it had already occurred to a number of others that the hard cement-like substance described by Baeyer might have utility as an item of commerce, only after several years of careful and painstaking work was Baekeland able to prove this premise and show that by using a small and controlled amount of base an appealing material could be obtained. On February 18 1907 he filed for a patent on this process[12] for making a material

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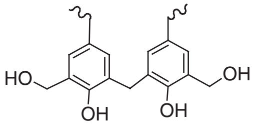
[10] For a brief account of the early history of phenol-formaldehyde chemistry *cf.* A. A. K. Whitehouse, E. G. K. Pritchett and G. Barnett, *Phenolic Resins*, American Elsevier, New York, **1968**.

[11] For biographies of Baekeland *cf.* (a) H. V. Potter, *Chem. Ind.* **1945**, 242, 251; (b) J. Gills and R. E. Osper, *J. Chem. Educ.* **1964**, 41, 224.

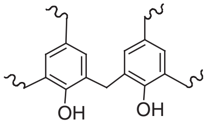
[12] L. H. Baekeland, US Patent 942,699; October **1908**.

that he eponymously called Bakelite. With this, the age of modern synthetic plastics had begun.

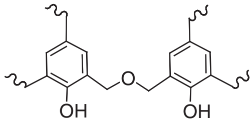
The Bakelite process, ultimately described in over 400 patents issued to Baekeland, constituted the first large-scale production of a synthetic plastic. Like most new things, it took time to gain acceptance, but once the induction period had come to a close an exponential growth phase ensued that brought great wealth to Baekeland and many others and that inspired a flood of research. One of the earliest reviews of the research on the chemistry of what were called "teerphenole" (tar phenols) was written in 1912 by Raschig,[13] who came to the conclusion that "über die Chemie des Bakelits tappen wir noch vollständig im Dunklen". Today, almost a century later we continue to be at least somewhat in the dark about the precise details of the Bakelites. The progress that has been made and the problems that remain unresolved are recounted in a variety of books and articles.[14] As had already been realized by Baeyer in 1872, however, it is CH_2 and CH_2OCH_2 groups that are the most likely linkages between pairs of aromatic rings in a formaldehyde-phenol condensation product. Thus, the dominant structural diaryl moieties in a typical resin are those shown in Plate 1-6; *viz*. resoles, novolaks and dibenzyl ethers.



resoles



novalaks



dibenzyl ethers

When resoles are heated they undergo conversion to novolak-like structures, and it is the changes that occur during this "curing" process that have attracted most of the attention not only from the process engineers in the production plant but also the research chemists in the laboratory. The former are interested in discovering how varying conditions affect the physical attributes of the final product; the latter are interested in discovering the nature of the chemical transformations that are occurring.

1.2 Glistening Crystals: The Zinke Products

It is the outcome of a study of the "curing" phase of the phenol-formaldehyde process that provided the next episode in this story, bringing to the fore the central subject of this book. In 1942 Alois Zinke, a professor of chemistry at the University of Graz in Austria, and his coworker Erich Ziegler decided to

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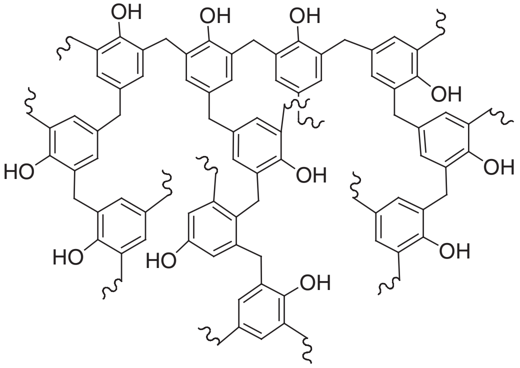
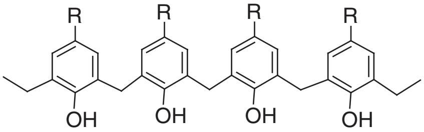
[13] F. Raschig, *Z. Angew. Chem.* **1912**, 25, 1939.

[14] For reviews of the Bakelite process *cf.* (a) A. Knop and L. A. Pilato, *Phenolic Resins*, Springer-Verlag, **1985**; (b) E. Muller in *Methoden der Organischen Chemie* (Houben-Weyl), George Thieme, **1963**, Volume XIV/2 of *Makromoleculare Stoffe*, Part 2; (c) N. J. L. Megson, *Phenolic Resin Chemistry*, Butterworths, London, **1958**; (d) R. W. Martin, *The Chemistry of Phenolic Resins*, John Wiley, New York, **1956**; (e) K. Hultzsch, *Chemie der Phenolharze*, Springer-Verlag, Berlin, **1950**.

"simplify" the problem by looking not at phenol itself but at *p*-substituted phenols in the condensation reaction with formaldehyde.[15] Whereas phenol reacts at both the *ortho*- and *para*- positions to form a highly cross-linked polymer in which almost all of the phenolic units are attached to three other phenolic residues, *viz*.



a *para*-substituted phenol can react only at the two *ortho*- positions, thereby reducing the cross-linking possibilities, *viz*.



It was anticipated that with this more limited reaction a more tractable product would be obtained that might provide insight into the curing process. A typical experiment in the Zinke and Ziegler study[16] is described in the 1944 paper as follows: "When 50 g of the resin which is obtained by heating 100 g of *p*-*tert*-butylphenol, 100 mL of 3 N NaOH, and 97 g of a 35% formaldehyde solution is heated with stirring with 200 g of linseed oil, it dissolves at 100–120 °C. At 140–160 °C there is a vigorous foaming, and turbidity appears which increases greatly upon further heating at 200–220 °C. The resulting brown waxy paste is stirred with ethyl acetate, washed thoroughly, and reprecipitated from CCl_4 with alcohol to give a crystalline product as platelets or rosettes that decompose above 300 °C." A product of presumably identical composition with the empirical formula $C_{11}H_{14}O$ had already been described in less detail by these authors three years earlier.[17] The lack of reactivity of this compound with HBr indicated the absence of ether linkages, but no structure was proposed in the 1941 paper. By 1944, however, the idea of a cyclic structure

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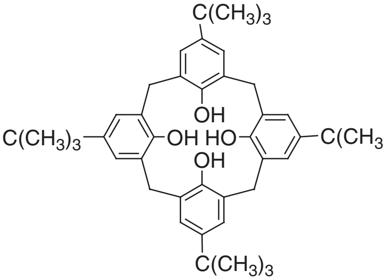
[15] For an account of the contribution of v. Euler, Hultzsch and Zinke to phenol- formaldehyde chemistry *cf*. ref 14(c).

[16] A. Zinke and E. Ziegler, *Ber*. **1944**, 77, 264.

[17] A. Zinke and E. Ziegler, *Ber*. **1941**, B74, 1729.

had sprung to the minds of several investigators and was "in the air", so to speak. Joseph Niederl and his coworker Heinz Vogel.[18] at New York University, for example, had proposed a cyclic tetrameric structure for compounds obtained by the *acid*-catalyzed treatment of aldehydes and resorcinol (*cf.* next section), so it was a propitious time for the Austrian workers to propose the cyclic tetrameric structure **1.1** for the *base*-induced product.[19]



1.1

Alois Zinke[20] was born in Bärnbach, a region of Voitsberg, Austria, in 1892. His early schooling was acquired in Voitsberg, but in 1912 he went to Graz for the completion of his training for the Doctorate from the University of Graz in 1915 under the tutelage of Roland Scholl. He remained in Graz for the rest of his life, starting his professional career at the University of Graz, transferring his allegiance to the Technische Hochschule for a brief four years and then returning to the university as a professor of pharmaceutical chemistry. In 1941 he was appointed director of the Institute für Organische und Pharmazeutische Chemie. During his distinguished career, which extended to his death in 1963, he carried out research in several areas, but his best known work is with the phenol-formaldehyde resins. When he started this work in 1936 there already were several well-established investigators in the field, including Koebner, Megson, v. Euler, Hultzsch and Adler. Undaunted by this competition, Zinke initiated his own program and went on to make numerous and important contributions including the seminal discovery of the cyclic oligomers.[21]

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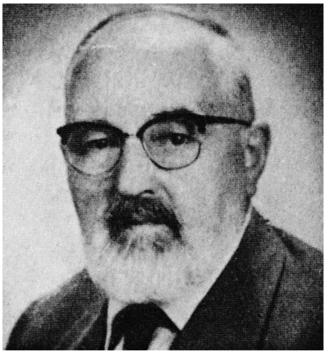
[18] J. B. Niederl and H. J. Vogel, *J. Am. Chem. Soc.* **1940**, 62, 2512.

[19] In a later paper (*cf.* ref 22) Zinke refers to an "observation by H. Hönels" in connection with the cyclic tetrameric structure, but nothing beyond this cryptic allusion is offered to indicate the nature of Honels' contribution.

[20] For a biography of A. Zinke *cf.* E. Ziegler, *Scientia Pharmaceutica* **1951**, 209; *idem*, *Arzneimittel Forschung* **1963**, 12, 208. We are deeply indebted to Prof. Dr Helge Wittman for making copies of these biographies of her father available to us.

[21] An intimate description of life in the Zinke laboratories in the 1940s is provided in a delightful essay by T. Kappa, *J. Inclusion Phenom. Mol. Recognit.* **1994**, 19, 3.



Alois Zinke

The product that Zinke and Ziegler described in their first experiment[17] was a crystalline acetate melting at 314 °C, which had the surprisingly high molecular weight of 1725. On the premise that the compound from which the acetate was derived was certainly a cyclic oligomer, this value would appear to indicate the presence of 8 or even 9 *p-tert*-butylphenol units in the cyclic array. However, this seemed so unlikely that they desisted from drawing any structure in 1941 and waited until 1944 before proposing the intuitively more appealing cyclic tetramer structure.

Zinke's choice of a cyclic tetrameric structure for the product obtained from the base-induced condensation of *p-tert*-butylphenol and formaldehyde seemed quite logical, and the high molecular weight value for the acetate was dismissed as a complication caused by mixed crystal or molecular compound formation. Additional examples of the condensation reaction, which Zinke refers to as one involving "nicht alkalifrei gewaschenen Resols in Leinöl ("resoles, not washed entirely free of base, in linseed oil"), were reported in a short paper four years later[22] in which *p*-phenylphenol, *p*-cyclohexylphenol and *p*-benzylphenol are all described as giving high melting, organic solvent-insoluble materials (*cf.* structures **1.2**). Cyclic tetrameric structures were assigned to all of these products, although no experimental data were provided. Not until 1952 was further information forthcoming in a paper that is the most detailed of all of Zinke's publications on the cyclic oligomers. Published with R. Kretz, E. Leggewie and K. Hössinger,[23] it provided additional examples of phenols reacting with formaldehyde to give high melting, organic solvent-insoluble substances. More importantly it provided additional evidence in support of the cyclic tetrameric structure. Zinke had recognized that an unequivocal proof of structure had not been given in his previous publications, and he implicitly acknowledged that the molecular weight of the acetate of the product from *p-tert*-butylphenol and formaldehyde constituted a puzzling complication. Thus, it must have been a great relief to him to find that the acetate of the product from *p*-1,1,3,3-tetramethylbutylphenol and formaldehyde, isolated as needles with mp 333 °C, had a cryoscopic molecular weight of only 876, in perfect agreement with that

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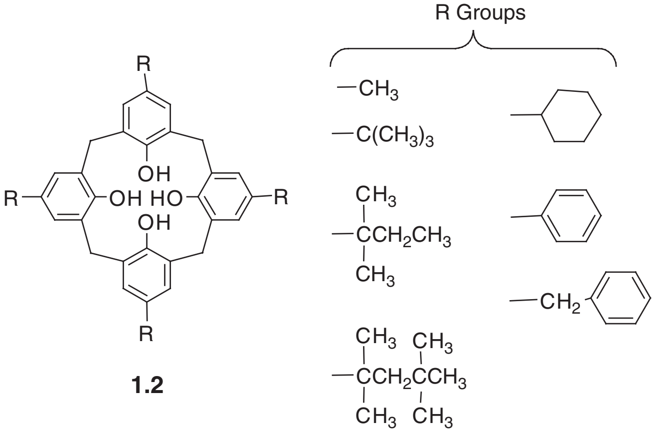
[22] A. Zinke, G. Zigeuner and K. Hössinger, *Monatsh.* **1948**, 79, 438.

[23] A. Zinke, R. Kretz, E. Leggewie and K. Hössinger, *Monatsh.* **1952**, 83, 1213.

calculated for a cyclic tetramer. Satisfied with this piece of evidence, Zinke concluded that all seven of the products he had obtained were cyclic tetramers, *viz*.



1.2

The four papers by Zinke that are discussed above represent only a small fraction of his total scientific output, but in the context of the present book they are his most important. This pioneering work gave glimpses of the treasures that are to be found in the resinous tar of a phenol-formaldehyde condensate, and they provide an important part of the scaffolding on which calixarene chemistry has been built. No matter how original one's contributions may appear to be, however, antecedents can usually be found lurking in the shadows. The case of the cyclic tetramer is no exception, for Raschig had suggested such a structure back in 1912 in the paper cited earlier in this chapter,[13] although his idea must be regarded as a lucky guess rather than a rational choice based on experimental evidence. To Zinke should go the honor of true parentage. But, as we shall see in later sections of this chapter, the complete character of his progeny was yet to be revealed.

1.3 More Crystals: The Niederl Products[24]

At this point we must retrace our steps, look once again at Baeyer's experiment in 1872 and follow another trail of events that flowed from these beginnings. Resorcinol was among the reactants that Baeyer used in his investigations with phenols and aldehydes, and he discovered that it reacts with aldehydes such as acetaldehyde and benzaldehyde under acidic conditions to produce crystalline, high-melting compounds. However, the products lacked the dye-stuff properties he was seeking, so he decided not to pursue their characterization but

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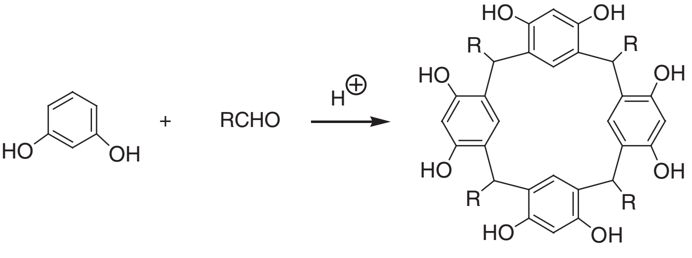
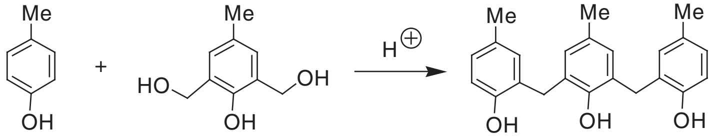
[24] Much more detailed descriptions of the resorcinol-derived cyclooligomers can be found in (a) D. J. Cram and J. M. Cram, "Container Molecules and Their Guests" in *Monographs in Supramolecular Chemistry*, ed. J. F. Stoddard, Royal Society of Chemistry, Cambridge, **1994** (*Apndx A-7*); (b) P. Timmerman, W. Verboom and D. N. Reinhoudt, *Tetrahedron* **1996**, 52, 2663 (*Apndx B-15*).

simply to conclude that they were 1:1 condensation products. The reaction was re-investigated a decade later by Michael,[25] who succeeded in isolating a pair of crystalline materials for which he postulated cyclic dimeric structures. Similar experiments were carried out in 1894 by Möhlau and Koch[26] and again in 1904 by Liebermann and Lindebaum,[27] but after that the compounds remained unattended until 1940 when Niederl and Vogel[18] reinterpreted their chemistry. These workers isolated solid, high melting condensation products from the reaction of resorcinol and aldehydes (*e.g.* acetaldehyde, propionaldehyde, isovaleraldehyde) and concluded, primarily on the basis of molecular weight determinations, that the products are best represented as cyclic tetramers **1.3**. In contrast to the Zinke tetrols in which four OH groups are intraannular (also designated as "*endo*-annular"), the eight OH groups in the Niederl octols are extraannular (also designated as "*exo*-annular").[28]



1.3

Extending their studies to include phenol-*formaldehyde* products, Niederl and McCoy[29] repeated an earlier experiment of Koebner,[30] who had claimed that a linear trimer is produced in the acid-catalyzed reaction of *p*-cresol and its bis-hydroxymethyl derivative.



Koebner product

However, clearly influenced by their work on the resorcinol-aldehyde products and relying on what they believed to be their more accurate molecular weight determinations, Niederl and McCoy[29] postulated that the Koebner product was actually the cyclic tetramer (**1.3**, $R = Me$). That this was an incorrect assumption and that Koebner's linear trimer structure was the correct one

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[25] A. Michael, *Am. Chem. J.* **1883**, 5, 338.

[26] R. Möhlau and P. Koch, *Ber.* **1894**, 27, 2887.

[27] C. Liebermann and S. Lindenbaum, *Ber.* **1904**, 37, 1171.

[28] Appreciation is expressed to Dr Högberg for providing a copy of his excellent thesis (Royal Institute of Technology, Stockholm, Sweden, 1977) in which the "intraannular" and "extra-annular" terminology is suggested.

[29] J. B. Niederl and J. S. McCoy, *J. Am. Chem. Soc.* **1943**, 65, 629.

[30] M. Koebner, *Z. Angew. Chem.* **1933**, 46, 251.

was shown first in 1950 by Finn and Lewis[31] and then again in 1961 by Foster and Hein.[32] Undoubtedly, the controversy arising from the incorrect structure assignment of the Koebner product cast doubt for some time on Niederl's claim of a cyclic tetrameric structure for the resorcinol-aldehyde products. Subsequent definitive experiments, however, showed the latter to be cyclic as Niederl had claimed, so the honor of being the first to correctly assign a cyclic tetrameric structure to a phenol- (*i.e.* resorcinol-)aldehyde product on the basis of solid experimental evidence perhaps should actually go to Niederl. It seems possible that his work might have had an influence on Zinke's assignment of structure, although there is no direct evidence for this conjecture.

1.4 Cyclic Tetramers: Proofs of Structure

By the 1950s the work of Zinke on the cyclic tetramers had become known to chemists interested in phenol-formaldehyde chemistry. Among these were B. T. Hayes and R. F. Hunter in the Research & Development Department of Bakelite Ltd, Tyseley, Birmingham, England. In 1956 this pair of chemists published a short account[33] of what they termed a "rational synthesis" of a "cyclic tetranuclear *p*-cresol novolak", following this in 1958 with a longer and more detailed account.[34]

The Hayes and Hunter synthesis, outlined in Figure 1.1, provides a classic example of the use of a blocking group that is added at one point to protect a reactive site and then removed at a later point to reopen that site to reaction. The protecting group that they chose was the bromine atom, introduced in the initial step of the sequence into one of the *ortho*- positions of *p*-cresol to give 2-bromo-4-methylphenol. Base-induced hydroxymethylation yielded 2-bromo-4-methyl-6-hydroxymethylphenol which was then treated with concentrated HCl and a large excess of *p*-cresol heated at 70 °C for 18 hours, and worked up to give a reasonably good yield of 3-bromo-2:2-dihydroxy-5:5′-dimethyldiphenylmethane. Repetitions of this *pas de deux*, *viz.* base-induced hydroxymethylation followed by acid-catalyzed arylation, produced a dimer, then a trimer, and finally a tetramer. One more hydroxymethylation followed by removal of the bromine by catalytic hydrogenation afforded the penultimate product, the mono-hydroxymethylated linear tetramer. Acid-catalyzed treatment under high dilution conditions effected cyclization to the cyclic tetramer in unstated yield. The material that was obtained was described as a light brown solid that did not melt below 300 °C, that was soluble in a variety of organic solvents and that did not undergo coupling with benzenediazonium chloride (indicating the absence of any reactive *ortho*- or *para*- positions). A molecular weight determination gave a value of 525, in reasonably close

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[31] S. R. Finn and G. J. Lewis, *J. Soc. Chem. Ind.* **1950**, 69, 132.
[32] H. M. Foster and D. W. Hein, *J. Org. Chem.* **1961**, 26, 2539.
[33] B. T. Hayes and R. F. Hunter, *Chem. Ind.* **1956**, 193.
[34] B. T. Hayes and R. F. Hunter, *J. Appl. Chem.* **1958**, 8, 743.

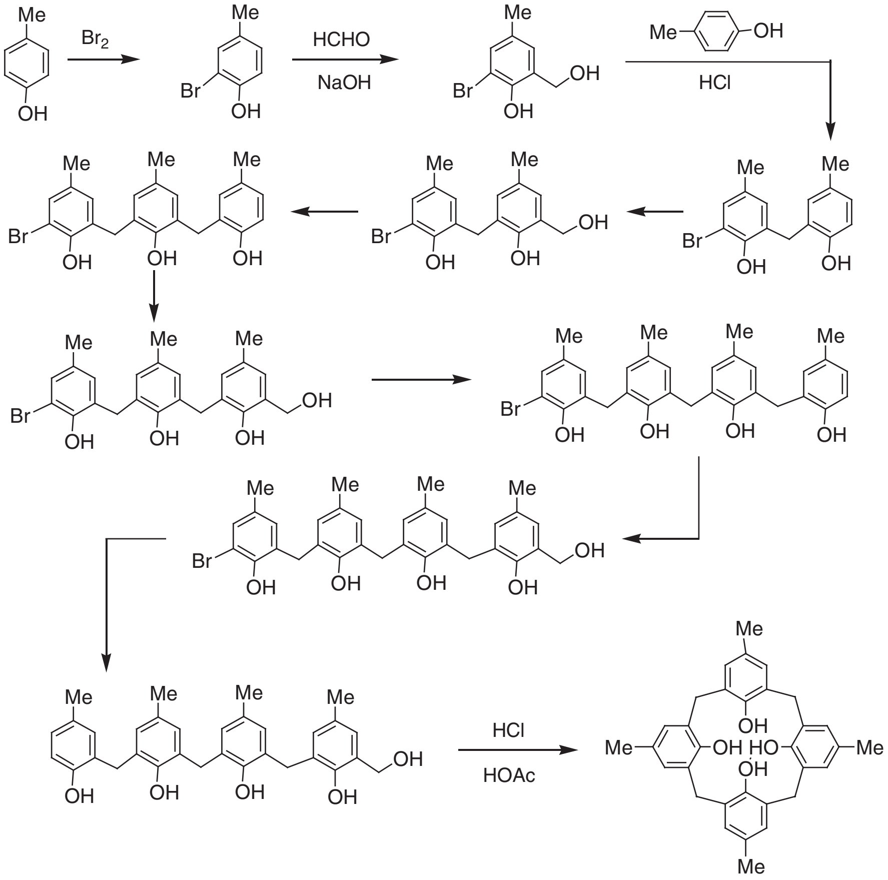

Figure 1.1 Hayes and Hunter stepwise synthesis of a calix[4]arene.

agreement with the calculated value of 480. Employing the then rather new technique of infrared analysis, Hayes and Hunter observed an absorption band in the tetraacetate of the product at 854 cm^{-1}, indicative of a 1,2,4,6-tetrasubstitution pattern on the aromatic rings. Elemental analysis of the product and its tetraacetate gave results commensurate with a cyclic tetramer, although in both cases the inclusion of a certain amount of water in the product had to be invoked to bring the observed values within range of the calculated values.

Hayes and Hunter concluded that their synthesis showed that "cyclic structures may be produced under suitable environmental conditions in the hardening process of phenol-formaldehyde resins", thereby confirming "that the analogous novolaks which Zinke and his collaborators claimed to have obtained by heating resoles such as 2,6-bis-hydroxymethyl-4-*tert*-butylphenol are, at least, sterically possible". That it did, indeed, establish the validity of a cyclic tetrameric structure is assured, and this synthesis, though simple and straightforward in concept, represents a significant contribution to the literature of phenol-formaldehyde chemistry. It was tacitly accepted as a proof of structure of all of the Zinke products in spite of the fact that at that time no direct comparison was made between the Hayes and Hunter compound and the one obtained by a Zinke reaction from *p*-cresol. Only many years later was such a direct comparison made.[35] The Hayes and Hunter synthesis represents a highly laudable achievement, and it established the basis for an extensive program carried out some years later by Hermann Kämmerer and coworkers. However, it may have delayed the more careful investigation of the Zinke reaction because of the implied assumption that it provided the capstone in the structure proof of the Zinke products.

Shortly after Zinke's 1952 paper describing the application of his procedure using a variety of *p*-substituted phenols, but before the Hayes and Hunter papers had appeared in print, another participant entered the field. Whereas Zinke as well as Hayes and Hunter were interested in the cyclic tetramers as a facet of the phenol-formaldehyde problem, the new entrant was interested in the cyclic structures *per se*. John W. Cornforth, a British chemist who was destined to win a Nobel Prize two decades later for his work on the stereochemistry of enzyme-catalyzed reactions, was interested in 1953 in the preparation of tuberculostatic substances. Among the compounds tested for this purpose were a variety of oxyethylated phenols, including linear phenol-formaldehyde oligomers as well as the then recently described Zinke products. When Cornforth and his coworkers[36,37] repeated the Zinke reaction using *p*-*tert*-butylphenol, they were surprised to find two materials rather than a single product. Both were crystalline, sparingly soluble compounds with high but non-identical melting points. Both had elemental analyses compatible with a $(C_{11}H_{14}O)_n$ formula, and both possessed the physical and chemical properties characteristic of a cyclic oligomer. When *p*-1,1,3,3-tetramethylbutylphenol (often referred to as *p*-*tert*-octylphenol) was employed as the starting material the outcome was similar, *viz.* two compounds with essentially identical properties but somewhat different melting points were isolated. For convenience these substances were referred to by Cornforth as (a) the high melting compounds HOC and HBC prepared from *p*-*tert*-butylphenol and *p*-*tert*-octylphenol, respectively, and (b) the low melting compounds as LOC and LBC also prepared from *p*-*tert*-butylphenol and *p*-*tert*-octylphenol, respectively.

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[35] C. D. Gutsche, B. Dhawan, K. H. No and R. Muthukrishnan, *J. Am. Chem. Soc.* **1981**, 103, 3782; *idem*, *ibid.* **1984**, 106, 1891 prepared *p*-*tert*-butylcalix[4]arene by the Hayes and Hunter route and showed it to be identical to one of the materials isolated from the base-induced condensation of *p*-*tert*-butylphenol and formaldehyde.

[36] J. W. Cornforth, P. D'Arcy Hart, G.A. Nicholls, R. J. W. Rees and J. A. Stock, *Br. J. Pharmacol.* **1955**, 10, 73.

[37] J. W. Cornforth, E. D. Morgan, K. T. Potts and R. J. W. Rees, *Tetrahedron* **1973**, 29, 1659.

John Cornforth

Since Zinke's work had given no indication that the products from the base-induced reaction of *p*-substituted phenols and formaldehyde might be mixtures, the isolation of a pair of compounds from both the *p*-*tert*-butylphenol and *p*-*tert*-octylphenol reactions was disturbing. One of the obvious structural possibilities for "the other compound" is that it is a linear oligomer. However, this was quickly ruled out by the elemental analyses which indicated the presence of the same ratio of CH_2 groups (from HCHO) and phenolic residues in all of the compounds isolated. Also, the failure of either the high-melting or low-melting compounds to react with *p*-nitrobenzenediazonium chloride indicated the absence of any reactive positions on the aromatic rings. The possibility that the high-melting and low-melting compounds might be cyclic oligomers of different ring sizes seemed to be negated by the results of X-ray crystallography. Dorothy Crowfoot Hodgkin, one of Britain's most eminent X-ray crystallographers, reported the following:

> "Both HOC and HBC have very complex crystal structures in which the asymmetric units have, respectively, four and three times the weight required for a tetrapolymer. Formally they admit several solutions for the molecular complexity of these compounds. HOC acetate is rather simpler; the molecule here from the X-ray evidence is most probably a 4-polymer (space group P1), but might be either an 8-polymer or possibly a 7-polymer (P1), since difficulty was experienced in measuring accurately the lattice constants of the triclinic crystals. LOC and LBC both have crystal structures which indicate they are tetrapolymers. Formally, in the case of LOC, the molecule might correspond with a twofold polymer or with an eightfold polymer having a center of symmetry in the molecule. The latter is, however, not a stereochemically probable solution, and the molecule here almost certainly corresponds with the crystal asymmetric unit. LBC crystallizes in the tetragonal system; here, the molecule proved not only to be a fourfold polymer but also to have either a fourfold or a fourfold-alternating axis of symmetry."

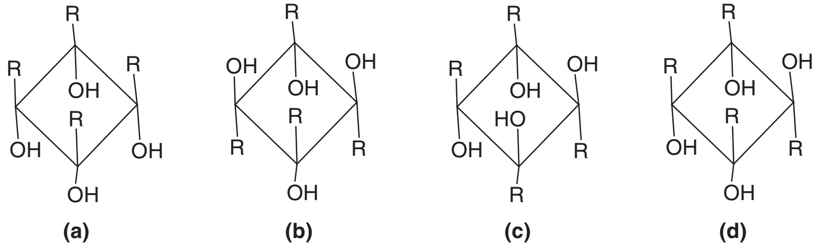

Figure 1.2 Rotational diastereoisomers of a cyclic tetramer.

With this evidence in hand Cornforth stated that "Though they do not establish with certainty the molecular complexity of all the compounds, the crystallographic data are consistent with the view that all four condensation products have a cyclic tetrameric structure." He goes on to say that cryoscopic molecular weight determinations of HBC, LBC, HOC and LOC all reinforce the conclusion and "refute the possibility, admitted by the crystallographic data, of molecules containing eight phenolic nuclei". But, if both the high-melting and low-melting compounds are cyclic tetramers how does one account for the difference in properties? To answer this question Cornforth proposed that the compounds are diastereoisomers arising from hindered rotation. Examination of molecular models revealed the possibility of four different structures, shown in Figure 1.2, and Cornforth assumed that "the phenolic nuclei cannot rotate about the bonds joining them to the methylene groups". Thus, each of these four structures, today called conformers, should be capable of independent existence. Since they bear a diastereoisomeric relationship to one another, they would be expected to have different chemical and physical properties. Other investigators came to similar conclusions from an examination of molecular models. For example, Ballard, Kay and Kropa[38] constructed these four conformers from space-filling molecular models, inspection of which led to their statement that the "phenolic nuclei cannot rotate around the methylene linkage".

By the late 1950s, therefore, the evidence seemed to be quite conclusive that the Zinke reaction produces only cyclic tetramers. Although Cornforth's experiments showed that the reaction is not as clean as seemed to be implied by Zinke's descriptions, the concept of the cyclic tetrameric structure appeared to be firmly supported and established. Only later would the truth of Henry David Thoreau's insight that "man is wise with the wisdom of his time only" be reaffirmed, the unappreciated flaw in this pre-NMR era of chemistry being too great a reliance on the accuracy of molecular models in reflecting the magnitude of rotation barriers.

1.5 The Petrolite Chapter

For eight decades the Petrolite Corporation was located in Webster Groves, Missouri, about four miles outside the city limit of St Louis and about ten miles

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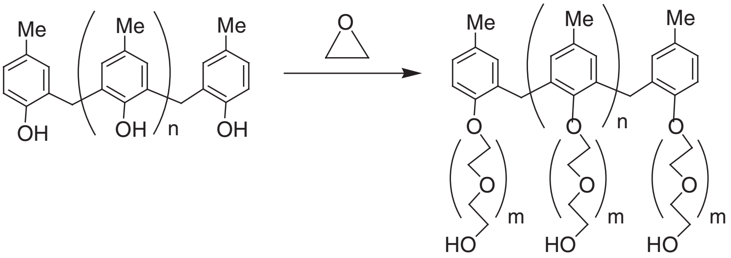
[38] J. L. Ballard, W. B. Kay and E. I. Kropa, *J. Paint Technology* **1966**, 38, 251.

from the Mississippi River. In the late 1990s it became the Baker Petrolite Company, a subsidiary of Baker Hughes Company located in Sugar Land, Texas. Started in 1916 by a young pharmacist named William S. Barnickel, it grew from very modest beginnings to become one of St Louis' larger companies. Important among its major products was a line of compounds for breaking crude oil emulsions, and it is one of these demulsifiers that played a critical role in the present story.

Crude oil as it comes out of the ground is usually mixed with water, generally as an emulsion that is difficult to break. What gave Barnickel his big chance to turn his back on pharmacy and enter the arena of business was his discovery, after several years of testing by trial and error, that ferrous sulfate was effective in breaking the emulsified oil from the large Caddo oil field near Shreveport, Louisiana. It soon became apparent, though, that ferrous sulfate was far from being a universal oil demulsifier. In fact, it was almost unique for the Caddo field emulsion, and it turns out that oil emulsions from wells in various other locations around the world each have their individual characteristics. A demulsifier that works on one may not necessarily work on another. Consequently, for Barnickel's newly emerged Petrolite Company to offer products for the world's spectrum of oil wells it was necessary that a range of tailor-made substances be made available. To explore the means for providing this range of products a scientist named Melvin DeGroote was hired in 1924. By the time that this remarkable man retired in 1960 he had been granted almost a thousand patents on crude oil demulsifiers, making him the world's record holder at that time for the greatest number of US chemical patents. Among the numerous products that DeGroote and his burgeoning research staff discovered were the oxyalkylated alkylphenol-formaldehyde resins. Initially employing an acid-catalyzed condensations procedure, they subsequently found that base-induction gave a better material as, for example, with the product from *p-tert*-butylphenol and formaldehyde, which they assumed to be a linear oligomer. Subsequent treatment with ethylene oxide introduced the oxyalkyl side chains to give the demulsifier, *viz*.



With great expectations, this material was marketed as a solution/suspension in a mixture of aromatic hydrocarbons. From the outset, however, complaints were received not only from the customers using this material in the oil fields but also from the workers in the Petrolite production plant making this material, the complaint being that sludges precipitated from the solution/suspension that made the handling and application of the product very difficult and cumbersome. Not understanding the cause of this unexpected behavior, the plant engineers turned to the chemists in the research laboratory for help. A five-person team consisting of Franklin Mange, Rudolf Buriks, Alan Fauke, John Munch and Jack Ludwig were assigned to the project which they addressed by first carrying out a laboratory procedure that simulated the one used in the production plant.

Melvin DeGroote (in picture)
Franklin Mange Rudolf Buriks Alan Fauke Jack Ludwig John Munch
Petrolite chemists

Much of this work was done by John Munch, whose procedure was to prepare a slurry of *p*-*tert*-butylphenol and paraformaldehyde in xylene, add a small amount of 50% KOH solution and reflux the mixture for several hours in an apparatus equipped with a Dean and Stark trap to remove water from the reaction mixture. During the course of the reaction a copious precipitate formed, which was removed by filtration and found to be a very high-melting, very insoluble compound crystallizable from chloroform as very small glistening needles. Intrigued by these properties, the Petrolite scientists proceeded next to search the chemical literature for related information whereupon they discovered the existence of the chemistry that has already been introduced in the first two sections of this chapter. On the basis of what they read they concluded that although their recipe for the synthesis was different from the one described by Zinke, the material that they had isolated seemed to be very similar to a Zinke cyclic tetramer. Patents were eventually filed[39,40,41] by the Petrolite group in 1976–1977 describing what has since come to be known as the "Petrolite Procedure" for making cyclic phenol-formaldehyde oligomers. It was assumed that these patents more correctly represented the composition of the demulsifier that had been marketed than had the earlier patents in which linear oligomeric structures were assigned.

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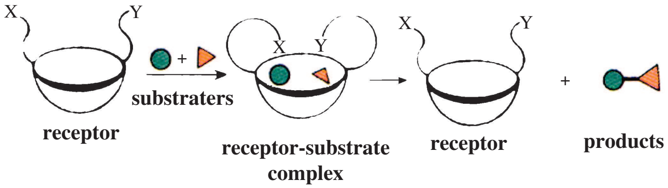
[39] R. S. Buriks, A. R. Fauke and J. H. Munch, US Patent 4,259,464; filed **1976**, issued **1981.**

[40] R. S. Buriks, A. R. Fauke and F. E. Mange, US Patent 4,098,717; filed **1977**, issued **1978**.

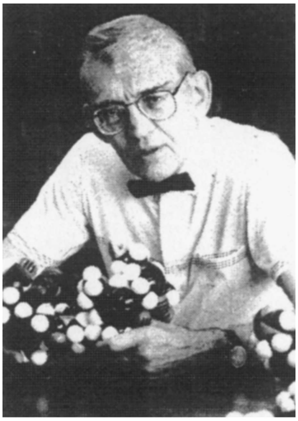
[41] R. S. Buriks, A. R. Fauke and F. E. Mange, US Patent 4,032,514; filed **1976**, issued **1977**.

1.6 Cyclic Tetramers and the Quest for Enzyme Mimics

In 1947 David Gutsche, fresh from graduate school at the University of Wisconsin where he received a Ph.D. degree under the direction of William S. Johnson, joined the Department of Chemistry of Washington University, which is located on the outskirts of St Louis only a few miles from the Petrolite Corporation. One of the results of this geographic proximity was a consulting arrangement that began in 1949 and continued for the next half century. Out of this association came an awareness on Gutsche's part of phenol-formaldehyde chemistry in general and cyclic oligomeric chemistry in particular. So, when he became intrigued in the early 1970s with the newly emerging area of bioorganic chemistry relating to enzyme mimics, the Zinke cyclic tetramers sprang to mind as potential candidates for molecular baskets. The basic idea of enzyme mimic building is to construct a receptor for a substrate molecule and equip the receptor with the functional groups that are appropriate for interacting in some fashion with the substrate molecule, *viz*.



To pursue the idea of constructing an enzyme mimic a research program was initiated in 1972 in the laboratories at Washington University with the goal of exploring the Zinke compounds as the appropriate cavity-containing substances, *i.e.* the molecular baskets.



David Gutsche

In 1972 there were few, if any, true molecular baskets accessible by easy synthesis in the laboratory. The cyclodextrins are beautiful baskets but are readily available only by isolation from natural sources. The crown ethers, although annular in shape and amenable to laboratory synthesis, are more disc-like than basket-like. Thus, the Zinke cyclic tetramers, accessible by easy laboratory synthesis and truly basket-like in shape, appeared to be the ideal choice, and visions of assembling a whole family of baskets by using various *p*-substituted phenols in the condensation reaction with formaldehyde took shape. This class of compounds, so seemingly attractive for the purpose at hand, immediately prompted a search for an appropriate and engaging name.

Zinke[22] referred to his cyclic tetramers as "Mehrkernmethylene-phenol-verbindungen", a quite descriptive name; Hayes and Hunter[34] called them "cyclic tetrameric novolaks", employing a term descriptive of phenol-formaldehyde oligomers lacking hydroxymethyl groups; Cornforth[36] sought a more systematic nomenclature and called them "1:8:15:22-tetrahydroxy-4:11:18:25-tetra-*m*-benzylenes". *Chemical Abstracts*[42] names the basic ring structure of the cyclic tetramer as "[19.3.1.$1^{3,7}1^{9,13}1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27), 15,17,19(26)21,23-dodecaene". In a now widely used nomenclature invented in 1951 by Cram and Steinberg[43,44] these compounds are classed as [1_n]metacyclophanes and can be named on this basis. However, Gutsche and coworkers sought a name for the Zinke cyclooligomers that would be more pictorially and descriptively appealing and that would fall more trippingly from the tongue than that of the *Chemical Abstracts*.

The non-planar character of the cyclic tetramer had already been pointed out by Cornforth[36] as well as by Megson[45] and Ott and Zinke[46] So, perceiving a similarity between the shape of a Greek vase called a calix crater, shown on the right-hand side of Figure 1.3, and a space-filling molecular model of a Zinke cyclic tetramer with all of the aryl moieties oriented in the same direction, shown on the left-hand side of Figure 1.3, Gutsche coined the name "calixarene" in 1975 (although it did not appear in print until 1978[47]). The name is derived from the Greek *calix* meaning "vase" or "chalice"; and *arene* which indicates the presence of aryl residues in the macrocyclic array. The name, initially considered unacceptable by IUPAC and *Chemical Abstracts*, eventually gained official status and has now been expanded to include any number of other kinds of structures that bear a general resemblance to the phenol-derived calixarenes.

The first set of experiments carried out in the Washington University program dealt with the scope and limitations of the phenol-formaldehyde cyclization reaction in order to determine which phenols yield a cyclic tetramer, a calixarene. The results of this early investigation seemed to indicate that a

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[42] A. M. Patterson, L. T. Capell and D. F. Walker, *The Ring Index*, 2nd ed., American Chemical Society, Washington, DC, **1960**, Ring Index No. 6485. We are indebted to Dr K. L. Loening of Chemical Abstracts for helpful guidance in nomenclature.

[43] D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.* **1951**, 73, 5691.

[44] IUPAC, *Tentative Rules for Nomenclature of Organic Chemistry*, Section E. Fundamental Stereochemistry; *cf. J. Org. Chem.* **1970**, 35, 284.

[45] N. R. I. Megson, *Oesterr. Chem. Ztg.* **1953**, 54, 317.

[46] R. Ott and A. Zinke, *Oesterr. Chem. Ztg.* **1954**, 55, 156.

[47] C. D. Gutsche and R. Muthukrishnan, *J. Org. Chem.* **1978**, 43, 4905.

Figure 1.3 Space-filling molecular model of a cyclic tetramer (left) and a calix crater (right).

variety of *p*-substituted phenols (including *p*-methyl-, *p*-*tert*-butyl-, *p*-phenyl-, *p*-methoxy- and *p*-carbomethoxy-) do, indeed, yield the desired products. If a high-melting, organic-solvent-insoluble precipitate was produced it was assumed to be the cyclic tetramer, since these structures were considered at the time to have been well-established by precedent. These results were confidently reported in 1975 by Gutsche, Kung and Hsu, first in Honolulu at an NSF-sponsored East-West Cultural Exchange Symposium and then later at the Midwest Regional Meeting of the American Chemical Society in Carbondale, Illinois.[48]

At this juncture the pathway to producing a wide variety of appropriately substituted molecular baskets was considered to be assured. Of particular interest was the product from *p*-phenylphenol, because space-filling molecular models showed that it has a very deep cavity that should be capable of enfolding other molecules of appreciable size. Then, two years after these initial reports had appeared, Patrick and Egan published a paper[49] that essentially duplicated these experiments. The authors of that study, using a slightly modified Petrolite Procedure employed potassium *tert*-butoxide as the base and tetralin as the solvent, reported the obtention of cyclic tetramers in precisely the same five cases that the Gutsche group had studied. Since the senior author Timothy Patrick was familiar with the research at Washington University, the appearance of this paper was greeted with some dismay by the Washington University researchers. The end result, however, proved beneficial, for it initiated a closer and more critical look at the Petrolite Procedure, the Zinke Procedure and the procedure employed by Patrick and Egan. Ultimately it provided a more complete and accurate understanding of the cyclooligomerization process.

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[48] C. D. Gutsche, T. C. Kung and M.-L. Hsu, Abstracts of 11th Midwest Regional Meeting of the American Chemical Society, Carbondale, IL, **1975**, No. 512.

[49] T. B. Patrick and P. A. Egan, *J. Org. Chem.* **1977**, 42, 382; *idem*, *ibid.* **1977**, 42, 4280.

1.7 Unraveling the Literature

A comparison of the Petrolite Procedure and the Patrick and Egan modification using the same *p*-substituted phenols showed considerable differences in the melting points of the products. Further examination of the IR spectra of the several products revealed small but persistent differences (*e.g.* well-resolved IR bands in some of the products at 800 and 780 cm^{-1} but in other products only a shoulder at 800 cm^{-1} along with a well-resolved band at 780 cm^{-1}). Then, silylation followed by thin layer chromatography indicated the presence of *more than one compound in every instance*, as had been noted earlier by Cornforth and coworkers[36,37] with *p-tert*-butyl- and *p-tert*-octylphenol. That the trimethylsilyl derivatives were not simply some kind of conformational isomers (*vide infra*) was demonstrated by hydrolytic removal of the silyl groups which yielded two, or more, *different* parent compounds. With the realization that mixtures comprising compounds *of different gross structures* were being produced, a careful and detailed study with *p-tert*-butylphenol was next undertaken.

Before further discussion of this investigation, however, let us look at still another group of experiments that, in a curious way, impeded the correct interpretation of calixarene chemistry for several years. In 1972 Hermann Kämmerer[50] at the University of Mainz started a reinvestigation of the Hayes and Hunter method for the stepwise synthesis of cyclic oligomers, improving and extending this synthesis by preparing a variety of calixarenes carrying methyl and/or *tert*-butyl groups in the *p*-positions. Among the analytical techniques applied to the characterization of these materials was that of temperature-dependant ^1H NMR spectroscopy, which revealed that the cyclic tetramers are considerably more flexible than had been thought by Cornforth and others. Space-filling molecular models, which earlier investigators had invoked to support the idea of severely restricted rotation, proved upon re-inspection in the light of the NMR data to be "softer" than had been supposed. Kämmerer found, for example, that the ^1H NMR spectrum of a cyclic tetramer at 20 °C in $CDCl_3$ shows a pair of doublets arising from the non-equivalent hydrogens on the CH_2 bridges between the aryl rings, while a spectrum at 60 °C shows only a sharp singlet.[48] This change in character of the resonance from the CH_2 hydrogens (discussed in Chapter 4) was initially interpreted by Kämmerer in terms of the Cornforth isomers, form-**a** in Figure 1.2 converting to form-**b** upon heating. Three years later, however, he re-interpreted the data in the currently accepted terms of mirror image conformational interconversion of form-**a** structures. Meanwhile, in the early 1970s Munch independently made similar observations for the temperature-dependent ^1H NMR spectra of the Petrolite product.[51] Unfortunately, the paper detailing his results was not accepted for publication when originally submitted, and it only appeared in print after Kämmerer's 1975 paper. The studies of both Kämmerer and Munch

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[50] H. Kämmerer, G. Happel and F. Caesar, *Makromol. Chem.* **1972**, 162, 179.

[51] J. H. Munch, *Makromol. Chem.* **1977**, 178, 69.

indicated that the cyclic tetramers are flexible structures that undergo conformational inversion in $CDCl_3$ at the rate of *ca.* 150 sec^{-1} at room temperature, thereby calling into question the validity of Cornforth's postulate that his LBC-HBC and LOC-HOC pairs of compounds are *conformational* isomers. Also, the apparent identity of the rates of inversion of the Petrolite product and the Kämmerer product, the latter known unequivocally to be the cyclic tetramer, seemed to provide additional proof for the cyclic tetrameric structure of the Petrolite product. As the next experiments show, however, this agreement is coincidental – one of Nature's devious accidents placed in the pathway of the unwary investigator.

Returning now to the research at Washington University, the results of the study of the product from the Petrolite Procedure using *p-tert*-butylphenol and formaldehyde are discussed. The crude product[47] was a colorless substance that melts at *ca.* 360–375 °C. Two recrystallizations from chloroform raised the melting point to above 400 °C and produced colorless fine needles that displayed very simple ^{1}H NMR and ^{13}C NMR spectra. The ^{13}C NMR spectra, in particular, provided a telling comparison between the linear and cyclic oligomers, as illustrated in Figure 1.4. An osmometric molecular weight determination gave a value of 1330, in agreement with a cyclic octamer. However, the strong mass spectral signal at m/e 648 and the close similarity of the temperature-dependent ^{1}H NMR spectrum with that of an authentic cyclic tetramer gave substance to the thought that high molecular weight value could be the result of association of a pair of cyclic tetramers. But, small signals at m/e values higher than 648 consistently appeared in the mass spectra, suggesting that the m/e 648 signal might *not* arise from the *mono*-cation of the parent molecule. This suspicion was confirmed when a trimethylsilyl derivative showed a strong mass spectral signal at m/e 1872. With this piece of evidence it finally

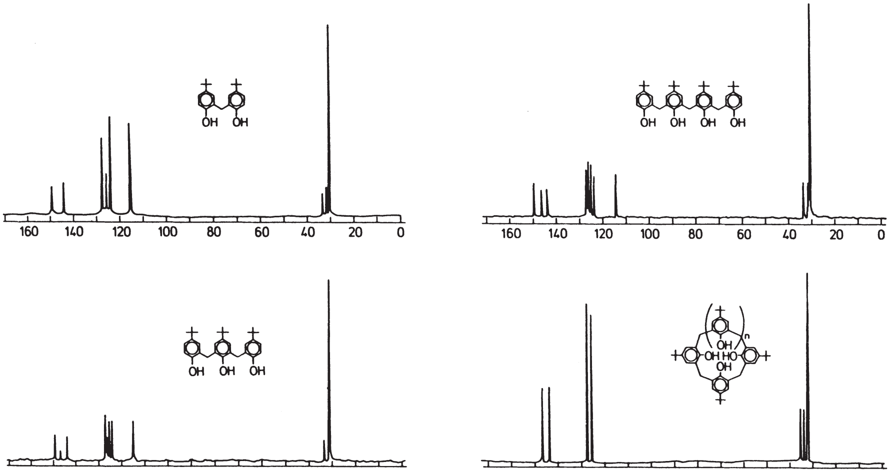
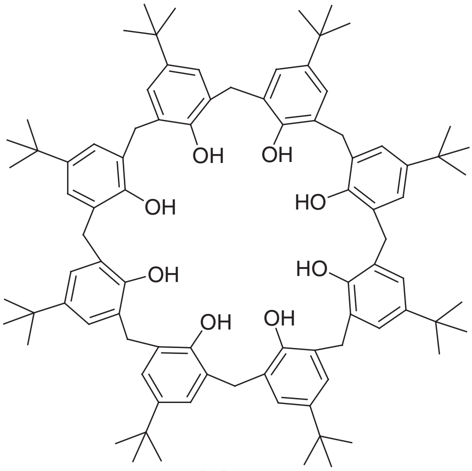


Figure 1.4 ^{13}C NMR spectra of linear oligomers and cyclic tetramer from *p-tert*-butylphenol.

became apparent that the Petrolite compound was not the cyclic tetramer but was the cyclic octamer **1.4**. The validity of this conclusion was later convincingly corroborated by X-ray crystallography.[52] The recognition of this structure as the cyclic octamer resolved some of the apparent discrepancies in the literature that had so long plagued calixarene chemistry.



1.4

As discussed above, Zinke's first paper[17] reported the isolation of a product from *p*-*tert*-butylphenol and formaldehyde that yielded an acetate showing a molecular weight of 1725, close to that expected for the acetate of *p*-*tert*-butyl cyclic octamer. It seems quite likely that this, indeed, is what he had isolated from that particular reaction mixture, although there is no doubt that some of the products reported in Zinke's later papers are certainly cyclic tetramers. Also, it should be recalled that the X-ray crystallographic data on the high-melting compound isolated by Cornforth[36] from *p*-*tert*-butyl- or *p*-octylphenol admitted the possibility of a cyclic octameric structure, and it is now known that the octamer was, in fact, the product he had isolated. What the Petrolite chemists had patented[39–41] and marketed as an oxyalkylated cyclic *tetramer* was actually mostly oxyalkylated cyclic *octamer*. It is now realized that *p*-substituted phenols generally do *not* form cyclic tetramers as the sole product but give mixtures that in most cases are exceedingly difficult to separate into pure components and that, indeed, may contain *none* of the cyclic tetramer. Thus, the thought at the outset of the Washington University project that this would be a neat, clean and general way for constructing a family of molecular baskets gave way to a more pessimistic view of the reaction.

Out of adversity often comes progress, however, and the exploration of the *p*-*tert*-butylphenol-formaldehyde reaction proved the truth of this platitude. Further investigation of the one-step process by the Washington University group, involving changes in solvents, bases, reactant ratios and other reaction

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[52] C. D. Gutsche, A. E. Gutsche and A. I. Karaulov, *J. Inclusion Phenom.* **1985**, 3, 447.

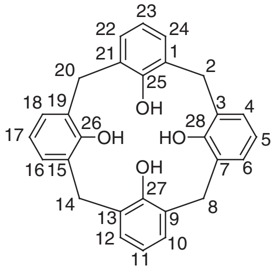
variables resulted in recipes that now permit the cyclic tetramer, cyclic hexamer and cyclic octamer from *p*-*tert*-butylphenol to be easily prepared in good and reproducible yields. These three compounds are now among the most accessible synthetic macrocyclic baskets, and they provide the starting point for a significant fraction of the phenol-derived cyclooligomer chemistry that is being carried out today. Phenol-derived calixarenes, born in Zinke's laboratory in 1941 out of the resinous tars that had been introduced to the world by Baeyer and Baekeland but largely unattended for the next thirty years, came of age as glistening crystalline solids in the 1970s mainly through the efforts of Kämmerer and his group in Mainz, the group in Parma led by Ungaro, Andreetti and Pochini whose contributions have yet to be discussed and Gutsche and his associates in St Louis. Concomitantly, the resorcinol-derived calixarene octols were also coming of age through the pioneering efforts of Erdtman and Sverker Högberg in Stockholm. The following chapters provide a detailed picture of the subsequent developments in calixarene chemistry.

1.8 Nomenclature and Representation of the Calixarenes

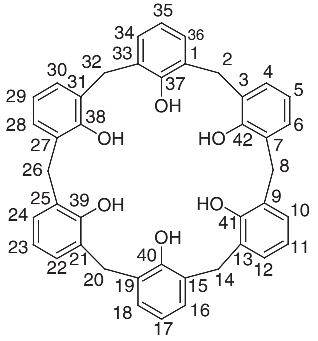
The name "calixarene" was originally conceived to connote the shape of the phenol-derived cyclic tetramer in the conformation in which all four aryl groups are oriented in the same direction. To accommodate the name to the subsequently discovered cyclooligomers containing more than four aryl groups a bracketed number is inserted between "calix" and "arene". The product from a Petrolite Procedure, for example, is a calix[8]arene, that from the Zinke Procedure a calix[4]arene, *etc*. Then, to indicate from which phenol the calixarene is derived the *p*-substituent is designated by name. The cyclic tetramer from *p*-*tert*-butylphenol, for example, is named *p*-*tert*-butylcalix[4]arene. Resorcinol-derived cyclooligomers have been called, *inter alia*, Högberg compounds, octols, resorcarenes, calix[*n*]resorcarenes, calix[*n*]resorcinarenes and calix[*n*]resorcinolarenes. Since the compounds are clearly members of the calixarene family it is logical that this fact be reflected in the name. However, like a rebellious child anxious to declare its independence by shedding the family ties, they have acquired the name "resorcarenes". By analogy, the calixarenes should have been called "phenarenes", which would rightly be considered to be a much less felicitous (and certainly less accurate) choice. Although it is probably beyond repair, this author continues to recommend that "calix[*n*]resorcarene be the preferred designation for the basic structure of the resorcinol-derived calixarenes, with the substituents named and numbered in appropriate fashion. The substituent at the methylene carbons of a calix[*n*]resorcarene (introduced by the particular aldehyde used) is indicated by a prefix "C-substituent". The product from resorcinol and *p*-bromobenzaldehyde, for example, is named "C-*p*-bromophenylcalix[4]resorcarene.

The nomenclature scheme discussed above implicitly includes the OH groups as part of the structure being named and is a useful nomenclature for general discussions of the calixarenes. However, a more systematic nomenclature has evolved in which the term "calixarene" is taken to apply only to the *basic structure devoid of substituents*. Accordingly, the cyclic tetramer from *p*-*tert*-butylphenol and formaldehyde acquires the name 5,11,17,23-tetra-*tert*-butyl-calix[4]arene-25,26,29,28-tetrol; the corresponding di-homooxa compound is 7,13,19,25-tetra-*tert*-butyl-2,3-dihomo-3-oxacalix[4]arene-27,28,29,30-tetrol; and the product from resorcinol and acetaldehyde is 2,8,14,20-tetra-methylcalix[4]resorcarene-4,6,10,12,16,18,22,24-octol. The phenol-derived and resorcinol-derived calixarenes can be differentiated by referring to the former as *endo*-OH calixarenes (*i.e.* the OH groups oriented toward the annulus) and the latter as *exo*-OH calixarenes (*i.e.* the OH groups oriented away from the annulus) Figure 1.5.

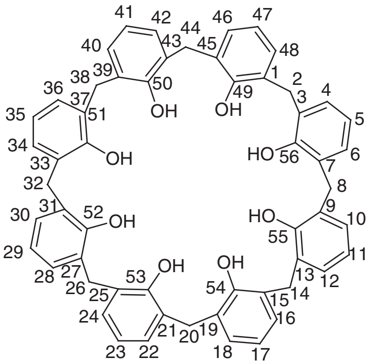
Since vases ordinarily stand upright on their bases and since calixarenes derive their name from a Greek vase, calixarene structures should preferably be drawn with their OH groups pointing downward (*endo*) and their *p*-substituents pointing upward (*exo*). Accordingly, the *endo* face was designated as the "lower



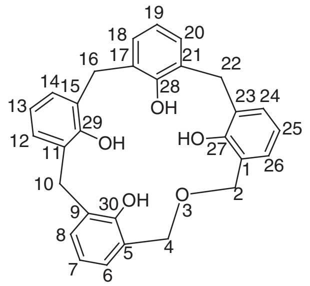
calix[4]arene-25,26,2,28-tetrol



calix[6]arene-37,38,39,40,41,42-hexol



calix[8]arene-49,50,51,52,53,54,55,56-octol



2,3-dihomo-3-oxocalix[4]arene-27,28,29,30-tetrol

Figure 1.5 Structures and numbering of calix[4]arenes, calix[6]arenes, calix[8]arenes and dihomooxacalix[4]arenes.

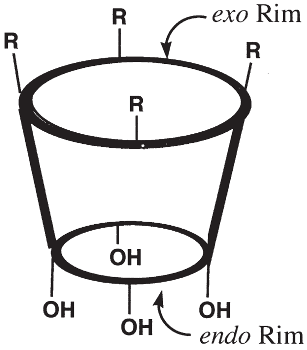


Figure 1.6 Representation of the calixarenes and designation of the rims.

rim" and the *exo* face as the "upper rim", as portrayed in Figure 1.6. However, "upside-down" representations often appear in the literature, so Böhmer has suggested the designations "narrow rim" and "wide rim" to avoid the orientation dependency. All such designations become vague, however, when applied to larger calixarenes in which there may be no well-defined "upper, wide" or "lower, narrow" rims. Still another designation, therefore, is based on the cyclic structure *per se*, without recourse to either its orientation or its shape. It designates the lower, narrow rim as the "*endo* rim" and the upper, wide rim as the "*exo* rim", and it is this nomenclature that will be used throughout the remainder of this book.

CHAPTER 2

Making the Baskets: Synthesis of Calixarenes

"We figure to ourselves the thing we like, and then we build it up as chance will have it, on the rock or sand"

Sir Henry Taylor, Philip van Artevelde, 1834

Creation myths in various cultures put basket-making among the first of the arts given to humankind, a result of *Homo sapiens*' innate desire to surround and transport objects. The present book deals with a modern facet of this ancient art and focuses on calixarenes as providing particular examples of how chemists can build molecular baskets. As will be seen in later chapters, calixarenes are baskets that, indeed, can serve as vehicles of transport for chemical baggage including metal ions as well as neutral molecules. Before discussing these interesting properties, however, it is necessary first to learn how to make the baskets, and it is with this that the present chapter is concerned.

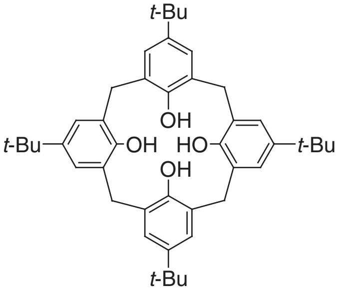
The previous chapter silhouetted the tortuous byways of phenol-formaldehyde chemistry that led in the 1970s to an unraveling of various apparent contradictions in the literature. One of the most useful results of these early studies was the emergence of recipes by which the resinous tar can be induced to yield glistening crystals of variously sized macrocyclic compounds.

2.1 One-step, Base-induced Synthesis of Phenol-derived Calixarenes

2.1.1 Synthesis of *p-tert*-Butylcalixarenes (*Apndx A-2, p. 1*)

For many years the preparation of *p-tert*-butylcalix[4]arene remained a capricious event. Workable yields of the desired product were obtained in some instances, but poor yields or even no yields were obtained in many other instances in reactions presumably carried out under identical conditions. The reasons for this variability remain somewhat puzzling, but a careful investigation of the influence of varying amounts of base at various temperatures[1] led to a set of instructions that are sufficiently reliable to insure easy reproducibility. The procedure originally formulated by Zinke[2] and then modified by Cornforth[3] and later by Gutsche is described as follows:

> *Modified Zinke–Cornforth Procedure* (Synthesis of *p*-*tert*-butylcalix[4]arene).[4] A mixture of *p*-*tert*-butylphenol, 37% formaldehyde and an amount of NaOH corresponding to 0.045 equivalents with respect to the phenol is heated for 2 hrs at 110–120 °C to produce a thick viscous mass called the "precursor". The "precursor" is then heated in refluxing diphenyl ether for 2 hrs, the reaction mixture is cooled, and the crude product is separated by filtration and recrystallized from toluene to give *ca.* 50% yield of glistening white rhombs with mp. 342–344 °C.



p-tert-Butylcalix[4]arene

In the procedure described by Zinke a "neutralization" of the "precursor" removes some, but not all, of the base which was initially added. The capricious results from one run to another using the original Zinke procedure, therefore, can probably be ascribed to the differing amount of base removed at this point. A neutron activation analysis[5] of a "neutralized precursor" revealed that even after extensive trituration some sodium ion is retained, presumably as the phenoxide. Thus, exhaustive washing removes too much base and changes the course of the reaction in a manner described below. This ambiguity in the amount of base that is present during the "thermal phase", therefore, can be eliminated by adding a known, calculated quantity at the beginning of the reaction and retaining it throughout the entire process, as described above.

That there is an optimum amount of NaOH for producing the calix[4]arene is indicated by the data in Figure 2.1, which show that the yield of cyclic *tetramer* reaches a maximum at 0.03–0.04 equivalents of base and falls off on either side of this range. With less base the yield falls to zero, and with more base it again falls as the product increasingly becomes the cyclic hexamer. With 0.30 or more

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[1] C. D. Gutsche, M. Iqbal and D. Stewart, *J. Org. Chem.* **1986**, 51, 742.

[2] A. Zinke and E. Ziegler, *Ber.* **1944**, 77, 264, 1729.

[3] J. W. Cornforth, P. D'Arcy Hart, G. A. Nicholls, R. J. W. Rees and J. A. Stock. *Br. J. Pharmacol.* **1955**, 10, 73; J. W. Cornforth, E. D. Morgan, K. T. Potts and R. J. W. Rees, *Tetrahedron* **1973**, 29, 1659.

[4] C. D. Gutsche and M. Iqbal, *Org. Synth.* **1990**, 68, 234.

[5] C. D. Gutsche and D. Stewart, unpublished work.

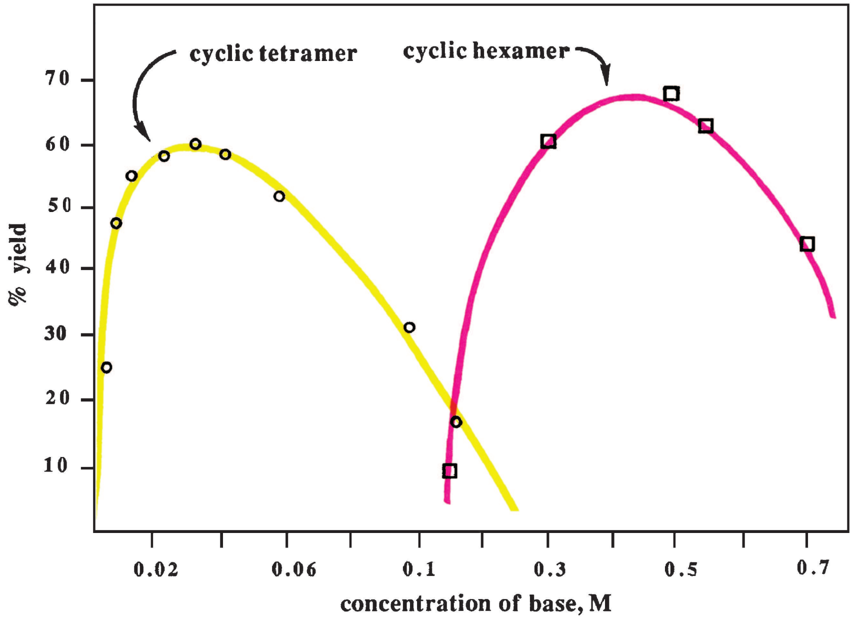

Figure 2.1 Effect of base concentration on the formation of *p-tert*-butylcalix[4]arene.

equivalents of base the cyclic *hexamer* becomes the major product,[6] isolable in excellent yield with the appropriate reaction conditions.

While the amount of base that is used in the cyclooligomerization process affects the outcome in a profound fashion, the cation that accompanies the basic anion also has a sometimes significant though smaller effect,[7] as follows: (a) LiOH is usually, but not always, an inferior base for the cyclooligomerization, (b) NaOH tends to give somewhat higher yields of cyclic octamer in the Petrolite Procedure and (c) KOH, RbOH and CsOH tend to give somewhat higher yields of cyclic hexamer in the Modified Petrolite Procedure as described below.

> *Modified Petrolite Procedure* (Synthesis of *p-tert*-Butylcalix[6]arene).[8,9] A mixture of *p-tert*-butylphenol, 38% of formaldehyde and an amount of KOH corresponding to 0.34 equivalents with respect to the phenol is heated for 2 hrs to yield a light yellow, taffy-like "precursor", which is then added to xylene and refluxed for 3 hrs. Filtration of the cooled reaction mixture yields a crude product that is neutralized and then recrystallized from chloroform-methanol to give an 80–85% yield of a white powder with mp 380–381 °C.

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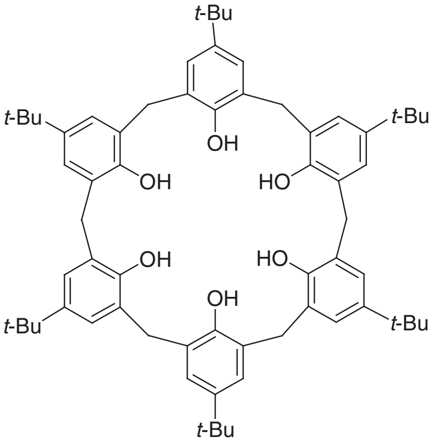
[6] This observation came not from a rational experiment but by chance in which ten times the intended amount of base was added as the result of a weighing error, leading to a product that was ultimately identified as *p-tert*-butylcalix[6]arene (C. D. Gutsche, D. Dhawan, K. H. No and R. Muthukrishnan, *J. Am. Chem. Soc.* **1981**, 103, 3782; *idem, ibid.* **1984**, 106, 1891).

[7] B. Dhawan, S.-I. Chen and C. D. Gutsche, *Makromol. Chem.* **1987**, 188, 921.

[8] Microwave heating has been advocated for large-scale production (V. Hedeboe, O. Jørgensen and H. D. Rasmussen, *Microwave and High Frequency Heating*, **1997**, 115).

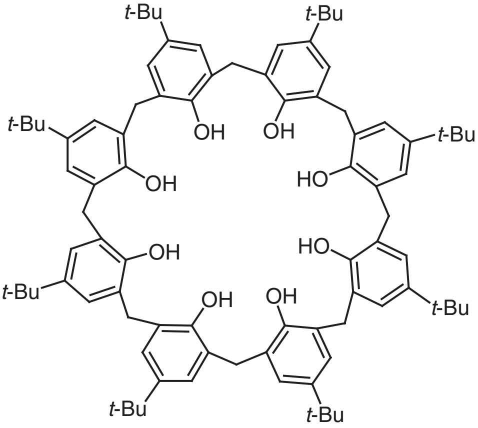
[9] C. D. Gutsche, B. Dhawan and M. Leonis, *Org. Synth.* **1990**, 68, 238.



p-tert-Butylcalix[6]arene

The best procedure for obtaining the cyclic octamer closely resembles that outlined in the Petrolite Patents and is described as follows:

> *Standard Petrolite Procedure* (Synthesis of *p-tert*-butylcalix[8]arene).[10] A slurry of xylene containing *p-tert*-butylphenol, paraformaldehyde and an amount of NaOH corresponding to 0.03 equivalents with respect to the phenol is refluxed for 4 hrs. The cooled reaction mixture is filtered, and the crude product is recrystallized from chloroform to give 60–65% of glistening crystals, which quickly change to a white powder with mp 411–412 °C (after several recrystallizations samples with mp as high as 418–420 °C can be obtained).



p-tert-Butylcalix[8]arene

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[10] J. H. Munch and C. D. Gutsche, *Org. Synth.* **1990**, 68, 243.

All three of these procedures for what are called the "Major Calixarenes" can be easily carried out in the laboratory, from very small scale to very large scale, making the *p*-*tert*-butylcalix[4], [6] and [8]arenes extremely readily available. Considerably less readily available, however, are the cyclic pentamer and cyclic heptamer, called the "Minor Calixarenes". *p*-*tert*-Butylcalix[5]arene[11] can be prepared in yields as high as 20%, although with a more demanding recipe than those for the major calixarenes.[12] Similarly, *p*-*tert*-butylcalix[7]arene[13] requires a more cumbersome synthesis and is obtainable in 11–17% yield.[14] For a number of years the calixarene family was thought to comprise only the three major and two minor calixarenes. However, experiments carried out in Gutsche's laboratories in the late 1980s resulted in the isolation and characterization of *p*-*tert*-butylcalix[9] and [10]arene[15] (and mass spectral evidence for the next two larger oligomers). Subsequent work from the same laboratory led to the isolation and characterization of "large calixarenes" ranging from the cyclic nonamer to the cyclic eicosomer.[16,17] It was also discovered that acid-catalysis of the *p*-*tert*-butylphenol/formaldehyde condensation likewise yields calixarenes and, in fact, provides a better route to the large calixarenes than the base-induced reaction. Another research group also contributing to the study of the large calixarenes was that of Lamartine and coworkers,[18] who characterized the *p*-*tert*-butylcalix[*n*]arenes from $n = 9$–12. *p*-Benzylcalix[10]arene, the only large calixarene with a *p*-substituent other than *tert*-butyl, has been reported.[19] The 17 known *p*-*tert*-butylcalixarene "benzylogues" now represent one of the largest families of well-characterized cyclooligomers (Figure 2.2).

2.1.2 Synthesis of Other *p*-Substituted Calixarenes

While *p*-*tert*-butylphenol is the quintessential reactant in the base-induced calixarene-forming reaction, it is not the only phenol that behaves in this fashion. *p*-*tert*-Pentylphenol[20] and *p*-(1,1,3,3-tetramethybutyl)phenol

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[11] (a) D. R. Stewart and C. D. Gutsche, *Org. Prep. Proc. Int.* **1993**, 25, 137; (b) Y. Nakamoto and S. I. Ishida, *Makromol. Chem. Rapid Commun.* **1982**, 25, 137.

[12] An alternative approach (I. Dumazet, N. Ehlinger, F. Vocanson, S. Lecocq, R. Lamartine and M. J. Perrin, *Inclusion Phenom. Molec. Recognit. Chem.* **1997**, 29, 175) employs the reaction of *p*-*tert*-butyldihomooxacalix[4]arene with *p*-*tert*-butylphenol in the presence of KOH which is reported to afford a 32% yield (HPLC) of the cyclic pentamer along with the cyclic tetramer, hexamer and octamer.

[13] A. Ninegawa and H. Matsuda, *Makromol. Chem. Rapid Commun.* **1982**, 3, 65; Y. Nakamoto and S. I. Ishida, *ibid.* **1982**, 3, 7005; F. Vocanson, R. Lamartine, P. Lanteri, R. Longeray and J. V. Gauvrit, *New J. Chem.* **1995**, 19, 825.

[14] F. Vocanson, R. Lamartine, P. Lanteri, R. Longeray and I. Gauvrit, *New J. Chem.* **1995**, 19, 825.

[15] C. D. Gutsche, J. S. Rogers, D. R. Stewart and K.-A. See, *Pure Appl. Chem.* **1990**, 62, 485.

[16] D. R. Stewart and C. D. Gutsche, Third International Calixarene Conference, Fort Worth, TX, **1995**, Abstract P-42; C. D. Gutsche, S. K. Sharma, D. R. Stewart, J. Wang and D. Xie, Fourth International Conference on Calixarenes, Parma, Italy, **1997**; Abstract IL.1.

[17] D. R. Stewart and C. D. Gutsche, *J. Am. Chem. Soc.* **1999**, 121, 4136.

[18] I. Dumazet, J. B. Regnouf-de-Vains and R. Lamartine, *Synth. Commun.* **1997**, 27, 2547.

[19] J. L. Atwood, M. J. Hardie, C L. Raston and C. A. Sandoval, *Org. Lett.* **1999**, 1, 1523.

[20] S. R. Izatt, R. T. Hawkins, J. J. Christensen and R. M. Izatt, *J. Am. Chem. Soc.* **1985**, 107, 63.

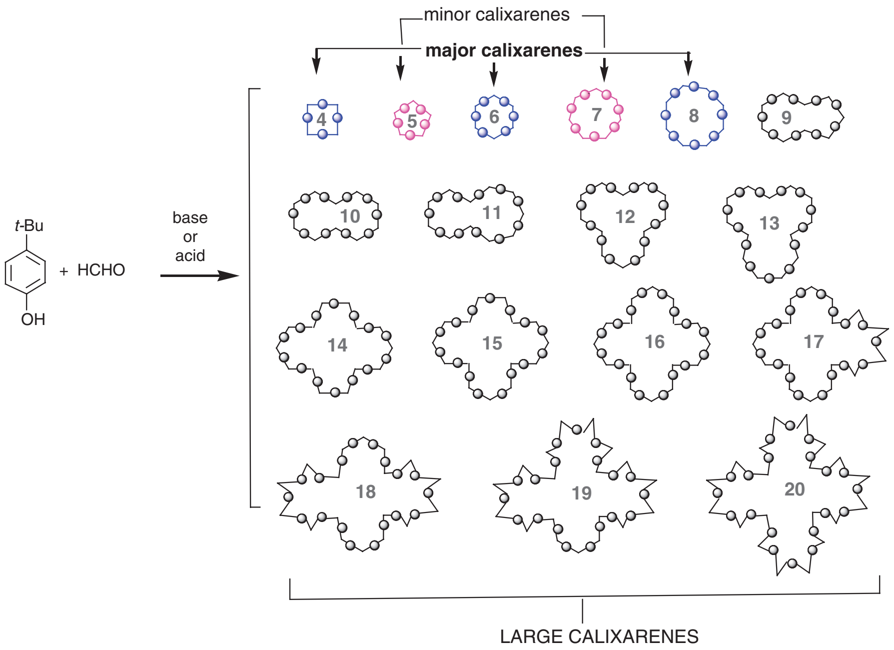

Figure 2.2 The extended calixarene family.

(*p*-*tert*-octylphenol)[3,21,22] both react rather comparably to *p*-*tert*-butylphenol, although the products are somewhat less tractable and the yields somewhat lower. With most other *p*-substituted phenols, however, the results are considerably less propitious. For example, 4-nitrophenol, 4-hydroxybenzoic acid, 4-hydroxyacetophenone, 1,4-dihydroxybenzene (hydroquinone), 4-phenoxyphenol, 4-hydroxybenzyl alcohol and 4-cyanophenol all yield amorphous unextractable materials.[23] Only with non-deactivating *p*-substituents, in particular *p*-alkyl groups, is there generally any promise of calixarene formation and this more often than not is in limited degree. Long chain *p*-alkyl groups often give poor results, but can yield cyclic hexamer and octamer.[24] *p*-Cresol is reported to give the cyclic hexamer[25] and heptamer[26] in 74% and 22% yields, respectively. *p*-Isopropylphenol produces the cyclic octamer in 3% yield,[27] and *p*-isopropenylphenol gives a mixture of cyclic hexamer and octamer (using ethylene glycol as solvent and Na B_4O_7 as base); *p*-phenylphenol gives a mixture containing cyclic tetramer, pentamer, hexamer and octamer in varying

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[21] V. Bocchi, D. Foina, A. Pochini and R. Ungaro, *Tetrahedron* **1982**, 38, 373.

[22] J. Vicens, T Pilot, D. Gamet, R. Lamartine and R. Perrin, *C. R. Acad. Sci. Paris* **1986**, 302, 15.

[23] M. Yilmaz, U. S. Vural, *Synth. React. Inorg. Met. Org. Chem.* **1991**, 21, 1231.

[24] Z. Asfari and J. Vicens, *Tetrahedron Lett.* **1988**, 29, 2659.

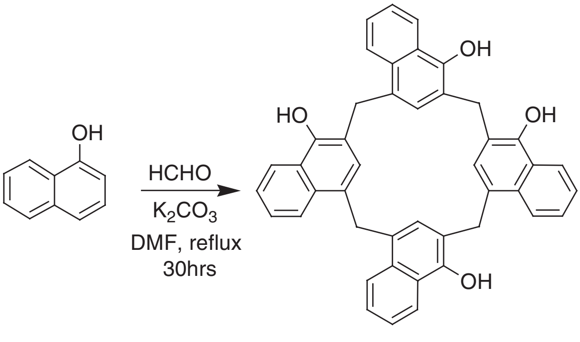
[25] Y. Seki, Y. Morishige, N. Wamme, Y. Ohnishi and S. Kishida, *Appl. Phys. Lett.* **1993**, 62, 3375.

[26] Z. Asfari and J. Vicens, *Makromol. Chem. Rapid. Commun.* **1989**, 10, 181.

[27] J. Vicens, H. T. Pilot and D. Gamet, *C. R. Acad. Sci. Paris* **1986**, 302, 15.

yields (tetramer up to 10%; pentamer up to 15%; hexamer up to 11%; octamer up to 38%) depending on the particular reaction conditions.[28] *p*-Benzylphenol is reported to give cyclic pentamer, hexamer and octamer in 33%, 16% and 12% yield.[29,30] *p*-Adamantylphenol,[31] the chiral *p*-(2-isopropyl-5-methyl-cyclohexyl)phenol[32] and *p*-(1,1-dimethyl-1-p′-methoxyphenyl)-methylphenol[33] all yield cyclic octamers in 72%, 30% and 51% yield, respectively, and the highly branched chiral 8-(*p*-hydroxyphenyl)-menthone reacts sluggishly with HCHO to give the cyclic pentamer, hexamer and octamer in 8–12% yields.[34] The activated phenol *p*-benzyloxyphenol gives 48% of cyclic octamer and smaller amounts of cyclic heptamer and tetramer,[35] but *p*-methoxyphenol and 1,4-dihyhydroxyphenol (hydroquinone) give intractable mixtures.

Other phenolic compounds have also been subjected to the formaldehyde condensation reaction. Among the best studied of these are the naphthols, extensively investigated by Paris Georghiou and coworkers.[36] For example, *o*-naphthol yields a mixture containing 16% of the calix[4]naphthalene **2.1** along with two other isomers in yields of 9.6% and 5%.



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[28] M. Makha and C. L. Raston, *Tetrahedron Lett.* **2001**, 42, 6215.

[29] B. Souley, Z. Asfari and J. Vicens, *Polish J. Chem.* **1992**, 66, 959.

[30] J. A. Atwood, M. J. Hardie, C. L. Raston and C. A. Sandoval, *Org. Lett.* **1999**, 1, 1523 reported obtaining the cyclic pentamer and heptamer in 15–20% yields, and they showed that subjecting a mixture containing *p*-benzylcalix[6] and [8]arene, paraformaldehyde, KOH and molecular sieves to ultra-high-frequency grinding for 4–16 hrs produced the cyclic pentamer and heptamer in 10–15% and 5–10% yields, respectively.

[31] E. Lubitov, E. A. Shokova and V. V. Kovalev, *Synlett* **1993**, 647, 32.

[32] J. Jauch and V. Schurig, *Tetrahedron: Asymmetry* **1997**, 8, 169.

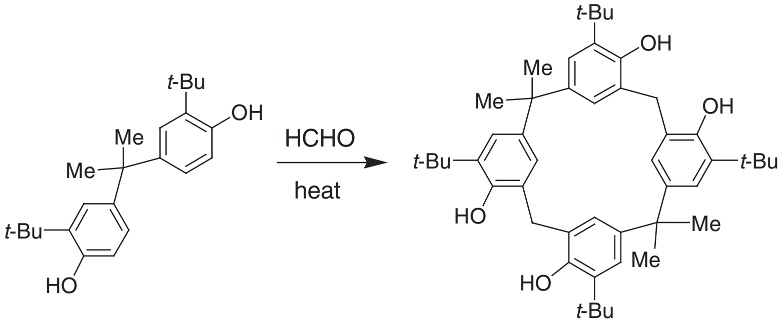
[33] C.-H. Tung and H.-F Ji, *J. Chem. Soc. Perkin Trans. 2* **1997**, 185.

[34] A. Soi, J. Pfeiffer, J. Jauch and V. Schurig, *Tetrahedron: Asymmetry* **1999**, 10, 177.

[35] A. Casnati, R. Ferdani, A. Pochini and R. Ungaro, *J. Org. Chem.* **1997**, 62, 6236.

[36] P. E. Georghiou and Z. Li, *Tetrahedron Lett.* **1993**, 34, 2887; P. E. Georghiou and Z. Li, *Inclusion Phenom. Molec. Recognit. Chem.* **1994**, 19, 55; P. E. Georghiou, M. Ashram, Z. Li and S. G. Chaulk, *J. Org. Chem.* **1995**, 60, 7284; P. E. Georghiou, Z. Li, M. Ashram and D. O. Miller, *ibid.* **1996**, 67, 3865; P. E. Georghiou, Z. Li and M. Ashram, *ibid.* **1998**, 63, 3648; S. Chowdhry and P. E. Georghiou, *ibid.* **2002**, 67, 6808.

In contrast to the phenol-derived compounds, these compounds contain the OH groups in *exo*-annular positions. Also containing *exo*-annular OH groups are the calixarenes obtained from a variety of bis-phenols,[37] an early example of which was published by Chasar,[37a] who simply heated the bis-phenol **2.2** with paraformaldehyde for 16 hours at 175 °C (*i.e.* no acid or base catalyst) to yield **2.3**. Other workers have used a BF_3Et_2O catalyst.[38]



2.2

2.3

2.2 One-step, Acid-catalyzed Synthesis of Calixarenes

2.2.1 Phenol-derived Calixarenes

Although the base-induced reaction of *p*-*tert*-butylphenol with formaldehyde remains the method of choice for synthesizing the major and minor calixarenes, acid-catalysis under appropriate conditions, also yields a product consisting of cyclic rather than linear oligomers,[15] with the large cyclic oligomers present in relatively larger amounts than in the base-induced product.

2.2.2 Resorcinol-derived Calixarenes

A product isolated from the acid-catalyzed reaction of resorcinol and formaldehyde in 1892 was initially assigned a linear dimeric structure,[39] but its non-crystalline and refractory character (decomposes at 250 °C without melting) suggested that it was actually a polymer. Resorcinol and formaldehyde are known to react under both base-induced and acid-catalyzed conditions to form strong adhesives with commercial applications. Aldehydes less reactive than formaldehyde, however, react with resorcinol to give cyclic tetramers, as discussed in Chapter 1. Subsequent to the work of Niederl in the 1940s,

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[37] (a) D. W. Chasar, *J. Org. Chem.* **1985**, 59, 545; (b) G. Sartori, C. Porta, F. Bigi, R. Maggi, F. Peri, E. Marzi, M. Lanfranchi and M. A. Pellinghelli, *Tetrahedron* **1997**, 53, 3287.

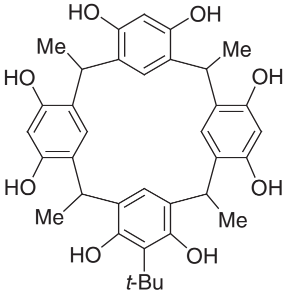
[38] T. N. Sorrell and H. Yaun, *J. Org. Chem.* **1997**, 82, 1899.

[39] N. Caro, *Ber.* **1892**, 25, 939.

considerable attention has been given to these resorcinol-derived calixarenes, and their structures have been conclusively proved. Högberg in particular studied them in detail[40] and devised a procedure that was adapted to large-scale operation by Cram and coworkers for the preparation of calix[4]resorcarenes.[41]

> *Niederl-Högberg Procedure* (Synthesis of C-methylcalix[4]resorcarene). A solution of resorcinol and acetaldehyde in aqueous ethanol is maintained at 80 °C for 16 hrs. The cooled mixture is filtered to give *ca.* 70% of a light yellow product that is pure enough for subsequent use.

For each particular aldehyde, however, the optimization of the conditions must be worked out.[42,43] Lewis acids ($AlCl_3$, $SnCl_4$, BF_3) in ether are also effective catalysts.[44] In keeping with the current emphasis on environmentally benign operations, a solvent-free, high-yield procedure has been reported in which resorcinol and benzaldehyde derivatives are mixed with a catalytic amount of solid acid at ambient temperature.[45]



C-Methylcalix[4]resorcarene

It is quite remarkable that a single compound is formed in such high yield in the resorcinol-aldehyde reaction, given the fact that conformational and configurational features make possible a rather large number of diastereoisomers. A particularly important piece of information from Högberg's studies is that the system is a dynamic equilibrium among the diastereoisomers which results in the product composition being a function of time. As illustrated in

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[40] A. G. D. Högberg, Ph.D. dissertation, Royal Institute of Technology, Stockholm, **1977**; *idem*, *J. Org. Chem.* **1980**, 45, 4498; *idem*, *J. Am. Chem. Soc.* **1980**, 102, 6046.

[41] D. J. Cram, S. Karbach, H. E. Kim, C. B. Knobler, E. F. Maverick, J. L. Ericson and R. C. Helgeson, *J. Am. Chem. Soc.* **1988**, 110, 2229.

[42] E. U. Thoden van Velzen, J. F. J. Engbersen and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1994**, 116, 3597.

[43] A. D. M. Curtis, *Tetrahedron Lett.* **1997**, 38, 4295.

[44] O. J. Pieroni, N. M. Rodriguez, B. M. Vuano and M. C. Cabaleiro, *J. Chem. Res.* **1994**, 188; *idem*, *ibid.* **1994**, 455.

[45] B. A. Roberts, G. W. V. Cave, C. L. Raston and J. L. Scott, *Green Chemistry* **2001**, 3, 280.

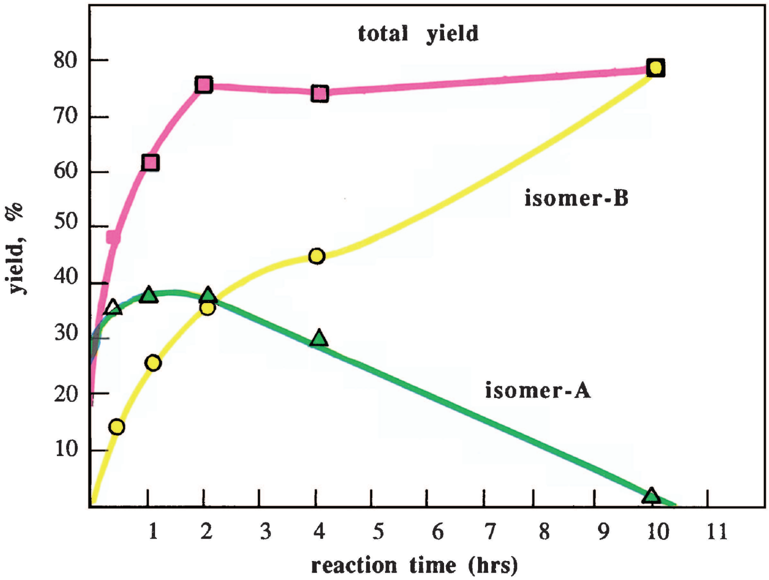

Figure 2.3 Acid-catalyzed reaction of resorcinol and benzaldehyde.[47]

Figure 2.3, isomer-A is the major product after 30 min and isomer-B is virtually the sole product after 10 hrs, a classic example of kinetic control *vs.* thermodynamic control. Other diastereoisomers may be present but generally in much smaller amounts.[46]

A wide variety of aldehydes have been used in the preparation of calixresorcarenes[48] including (a) simple aliphatic aldehydes from ethanal to undecanal;[49,50] (b) functionalized aliphatic aldehydes such as 5-chloropentanal,[48] 4-hydroxybutanal[51] and 2-sulfonatoethanal;[52] (c) aralkyl aldehydes such as phenylethanal;[48] (d) unsaturated aliphatic aldehydes such as 9-decenal;[92] (e) benzaldehydes, including those with substituents such as alkyl or arylalkyl,[53] OH,[54] NO,[55] halogen,[48] CN,[48] NH$_2$,[56]

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[46] L. Abis, E. D. Dalcanale, A. Du Vosel and S. Spera, *J. Org. Chem.* **1988**, 53, 5475.

[47] H. Erdtman, S. Högberg, S. Abrahamsson and B. Nilsson, *Tetrahedron Lett.* **1968**, 1679.

[48] L. M. Tunstad, J. A. Tucker, E. Dalcanale, J. Weiser, J. A. Bryant, J. C. Sherman, R. C. Helgeson, C. B. Knobler and D. J. Cram, *J. Org. Chem.* **1989**, 54, 1305.

[49] D. J. Cram, S. Karbach, H.-E. Kim, C. B. Knobler, E. F. Maverick, J. L. Ericson and R. C. Helgeson, *J. Am. Chem. Soc.* **1988**, 110, 2229.

[50] Y. Aoyama, Y. Tanaka, H. Toi and H. Ogoshi, *J. Am. Chem. Soc.* **1988**, 110, 634; Y. Aoyama, Y. Tanaka and S. Sugahara, *ibid.* **1989**, 111, 5397.

[51] B. C. Gibb, R. G. Chapman and J. C. Sherman, *J. Org. Chem.* **1996**, 61, 1505.

[52] K. Kobayashi, Y. Asakawa, Y. Kato and Y. Aoyama, *J. Am. Chem. Soc.* **1992**, 114, 10307.

[53] U. Schneider and H.-J. Schneider, *Chem. Ber.* **1994**, 127, 2455.

[54] A. Shivanyuk, E. F. Paulus, V. Böhmer and W. Vogt, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 130; Y. Yamakawa, J. Ueda, R. Nagahata, K. Takeuchi and M. Asai, *J. Chem. Soc. Perkin Trans. 1* **1998**, 4135.

[55] F. Wendt and H.-J. Schneider, *J. Org. Chem.* **1991**, 56, 5527.

[56] T. Kijima, Y. Kato, K. Ohe, M. Machida, Y. Matsushita and T. Matsui, *Bull. Chem. Soc. Jpn.* **1994**, 67, 2125.

MeCO,[48] $B(OR)_2$,[57] crown ether[58] and glycosyl;[59] (f) heterocyclic aldehydes;[60] and (g) ferrocenylaldehyde.[61] Highly hindered aldehydes such as 2,4,6-trimethylbenzaldehyde or aldehydes containing functionality proximate to the aldehyde function such as $ClCH_2CHO$ fail to react.[48]

2-Substituted resorcinols can also be used, including 2-methylresorcinol, 2-bromoresorcinol, 2-hydroxyresorcinol (pyrogallol), although 2-nitroresorcinol fails to react. In the case of pyrogallol, even paraformaldehyde can be used, producing the corresponding calix[4]resorcarene, isolated as the ester, in 53% yield.[62] 2-Propylresorcinol reacts with $H_2C(OEt)_2$ to give a mixture of cyclic tetramer, pentamer and hexamer at short reaction times but only the cyclic tetramer after longer reaction times.[63] At least one base-induced condensation has been reported: the reaction of 2-butylresorcinol, paraformaldehyde and $KOBu^t$ to give a 56% yield of cyclic tetramer.[64]

2.3 Multi-step Synthesis of Calixarenes

2.3.1 Non-convergent Stepwise Syntheses

The 10-step procedure employed by Hayes and Hunter[65] for the synthesis of *p*-methylcalix[4]arene was discussed in Chapter 1 (see Figure 1.1). It represents a completely linear, non-convergent approach which, though long and tedious, in principle is amenable to considerable variation through the use of different phenols in each of the individual arylation steps. It is an approach that was subsequently exploited and improved in impressive fashion by Kämmerer and his group at the University of Mainz in Germany. Hermann Kämmerer was born in 1911 in Milan and received his Ph.D. degree from the University of Fribourg under the direction of Hermann Staudinger (Nobel Laureate in 1953).

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[57] P. T. Lewis, C. J. Davis, M. C. Saraiva, W. Treleaven, T. D. McCarley and R. M. Strongin, *J. Org. Chem.* **1997**, 62, 6110.

[58] P. D. Beer, E. L. Tite and A. Ibbotson, *J. Chem. Soc. Chem. Commun.* **1989**, 1874.

[59] A. D. M. Curtis, *Tetrahedron Lett.* **1997**, 38, 4295.

[60] R. J. M. Egberink, P. L. H. M. Cobben, W. Verboom, S. Harkema and D. N. Reinhoudt, *J. Inclusion Phenomen. and Molec. Recognit.* **1992**, 12, 151.

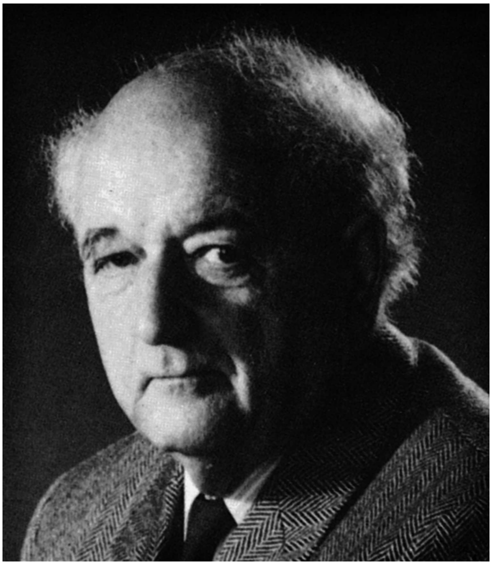
[61] P. D. Beer, E. L. Tite, M. G. B. Drew and A. Ibbotson, *J. Chem. Soc. Dalton Trans.* **1990**, 2543.

[62] H. Konishi, Y. Iwasaki, O. Morikawa, T. Okano and J. Kiji, *Chem. Express* **1990**, 5, 869; G. Cormetti, E. Dalcanale, A. Du Vosel and A. M. Levelut, *Liquid Crystals* **1992**, 11, 93; H. Konishi and O. Morikawa, *J. Chem. Soc. Chem. Commun.* **1993**, 34; O. Morikawa, R. Ueno, K. Nakajima, K. Kobayashi and H. Konishi, *Synthesis* **2002**, 6, 761.

[63] H. Konishi, K. Ohata, O. Morikawa and K. Kobayashi, *J. Chem. Soc. Chem. Commun.* **1995**, 309; H. Konishi, T. Nakamura, O. Kazunobu, K. Kobayashi and O. Morikawa, *Tetrahedron Lett.* **1996**, 37, 7383.

[64] H. Konishi and Y. Iwasaki, *Synlett* **1995**, 612.

[65] B. T. Hayes and R. F. Hunter, *Chem. Ind.* **1956**, 193; B. T. Hayes and R. F. Hunter, *J. Appl. Chem.* **1958**, 8, 743.



Hermann Kämmerer

His doctoral thesis had already kindled in him an interest in polymer chemistry, so when in 1947 he joined the staff at the University of Mainz he started work on phenol-formaldehyde resins with the particular aim of discerning their structure. To this end he undertook the synthesis of a series of well-defined oligomers. At the outset all of these were linear oligomers, although in a paper published in 1962 reference was made to the cyclic tetramers of Zinke. Eventually his synthetic efforts did turn to the cyclics, which led to a series of elegant and detailed papers[66] dealing with their synthesis. In the first paper of the series the Hayes and Hunter synthesis was repeated essentially without change, leading to *p*-methylcalix[4]arene as shown in Figure 2.4. In the light of subsequent developments in calixarene chemistry, perhaps the most significant contribution in this first paper was the observation of the temperature-dependent character of the ^{1}H NMR spectral resonances arising from the bridging CH_2 groups, a feature destined to become of great importance in studying the conformational behavior of these compounds (*cf*. Chapter 4).

The Hayes and Hunter method is not limited to the synthesis of the cyclic tetramers, for mono-hydroxymethyl linear oligomers of other lengths also have the potential for cyclization to the corresponding cyclooligomers. This was nicely demonstrated by Kämmerer and coworkers in the synthesis of more than a dozen cyclooligomers containing five, six and seven aromatic residues with

---

[66] (a) H. Kämmerer, G. Happel and F. Caesar, *Makromol. Chem.* **1972**, 162, 179; (b) G. Happel, B. Mathiasch and H. Kämmerer, *ibid.* **1975**, 176, 3317; (c) H. Kämmerer and G. Happel, *ibid.* **1978**, 179, 1199; (d) H. Kämmerer, G. Happel, V. Böhmer and D. Rathay, *Monatsh. Chem.* **1978**, 109, 767; (e) H. Kämmerer and G. Happel, *Makromol. Chem.* **1980**, 181, 2049; (f) *idem*, *ibid.* **1981**, 112, 759; (g) H. Kämmerer, G. Happel and B. Mathiasch, *ibid.* **1981**, 182, 1685; (h) H. Kämmerer and G. Happel in *Weyerhauser Science Symposium on Phenolic Resins. 2*, Tacoma, Washington, **1979**. Weyerhauser Publishing Co., Tacoma, **1981**, p. 143.

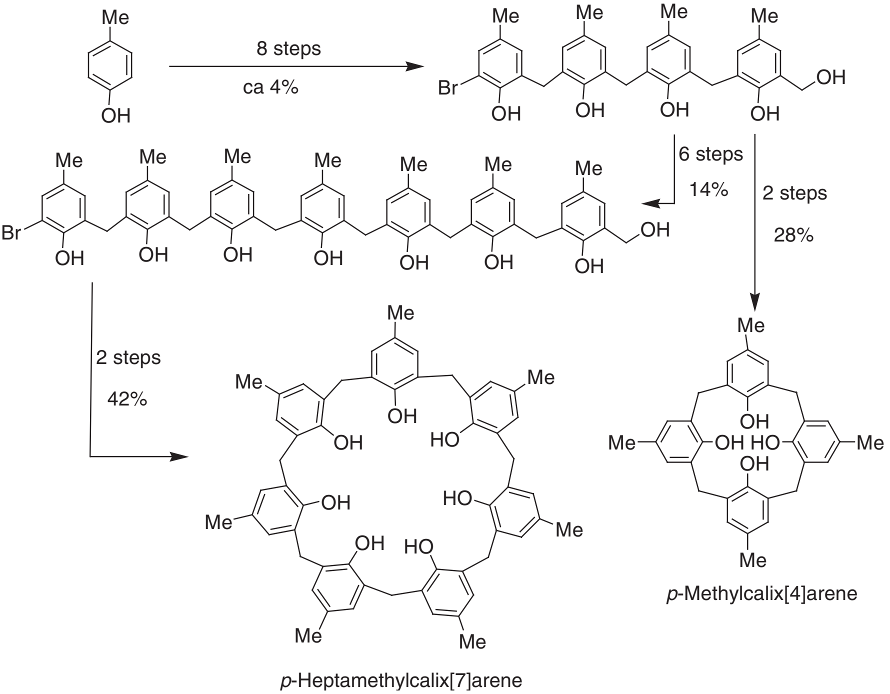


Figure 2.4 Stepwise synthesis of a calix[4]arene and a calix[7]arene.[67]

hydrogen, methyl and *tert*-butyl groups in the *p*-positions. In a *tour de force* sixteen-step reaction sequence whose repetitive nature is reminiscent of polypeptide and polynucleotide syntheses, Kämmerer and Happel[66e] prepared a calix[7]arene carrying six *p*-methyl groups and one *p*-*tert*-butyl group, the final cyclization step proceeding in an impressive overall 62% yield.

A more recent example of the Hayes and Hunter synthesis is that of *p*-phenylcalix[4]arene, prepared by Gutsche and No[68] in connection with an investigation of the composition of the product from the one-step reaction of *p*-phenylphenol and formaldehyde. The synthesis proved to be less facile than that of the *p*-alkyl-substituted calixarenes, and the overall yield was only *ca.* 0.5% as compared with the *ca.*11% for *p*-*tert*-butylcalix[4]arene.

2.3.2 Convergent Stepwise Syntheses (Fragment Condensation Procedure)

The Hayes and Hunter stepwise synthesis is long and rather tedious. Although its individual steps usually proceed in reasonably good yield and the overall yield can be as high as 25–30%, more often it is considerably lower.

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[67] H. Kämmerer and G. Happel, *ibid.* **1978**, 179, 1199.

[68] K. H. No and C. D. Gutsche, *J. Org. Chem.* **1982**, 47, 2713.

Recognizing these deficiencies, several research groups have devised convergent pathways that reduce the total number of steps and greatly improve the synthetic utility of the stepwise procedure. Böhmer's group at the University of Mainz has been foremost in developing and exploiting this approach.

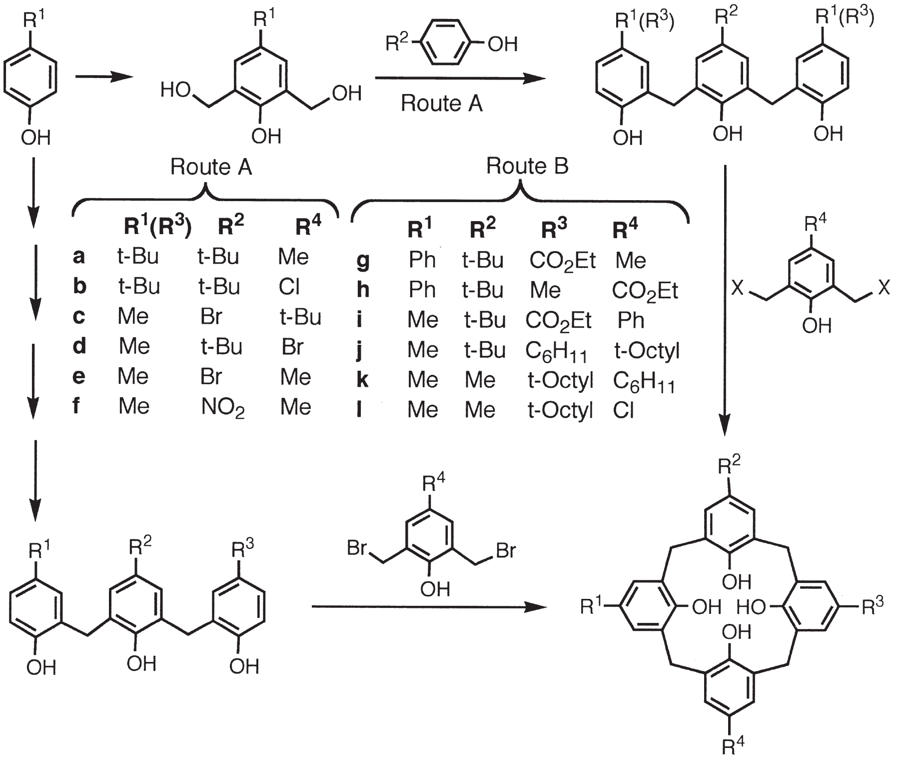
Volker Böhmer

Volker Böhmer was born in Rauscha, Germany, in 1941 and received his Ph.D. training at the University of Mainz under the direction of Hermann Kämmerer. Conversant with phenol-formaldehyde chemistry and the stepwise synthesis of linear as well as cyclic oligomers through his doctoral training, Böhmer's entry into calixarene chemistry perhaps was predestined. Eventually becoming a member of the faculty at the University of Mainz, he inherited the mantle of Kämmerer and carried on a tradition that pays homage to detailed organic synthesis as well as physical organic chemical investigation. To extend his earlier studies of hydrogen bonding effects in polyphenolic systems Böhmer sought cyclic oligomers with chemically more interesting functionality than those provided by the Kämmerer syntheses, and it was this quest that led him to explore what is characterized as a "3 + 1" approach in which a linear trimer is condensed with a 2,5-bis-halomethyl phenol, as illustrated in Figure 2.5.[69,70] The shorter Route-A involves a symmetrical linear trimer (R^1, R^2, R^1) prepared by treating a hydroxymethylphenol with an excess of a phenol. If an unsymmetrical linear trimer (R^1, R^2, R^3) is desired, the longer Route-B must be used, involving protection and deprotection procedures. These convergent

---

[69] V. Böhmer, P. Chhim and H. Kämmerer, *Makromol. Chem.* **1979**, 180, 2503.

[70] V. Böhmer, F. Marschollek and I. Zetta, *J. Org. Chem.* **1987**, 52, 3200. In what, in essence, is a "3 + 1" fragment condensation, the reaction of a 1,3-bis-propargylbenzene with a benzene carrying a pair of carbene complex moieties in the 1,3-positions produces a calix[4]arene in which two of the four rings are generated in the process of the condensation (V. Gopalsamuthiram and W. D. Wulff, *J. Am. Chem. Soc.* **2004**, 126, 13936).



Route A

	$R^1(R^3)$	R^2	R^4
a	t-Bu	t-Bu	Me
b	t-Bu	t-Bu	Cl
c	Me	Br	t-Bu
d	Me	t-Bu	Br
e	Me	Br	Me
f	Me	NO_2	Me

Route B

	R^1	R^2	R^3	R^4
g	Ph	t-Bu	CO_2Et	Me
h	Ph	t-Bu	Me	CO_2Et
i	Me	t-Bu	CO_2Et	Ph
j	Me	t-Bu	C_6H_{11}	t-Octyl
k	Me	Me	t-Octyl	C_6H_{11}
l	Me	Me	t-Octyl	Cl

Figure 2.5 "3 + 1" convergent stepwise synthesis of calix[4]arenes.[69,70]

fragmentation condensation procedures can afford yields of 25–30% in some cases, but more frequently in the range of 10–20% down to 2–7%, particularly in the more interesting examples in which hetero atoms and functional groups are included as *p*-substituents. The use of excess $TiCl_4$ as the catalyst[70] somewhat improves the yields and also has the advantage of obviating the necessity for high dilution.

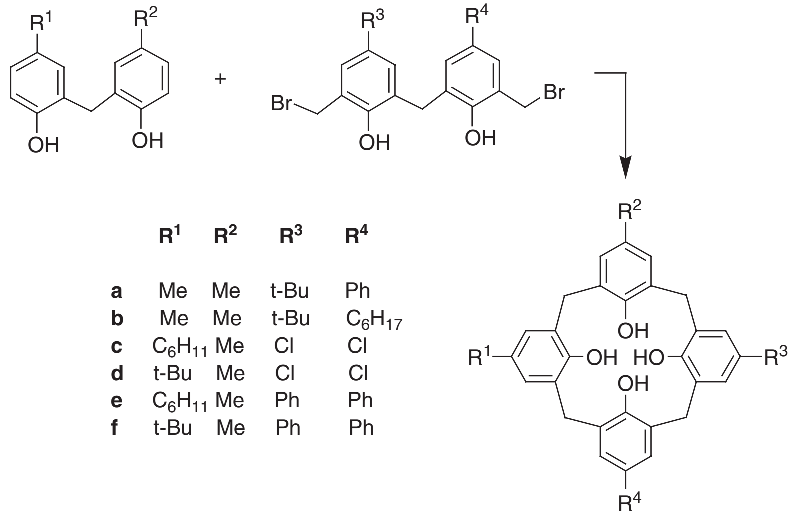
The complementary approach, the "2 + 2" procedure, has also been extensively studied by Böhmer and coworkers,[71] as illustrated in Figure 2.6. The condensation of *p,p′*-dichlorodiphenylmethane in a "2 + 2" procedure has been reported to yield *p*-chlorocalix[4]arene.[72] A calix[4]arene carrying *exo*-annular OH groups is the product of the reaction of the hydroxymesitylene **2.4** and the bis-chloromethylmesitylene **2.5** to give **2.6**.[73] Further condensation of

---

[71] V. Böhmer, L. Merkel and U. Kunz, *J. Chem. Soc. Chem. Commun.* **1987**, 896.

[72] A. A. Moshfegh *et al.*, *Helv. Chim. Acta* **1982**, 65, 1223, 1229 and 1264, who also reported the "2 + 1" synthesis of *p*-chloro-calix[3]arene. However, attempts by others to repeat this synthesis have failed; calix[3]arenes remain unknown, and molecular models suggest that they would probably be too strained to be stable.

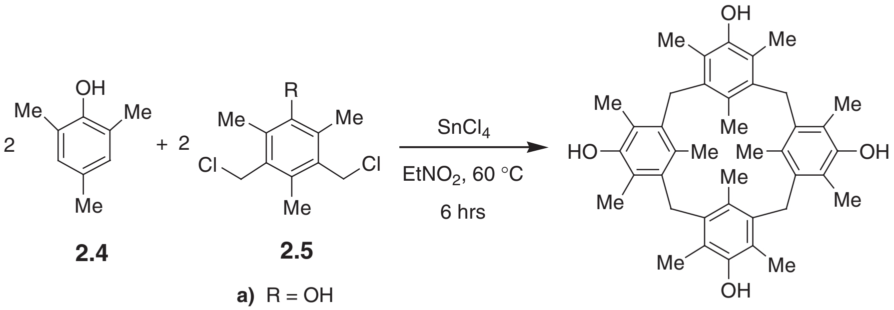
[73] S. Pappalardo, G. Ferguson and J. F. Gallagher, *J. Org. Chem.* **1992**, 57, 7102.



	R^1	R^2	R^3	R^4
a	Me	Me	t-Bu	Ph
b	Me	Me	t-Bu	C_6H_{17}
c	C_6H_{11}	Me	Cl	Cl
d	t-Bu	Me	Cl	Cl
e	C_6H_{11}	Me	Ph	Ph
f	t-Bu	Me	Ph	Ph

Figure 2.6 "2 + 2" convergent stepwise synthesis of calix[4]arenes.[71]

the *exo*-hydroxylated calix[4]arene **2.7** with a bis-bromomethylphenol **2.8** affords bis- and tris-calixarenes **2.9** and **2.10** in 7–8% yield.[74] Reaction of the *p,p′*-dihydroxyphenylalkane **2.11** with its tetrakis-bromomethylated counterpart **2.12** yields compound **2.13** carrying four bridges between a pair of calixarene units.[75]



2.4

2.5

a) R = OH

b) R = H

2.6

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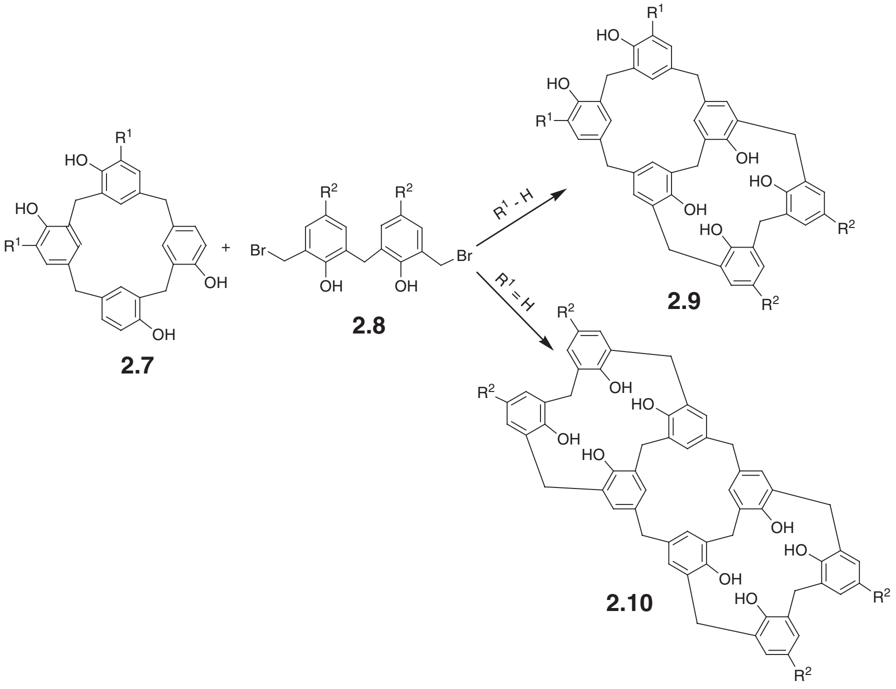
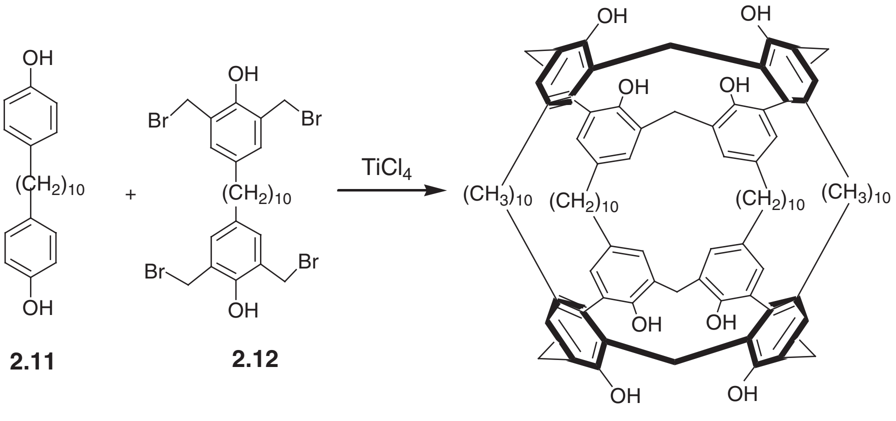
[74] V. Böhmer and W. Vogt, *Pure Appl. Chem.* **1993**, 65, 403; V. Böhmer, R. Dörrenbächer, M. Frings, M. Heydenreich, D. de Paoli, W. Vogt, G. Ferguson and I. Thondorf, *J. Org. Chem.* **1996**, 61, 54.

[75] V. Böhmer, H. Goldmann, W. Vogt, J. Vicens and Z. Asfari, *Tetrahedron Lett.* **1989**, 30, 1391.



2.7 **2.8** **2.9** **2.10**



2.11 **2.12** **2.13**

The choice between the "3 + 1" and "2 + 2" procedures often depends on the relative ease of construction of the component parts. Employment of a diarylmethane, which carries a substituent on the bridging carbon (**2.15**), leads to the doubly C-substituted calix[4]arene **2.16**.[76]

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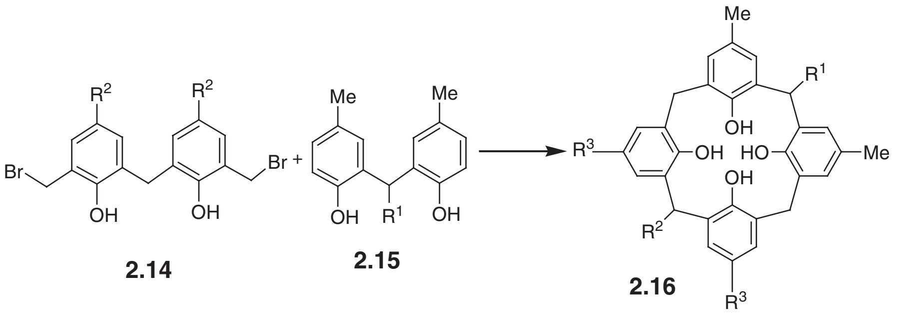
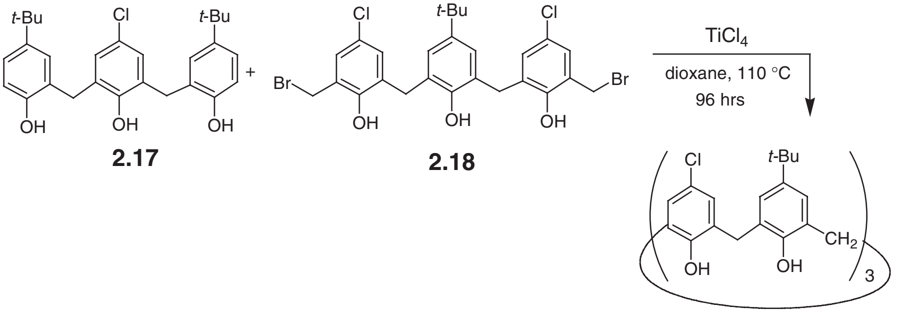
[76] C. Grüttner, V. Böhmer, W. Vogt, I. Thondorf, S. E. Biali and F. Grynszpan, *Tetrahedron Lett*. **1994**, 35, 6267; S. E. Biali, V. Böhmer. S. Cohen, G. Ferguson, G. Grüttner, F. Grynszpan, E. F. Paulus, E. Thondorf and W. Vogt, *J. Am. Chem. Soc*. **1996**, 118, 12938.



2.14 **2.15** **2.16**

Extension of the fragment condensation to the synthesis of larger calixarenes has had some success. For example, the "3 + 3" procedure involving the trimer **2.17** and the bis-bromomethyl trimer **2.18** has been used by deMendoza and coworkers[77] to obtain the calix[6]arene **2.19** in 9% yield.



2.17 **2.18** **2.19**

Initial attempts to prepare calix[5]arenes in "3 + 2" reactions yielded only the calix[4]arene,[78] possibly due to the template effect of the $TiCl_4$ catalyst. However, using only heat-induced reactions, a variety of calix[5]arenes have been reported,[79] and in similar fashion a calix[6]arene carrying three different *p*-substituents has been prepared in 27–32% yield.[80] Even a calix[8]arene has been constructed via a fragment condensation procedure in which treatment of the linear trimer **2.17** with 2,6-bis-hydroxymethyl-4-carbethoxyphenol yields a linear heptamer which in a "7 + 1" condensation reaction with another equivalent of the bis-hydroxymethylphenol produces a 9.1% yield of cyclic octamer[81] accompanied by a variety of other cyclic and acyclic products. In what is classed as a "2 + 1 + 1" condensation, di-(*p*-hydroxyphenyl)alkanes

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[77] J. deMendoza, P. M. Nieto, P. Prados and C. Sánchez, *Tetrahedron* **1990**, 46, 671.

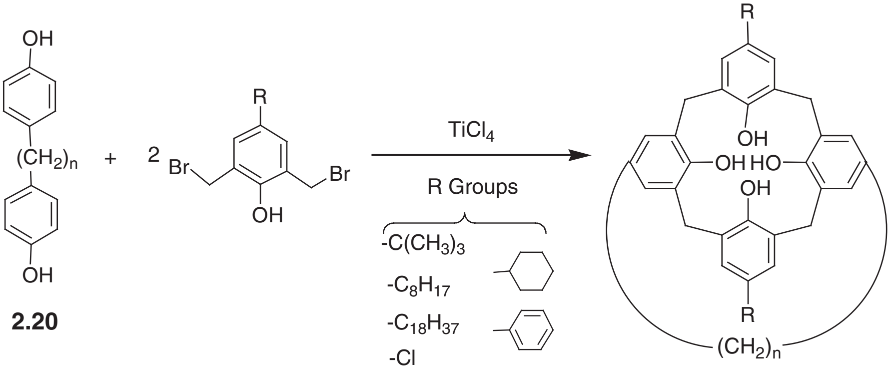
[78] V. Böhmer, F. Marschollek and I. Zetta, *J. Org. Chem.* **1987**, 52, 3200.

[79] S. Usui, K. Deyama, R. Kinoshita, Y. Odagaki and Y. Fukazawa, *Tetrahedron Lett.* **1993**, 34, 8127; T. Haino, T. Harano, K. Matsumura and Y. Fukazawa, *ibid.* **1995**, 36, 5793; S. E. Biali, V. Böhmer, I. Columbus, G. Ferguson, C. Grüttner, F. Grynszpan, E. F. Paulus and I. Thondorf, *J. Chem. Soc. Perkin Trans. 2* **1998**, 2261.

[80] K. No and K. M. Kwon, *Synthesis* **1996**, 1293.

[81] H. Tsue, M. Ohmori and K.-I. Hirao, *J. Org. Chem.* **1998**, 63, 4866; H. Tsue, K. Enyo and K.-I. Hirao, *Org. Lett.* **2000**, 2, 3071.

2.20 have been condensed with bis-dibromomethylphenols to give *exo*-annularly bridged calix[4]arenes (**2.21**),[82] named by Böhmer as "arrichoarenes" (Greek *arriches* meaning basket with a handle).



2.20

2.21

Treatment of 2-hydroxymethylphenols with $TiCl_4$ produces calix[4]arenes in 18–30% yields in a "1 + 1 + 1 + 1" process, in essence a one-step synthesis.[83]

A monohydroxymethyl linear tetramer (**2.24**), obtained in a "2 + 1 + 1" convergent synthesis of **2.23** from *p*-phenylphenol and **2.22** followed by hydroxymethylation, can be cyclized to a calix[4]arene (**2.25**) carrying two different pairs of *p*-substituents (Figure 2.7).[68] In what might be classed as a "1 + 1" synthesis, a methoxynaphthalene linear tetramer has been prepared,[84] which by subsequent insertion of a methylene group between the terminal residues gives a calix[4]naphthalene carrying four *endo* oxygen moieties (in contrast to **2.1** on p. 33).

2.4 Synthesis of Calixarene-related Compounds

2.4.1 Norcalixarenes and Homocalixarenes (*Apndx A-2, p. 219*)

Calixarenes in which one or more of the aryl moieties are directly connected can be referred to as "norcalixarenes", indicating the absence of one or more methylene bridge groups. For example, condensation of bis-phenol **2.26** ($n = 0$) with formaldehyde gives the tris-norcalix[6]arene (**2.27a**) and the corresponding tetrakis-norcalix[8]arene in 52% and 66% yield, respectively.[85a] A variety of homocalixarenes have been prepared in which two or more carbons comprise one or more of the bridges between the aryl moieties. For example,

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[82] V. Böhmer, H. Goldman and W. Vogt, *J. Chem. Soc. Chem. Commun.* **1985**, 667; E. Paulus, V. Böhmer, H. Goldman and W. Vogt, *J. Chem. Soc. Perkin Trans. 2* **1987**, 1609; V. Böhmer, H. Goldmann, R. Kaptein and I. Zetta, *J. Chem. Soc. Chem. Commun.* **1987**, 1358; H. Goldmann, W. Vogt, E. Paulus and V. Böhmer, *J. Am. Chem. Soc.* **1988**, 110, 6811.

[83] V. Böhmer, L. Merkel and U. Kunz, *J. Chem. Soc. Chem. Commun.* **1987**, 896.

[84] S. Chowdhury and P. E. Georghiou, *J. Org. Chem.* **2002**, 67, 6808.

[85] (a) T. Yamato, K-I. Hawegawa, Y. Saruwatari and L. K. Doamekpor, *Chem. Ber.* **1993**, 126, 1435. (b) T. Yamato, Y. Saruwatari, S. Nagayama, K. Maeda and M. Tashiro, *J. Chem. Soc. Chem. Commun.* **1992**, 861.

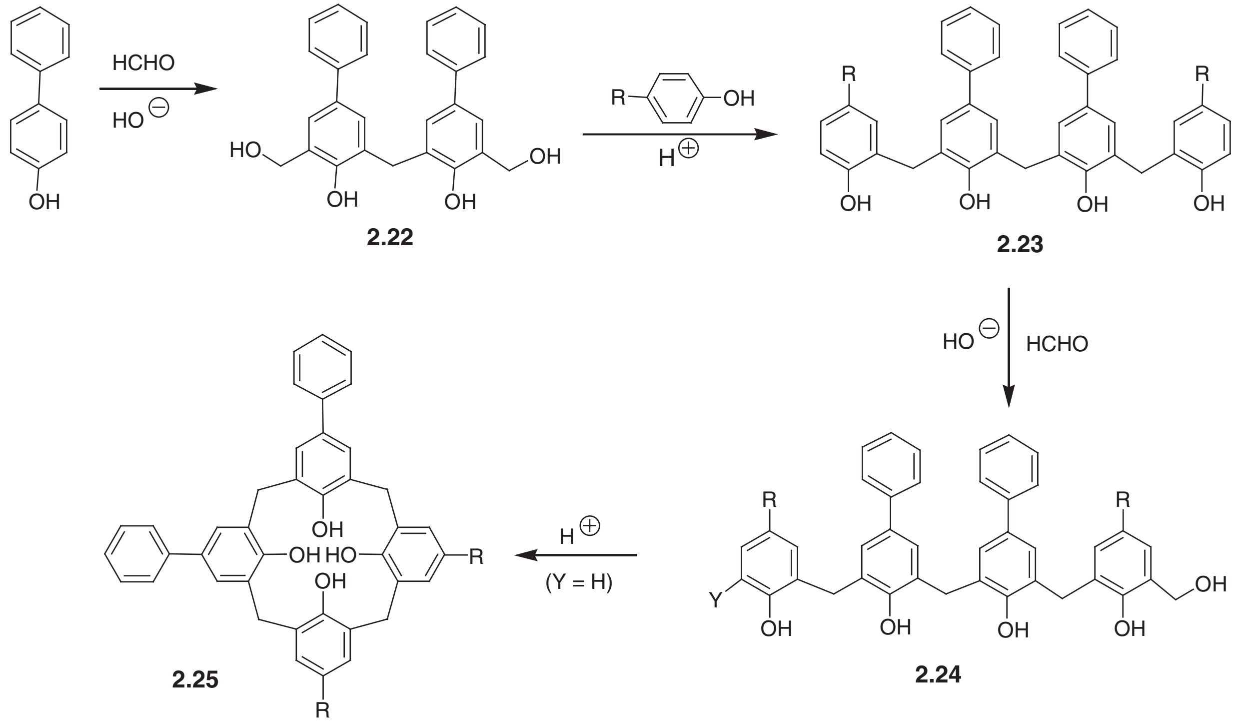
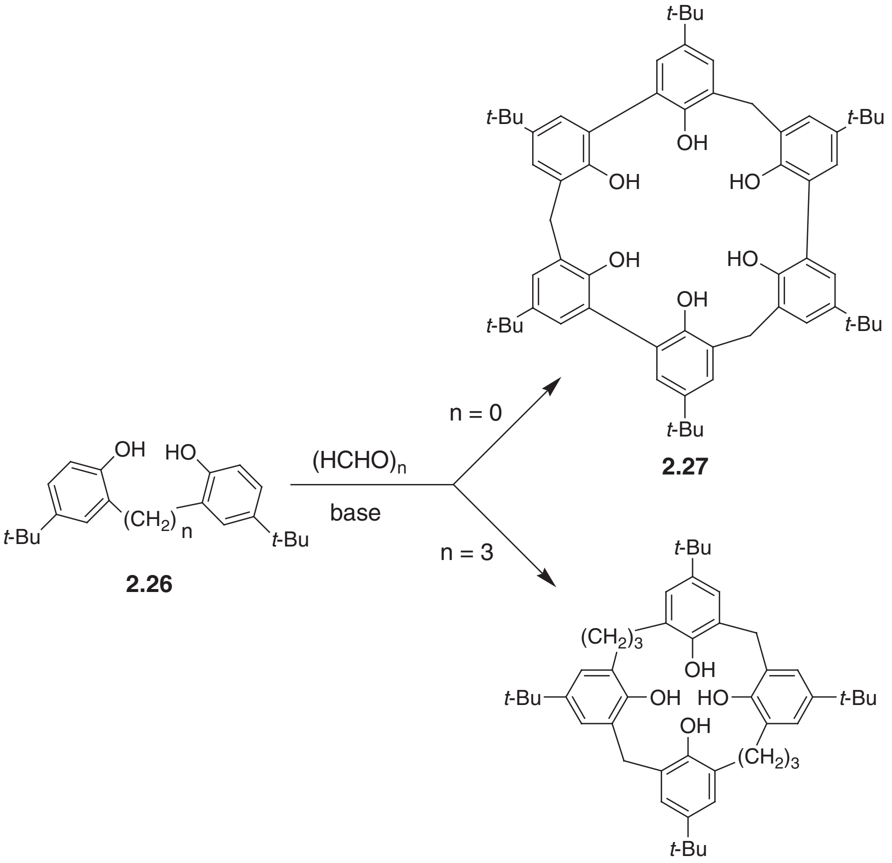


Figure 2.7 A "2 + 1 + 1" convergent stepwise synthesis of calix[4]arenes.[68]

condensation of **2.26** ($n = 3$) gives the tetrahomocalix[4]arene **2.28**,[85b] and a calixarene carrying four CH_2CH_2 bridging moieties, designated as an "all-homocalixarene", has been prepared.[86]



2.26

2.27

2.28

2.4.2 Oxacalixarenes, Azacalixarenes and Thiacalixarenes

[1_n]Metacyclophanes containing heteroatoms such as oxygen, nitrogen and sulfur rather than methylene groups as bridging moieties also qualify as members of the calixarene family. Oxacalixarenes (**2.29**, Y = O) were first synthesized in modest yield several decades ago by the condensation of *m*-dichloroarenes[87] or *m*-difluoroarenes[88] with resorcinols (Y = OH). They

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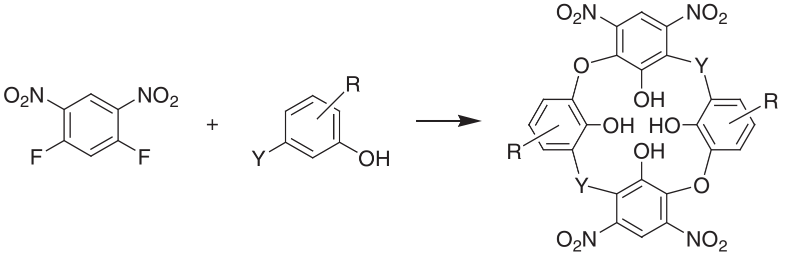
[86] G. Brodesser, R. Güther, R. Hoss, S. Meier, S. Ottens-Hildebrandt, J. Schmitz and F. Vögtle, *Pure Appl. Chem.* **1993**, 65, 2325; J. Schmitz, F. Vögtle, F. Nieger, K. Gloe, H, Stephan, O. Heitzsch, H.-J. Buschmann, W. Hasse and K. Cammann, *Chem. Ber.* **1993**, 126, 2843.

[87] N. Sommer and H. A. Staab, *Tetrahedron Lett.* **1966**, 2837; E. E. Gilbert, *J. Heterocyclic Chem.* **1974**, 11, 899.

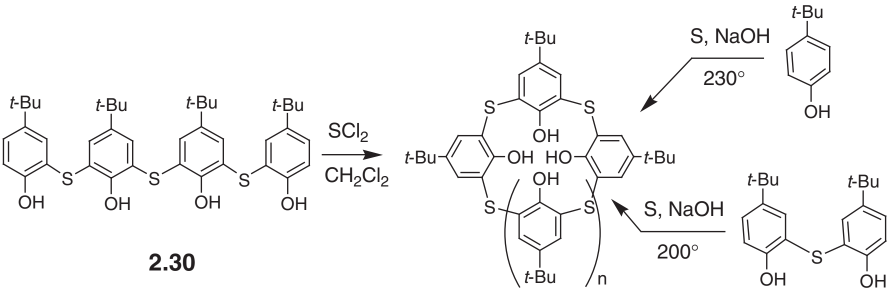
[88] P. A. Lehman, *Tetrahedron* **1974**, 30, 727.

have recently gained renewed attention from Katz and coworkers,[89] who have prepared **2.29** ($Y = O$, $R = OH$, CO_2Me, alkyl, CHO) in yields of 75–92%. In like fashion the 2,14-diaza-8,20-dioxazarene **2.29** ($Y = NH$) is produced by condensation with *m*-aminophenols ($Y = NH_2$).[88]



2.29

The thiacalixarenes (*e.g.* **2.31**) have attracted considerable and increasing interest as alternatives to the "carbocalixarenes", for they provide possibilities for additional structural manipulation *via* the sulfur atoms (*Apndx B-2; C-6; D-5*). They have been made by both stepwise and single step procedures. Employing a Hayes and Hunter type synthesis, Sone and coworkers[90] prepared linear tetramers (containing 1, 2 and 3 sulfur bridges) which, upon cyclization with SCl_2, yield the corresponding thiacalix[4]arenes. The tetrathiacalix[4]arene **2.31** ($n = 1$) was prepared in 4.1% yield by treating the trithia linear tetramer **2.30** with SCl_2 followed by cyclization. Far easier, however, is the single-step synthesis[91] in which a mixture of *p-tert*-butylphenol, elemental sulfur and NaOH is heated to 230 °C in a high boiling solvent such as tetraglyme to give **2.31** ($n = 1$) in 49% yield.



2.30 **2.31** **2.32**

This accomplishment provides another interesting illustration of the power of the industrial/academic interaction. It was during an investigation directed to the

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[89] J. L. Katz, M. B. Feldman and R. Conry, *Org. Lett.* **2005**, 7, 91 and 3505.

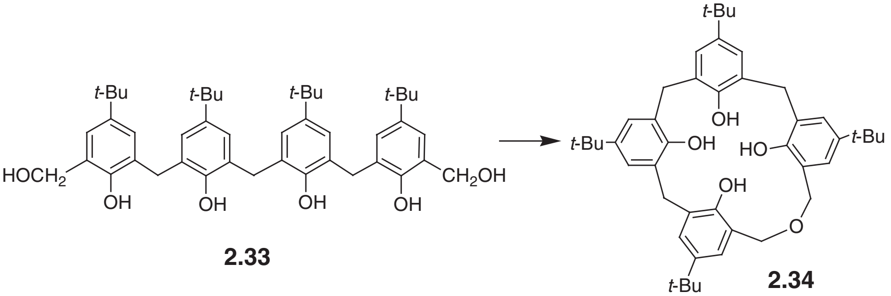
[90] T. Sone, Y. Ohba, K. Moriya, H. Kumada and I. Kazuski, *Tetrahedron* **1997**, 53, 10689.

[91] H. Kumagai, M. Hasegawa, S. Miyanari, Y. Sugawa, Y. Sato, T. Hori, S. Ueda, H. Kamiyama and S. Miyano, *Tetrahedron Lett.* **1997**, 38, 3971; N. Iki, C. Kabuto, T. Fukushima, H. Kumagai, H. Takeya, S. Miyanari, T. Miyashi and S. Miyano, *Tetrahedron* **2000**, 56, 1437.

development of alkaline cleaning additives for lubricants (carried out by engineers at the Cosmo Oil Company in Japan in collaboration with Sotaro Miyano of Tohoku University in Sendai) that this facile synthesis of *p*-*tert*-butyltetrathiacalix[4]arene was discovered. It has been further improved[92] by starting with the sulfur-bridged dimer **2.32**, which increases the yield of **2.31** ($n = 1$) to 83% and also produces small but isolable amounts (4–5%) of the larger cyclic oligomers **2.31** ($n = 3$ and 5). As has been the case with the "carbocalixarenes", the now easy accessibility of the thiacalixarenes has encouraged a similarly wide-ranging investigation of their properties, which are qualitatively similar but frequently quantitatively different from those of their older forebears.

2.4.3 Homooxacalixarenes and Homoazacalixarenes (*Apndx A-2, p. 235*)

In the Standard Petrolite Procedure for calixarene synthesis one of the compounds in the product mixture is *p*-*tert*-butyldihomooxacalix[4]arene (**2.34**),[93] present in large amounts in the early phases of the reaction but giving way to calixarenes as the reaction progresses.



2.33

2.34

That it is a true obligatory intermediate in calixarene formation is doubtful, although it may serve a storage function. Even in mixtures in which it is present in significant amount it is difficult to isolate and purify, and a useful alternative is to prepare it by dehydration of the bis-hydroxymethyl linear tetramer **2.33**. Cyclization occurs in almost quantitative yield. In contrast, the bis-hydroxymethyl compounds from shorter linear oligomers undergo intermolecular rather than intramolecular dehydration. Thus, the bis-hydroxymethyl linear trimer **2.35** yields the cyclic hexamer **2.36**,[94] the bis-hydroxymethyl linear dimer **2.37** yields the cyclic tetramer **2.38** and the bis-hydroxymethylmonomer **2.40** yields the cyclic trimer **2.39**.[93,95,96]

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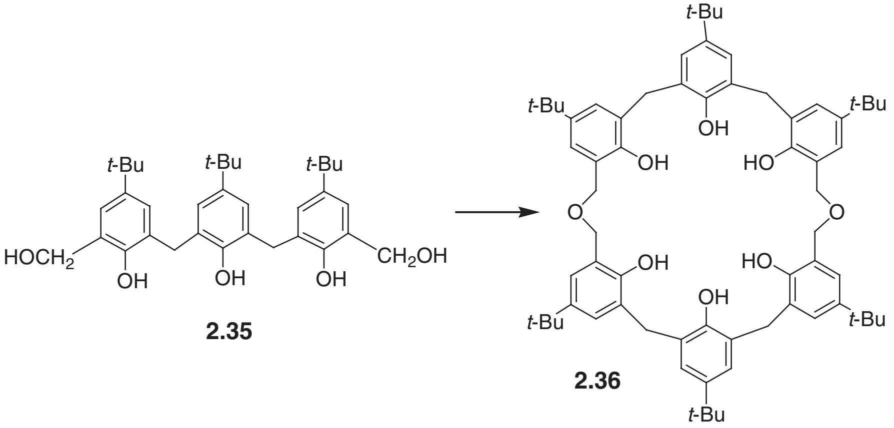
[92] N. Kon, N. Iki and S. Miyano, *Tetrahedron Lett.* **2002**, 41, 2231; Y. Kondo, K. Endo, N. Iki, S. Miyano and F. Hamada, *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, 52, 45.

[93] B. Dhawan and C. D. Gutsche, *J. Org. Chem.* **1983**, 48, 1536; T. Tanno and Y. Mukoyama, *Netsu. Kokasei Jushi* **1981**, 2, 132 (*Chem. Abstr.* 96: 52791k).

[94] K. Hultzsch, *Kunststoffe* **1962**, 52, 19; B. Masci, *J. Org. Chem.* **2001**, 66, 1497.

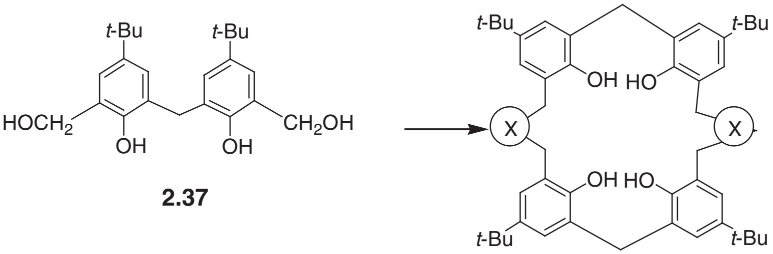
[95] P. Zerr, M. Mussrabi and J. Vicens, *Tetrahedron Lett.* **1991**, 32, 1879.

[96] Y. Mukoyama and T. Tanno, *Org. Coating Plastics Chem.* **1979**, 40, 894.



2.35

2.36



2.37

2.38

a) X = O

b) X = NR

The synthesis of the last of these three types of compounds has been studied in some detail by (a) Philip Hampton and coworkers,[97] who improved on the earlier reported yields and ease of isolation; (b) Cragg and coworkers,[98] who showed that the purity of the bis-hydroxymethylphenol plays an important part (the more pure, the lower the yield) and that *p*-toluenesulfonic acid is the catalyst of choice; (c) Komatsu,[99] who employed 2,5-diformylphenols as starting materials in a reductive coupling reaction and (d) Fuji and coworkers,[100] who investigated a stepwise approach. bis-Hydroxynaphthols have also been shown to yield the corresponding hexahomotrioxacalix[3]naphthalenes.[101]

Closely related to the homooxacalixarenes are the homoazacalixarenes. For example, treatment of **2.40a** or **2.40b** with an amine such as methylamine or benzylamine yields a hexahomotriazacalix[3]arene **2.41**,[102] and treatment of

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[97] P. D. Hampton, A. Bencze, W. Tong and C. E. Daitch, *J. Org. Chem.* **1994**, 59, 4838.

[98] M. Miah, N. N. Romanov and P. J. Cragg, *J. Org. Chem.* **2002**, 67, 3124.

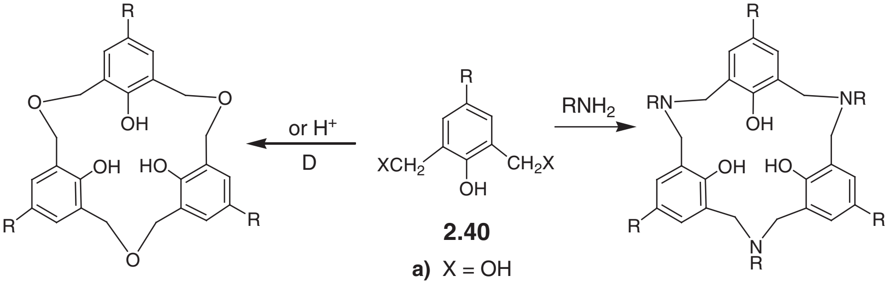
[99] N. Komatsu, *Tetrahedron Lett.* **2001**, 42, 1733.

[100] K. Tsubaki, T. Otsubo, K. Tanaka, K. Fuji and T. Kinoshita, *J. Org. Chem.* **1998**, 63, 3260.

[101] M. Ashram, S. Mizyed and P. E. Georghiou, *J. Org. Chem.* **2001**, 66, 1473.

[102] H. Takemura, K. Yoshimura, I. U. Khan, T. Shinmyozu and T. Inazu, *Tetrahedron Lett.* **1992**, 33, 5775; I. U. Khan, H. Takemura, M. Suenaga, T. Shinmyozu and T. Inazu, *J. Org. Chem.* **1993**, 58, 3158; P. Thuéry, M. Nierlich, J. Vicens and H. Takemura, *J. Chem. Soc. Dalton Trans.* **2000**, 279.

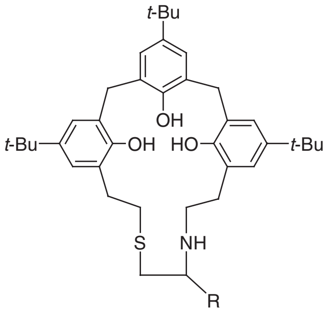
2.37 in similar fashion yields a tetrahomodiazacalix[4]arene **2.38b**.[103] A pentahomothiazacalix[3]arene (**2.42**) carries a sulfur atom in addition to the nitrogen in a bridging moiety.[104]



2.39

2.40
a) X = OH
b) X = Cl

2.41



2.42

2.4.4 Heterocalixarenes (*Apndx A-2, p. 250*)

Although cyclooligomers containing furan residues have been known almost as long as the calixarenes,[105] they have commanded much less attention and have been the subject of only occasional research in recent years. By acid-catalyzed condensation of aldehydes or ketones with furan[106] or by using linear oligomers of furan,[106b] calixfurans (**2.43** with $n = 1,2,3,5$) have been prepared. For the formaldehyde-derived compounds $H_2C(OMe)_2$ is the reagent of choice, leading

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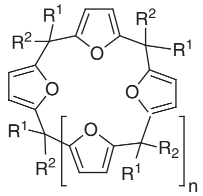
[103] P. D. Hampton, W. Tong, S. Wu and E. N. Deusler, *J. Chem. Soc. Perkin Trans 2* **1996**, 1127; H. Takemura, Y. Kozima and T. Inazu, *Tetrahedron Lett.* **1999**, 40, 6431.

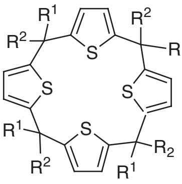
[104] K. Ito, Y. Ohba and T. Sone, *Chem. Lett.* **1996**, 183.

[105] (a) R. G. Ackerman, W. H. Brown and G. F. Wright, *J. Org. Chem.* **1955**, 20, 1147; (b) W. H. Brown and W. N. French, *Can. J. Chem.* **1958**, 38, 537; (c) M. Chastrette and F. Chastrette, *J. Chem. Soc. Chem. Commun.* **1973**, 534; (d) J. M. Timkom and D. J. Cram, *J. Am. Chem. Soc.* **1974**, 96, 7159; (e) Y. Kobuke, K. Hanji, K. Horiguchi, M. Asada, Y, Nakayama and J. Furukawa, *J. Am. Chem. Soc.* **1974**, 98, 7414.

[106] (a) M. de Sousa Healy and A. J. Rest, *J. Chem. Soc. Perkin Trans.II* **1985**, 973; (b) R. M. Musau and A. Whiting, *J. Chem. Soc. Chem. Commun.* **1993**, 1029; (c) R. M. Musau and A. Whiting, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2881; (d) G. Cafeo, F. H. Kohnke, G. L. La Torre, A. J. P. White and D. J. Williams, *Angew. Chem. Intl. Ed. Engl.* **2000**, 39, 1496.

to linear oligomers of which only the linear tetramer can be converted to the cyclic tetramer in reasonable yield.[106b,c] The thiophene analogues, calixthiophenes (**2.44**), are less easily prepared but are known entities.[107]


2.43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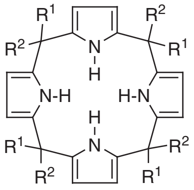
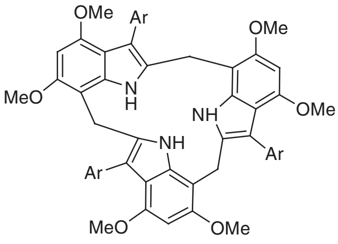
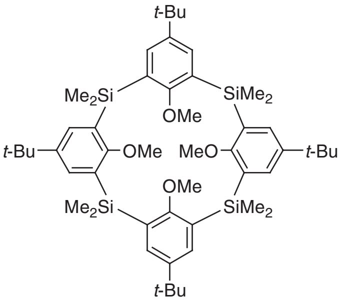
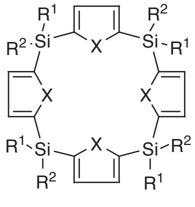

2.45


2.46

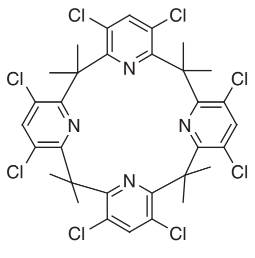

2.47

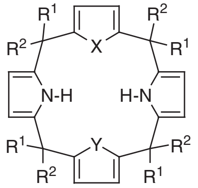

2.48

a) X = O

b) X = S

c) X = NMe

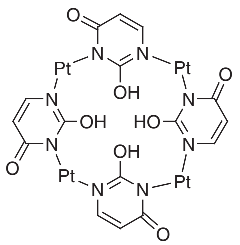

2.49


a) X = Y = O

b) X = Y = S

c) X = O, Y = S

2.50


2.51

Well over a century ago Baeyer isolated a cyclic tetramer (**2.45**) from the acid-catalyzed condensation of pyrrole and acetone.[108] However, compounds

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[107] E. Vogel, M. Pohl, A. Herrmann, T. Wiss, C. König, J. Lex, M. Gross and J. P. Gisselbrecht, *Angew. Chem. Intl. Ed. Engl.* **1996**, 35, 1520; N. Komatsu, A. Taniguchi and H. Susuki, *Tetrahedron Lett*. **1999**, 40, 3749.

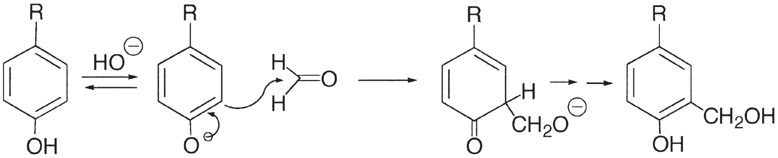
[108] A. Baeyer, *Ber*. **1886**, 19, 2184.

possessing this macrocyclic structure received only sporadic attention[109] until the work of Floriani and coworkers[110] in the 1990s and, even more recently, the extensive investigations by Sessler and coworkers, who demonstrated the utility of these compounds for anion binding.[111] They assigned the name "calix[*n*]pyrroles". Other classes of compounds to which the name "calixarene" has been attached include, *inter alia*, the calix[3]indoles (**2.46**), prepared by acid-catalyzed condensation of 4,6-dimethyoxy-3-methylindole with aryl aldehydes,[112] silacalix[4]arenes (**2.47** and **2.48 a-c**),[113] a calix[4]pyridine (**2.49**)obtained via carbene insertion of a calix[4]pyrrole,[114] a variety of mixed heterocycle calix[4]arenes (**2.50**)[115] and a platinocalix[4]uracil (**2.51**).[116]

2.5 Mechanism of Calixarene-forming Reactions

2.5.1 Mechanism of the Base-induced Reaction

The mechanism, or perhaps better called the "pathway", of base-induced oligomerization of phenols and formaldehyde has been the subject of study for many years, dating back to the early twentieth century. The process is initiated by the formation of a phenoxide which, acting as a carbon nucleophile, effects a nucleophilic addition to the highly reactive carbonyl group of formaldehyde, *viz*.



Under mild conditions the reaction can be terminated at this point, and hydroxymethyl phenols can be isolated and characterized.[117] Under somewhat more strenuous conditions, however, the reaction proceeds further to give

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[109] V. V. Chelintzev and B. V. Tronov, *J. Russ. Phys. Chem. Soc.* **1916**, 48, 105 correctly assigned the cyclic tetrameric structure.

[110] C. Floriani and R. Floriani-Moro in *The Porphyrin Handbook Vol. 3*, ed. K. M. Kadish, K. M. Smith and R. Guilard, Academic Press, San Diego, CA, **2000**, pp. 385–403; 405–420.

[111] P. A. Gale, J. L. Sessler, V. Král and V. Lynch, *J. Am. Chem. Soc.* **1996**, 118, 5140. An environmentally friendly synthesis using molecular sieve catalysts is reported by M. R. Kishn, V. R. Rani, S. J. Kulkarni and K. V. Raghavan, *J. Molec. Catalysis A Chemical 237* **2005**, 155. A synthesis of larger calixpyrroles and mixed calixpyrrole/furan compounds is described in ref. 106(d).

[112] (a) D. St. C. Black, D. C. Craig and N. Kumar, *J. Chem. Soc. Chem. Commun.* **1989**, 425; (b) D. St. C. Black, M. C. Bowyer, N. Kumar and P. S. R. Mitchell, *ibid.* **1993**, 819; (c) D. St. C. Black, D. C. Craig, N. Kumar and D. B. McConell, *Tetrahedron Lett.* **1996**, 37, 241.

[113] B. König, M. Rodel, P. Bubenitschek and P. G. Jones, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 661.

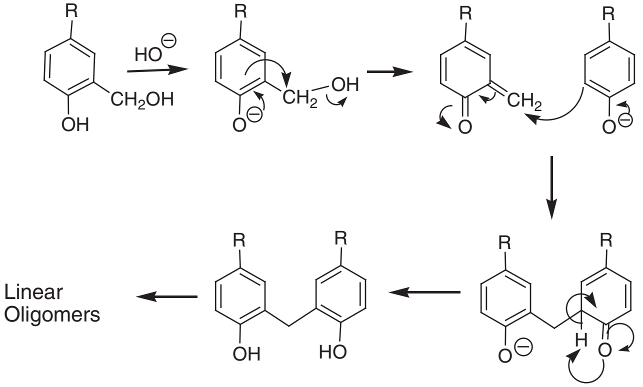
[114] V. Král, P. A. Gale, P. Anzenbacher, P. Jr. K. Jurskková, V. Lynch and J. L. Sessler, *Chem. Commun.* **1998**, 9. A pyridine analogue of a calix[4]resorcarene has been reported by T. Gerkensmeier, J. Mattay and C. Näther, *Chem. Eur. J.* **2001**, 7, 465.

[115] Y. S. Jang, H. J. Kim and P. H. Lee, *Tetrahedron Lett.* **2000**, 41, 2919.

[116] H. Rauter, E. C. Hillgeris, A. S. Erxleben and B. Lippert, *J. Am. Chem. Soc.* **1994**, 116, 616.

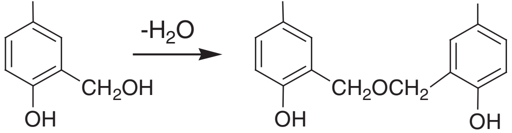
[117] F. Ullmann and K. Brittner, *Ber.* **1909**, 42, 2539.

diarylmethyl compounds, presumably *via* a pathway that involves *o*-quinonemethide intermediates which react with the phenoxide in a Michael-like process, *viz.*



For example, a mixture of *p*-*tert*-butylphenol and aqueous formaldehyde held at 50 °C for 4 days yields a mixture from which, *inter alia*, the bis-hydroxymethyl dimer can be isolated.[118] The suggestion that *o*-quinonemethides are intermediates in the formation of these oligomers was made as long ago as 1912[119] and was subsequently resurrected by Hultzsch,[120] v. Euler[121] and others. Although a contrary view has been expressed[122] because of the very high temperatures that are required to transform methoxymethylphenols to quinonemethides,[123,124] it is known that reactions such as the oxy-Cope rearrangement proceed with far greater facility with the anions than with the corresponding neutral compounds. It seems reasonable, therefore, to invoke the existence of quinonemethides under the conditions of the phenol-formaldehyde oligomerization reactions.

Another reaction of hydroxymethylphenols that can occur instead of, or concurrent with, the formation of the diarylmethanes is the dehydration to dibenzyl ethers, *viz.*



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[118] A. Zinke, R. Kretz, E. Leggewie and K. Hössinger, *Monatsh. Chem.* **1952**, 83, 1213.

[119] A. Wohl and B. Mylo, *Ber.* **1912**, 45, 2046.

[120] K. Hultzsch, *Ber.* **1942**, 75B, 106.

[121] H. v. Euler, E. Adler, J. O. Cedwall and O. Törngren, *Ark. Kemi. Mineral. Geol.* **1941**, 15A, No. 11.1.

[122] R. Wegler and H. Herlinger, *Methoden der Organischen Chemie*, Houben-Weyl: XIV/2. Makromolecular Stoffe, Thieme Verlag, Stuttgart, **1963**, p. 257.

[123] P. D. Gardner, H. Sarrafizadeh and R. I. Brandon, *J. Am. Chem. Soc.* **1959**, 81, 5515.

[124] D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.* **1975**, 97, 4765; R. W. Thies and E. P. Seitz, *J. Org. Chem.* **1978**, 43, 1050.

Thus, the mixtures from which calixarenes arise contain diphenylmethane-type and dibenzyl ether-type compounds in various degrees of oligomerization. An HPLC analysis of the "precursor" in a Modified Zinke–Cornforth Procedure (see Section 2.1) indicated that at least three dozen non-cyclic components are present.[125] A reaction carried out using the *Organic Synthesis* conditions[9] by Vocanson and coworkers[126] for the preparation of *p*-*tert*-butylcalix[6]arene was followed by means of GC and TLC analyses. At the end of the first phase of the reaction relatively small amounts of linear trimer and tetramer were present, but appreciable amounts of linear hexamer had also formed. This was quite logically interpreted as indicating that the precursor to the cyclic hexamer is the linear hexamer. In a companion investigation[127] similar experiments were carried out using the *Organic Synthesis* preparations for the cyclic tetramer[4] and cyclic octamer[10] and measuring the product composition as a function of time. The results were viewed as favoring the linear tetramer (a "pseudo-calix[4]arene") as the precursor for the cyclic tetramer, but the failure to detect linear octamer provides support for a different pathway in which a pair of mono- or bis-hydroxymethylated linear tetramers form an intermolecularly hydrogen-bonded dimer (a "hemicalix[8]arene") which, as suggested by Gutsche,[128] extrudes water and/or formaldehyde at the termini of each of the members of the dimer to produce the cyclic octamer (the calix[8]arene) as depicted in Figure 2.8 and Figure 2.9.

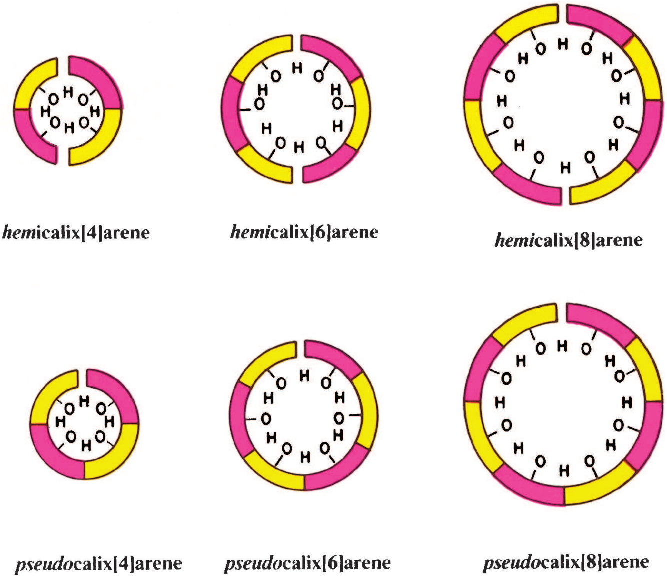

Figure 2.8 Schematic representation of hemicalixarenes and pseudocalixarenes.

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[125] Dr J. F. Ludwig of the Petrolite Corporation, unpublished observations.

[126] F. Vocanson, R. Lamartine and R. Perrin, *Supramol. Chem.* **1994**, 4, 153.

[127] F. Vocanson and R. Lamartine, *Supramol. Chem.* **1996**, 7, 19.

[128] C. D. Gutsche, *Accts. Chem. Res.* **1983**, 16, 161.

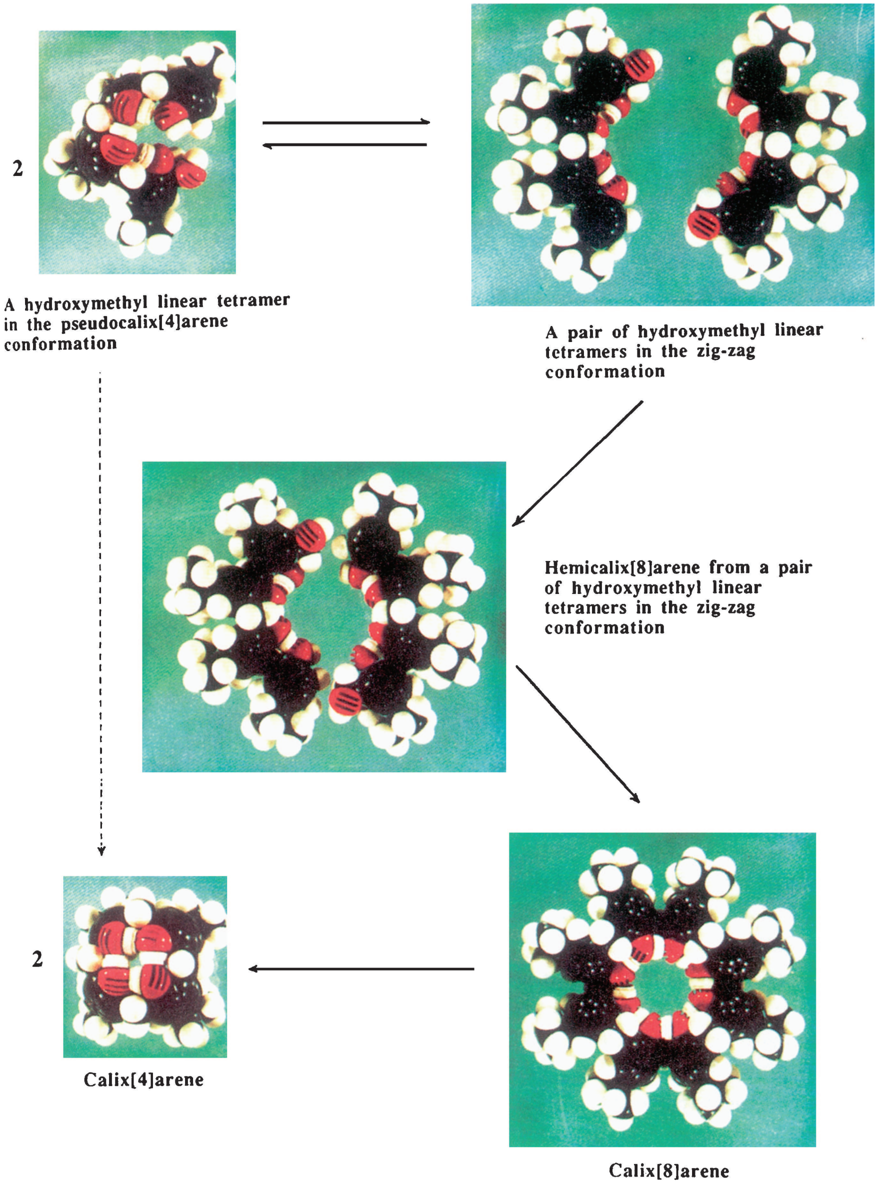


Figure 2.9 Conversion of a linear tetramer into a calix[8]arene and a calix[4]arene as depicted with space-filling molecular models.[7]

Similar pathways involving pairs of linear dimers or trimers can be invoked as the pathway to other cyclic oligomers, including the cyclic tetramer and cyclic hexamer, but there is little or no experimental evidence in support of this possibility.

That at least some of the components of the "precursor" mixture may be in equilibrium with one another prior to cyclization is suggested by the fact that the product mixture in a calixarene-forming reaction is much more dependent on the particular reaction conditions than on the starting material. For example, hydroxymethyl monomers, dimers, trimers, and tetramers all give quite similar product mixtures under a particular set of conditions; *i.e.* Modified Zinke–Cornforth, Standard Petrolite or Modified Petrolite procedures.[7] Another example of interconversion is seen in the transformation of both the *p-tert*-butylcalix[6] and [8]arene to *p-tert*-butylcalix[4]arene in yields of 75% or higher under the conditions of the Modified Zinke–Cornforth procedure. Viewing the cyclic octamer as the product of kinetic control (formed under relatively mild conditions) and the cyclic tetramer as the product of thermodynamic control (formed under much more strenuous conditions), Gutsche and coworkers speculated that the transformation of cyclic octamer to cyclic tetramer might follow a "molecular mitosis" pathway wherein the cyclic octamer pinches together to form a figure-eight conformer which then splits into a pair of cyclic tetramers. To test this hypothesis, a study was carried out in which a 50:50 mixture of fully deuterated and fully proteated *p-tert*-butylcalix[8]arenes was converted to *p-tert*-butylcalix[4]arene (referred to as the "reversion reaction"). If molecular mitosis is the only pathway, the reaction mixture would comprise equal amounts of fully deuterated and fully proteated cyclic tetramer. If complete fragmentation/recombination is the only pathway the reaction mixture would comprise fully deuterated as well as partially deuterated/proteated cyclic tetramers in a 1:4:6:4:1 ratio, as shown in Figure 2.10. The observed

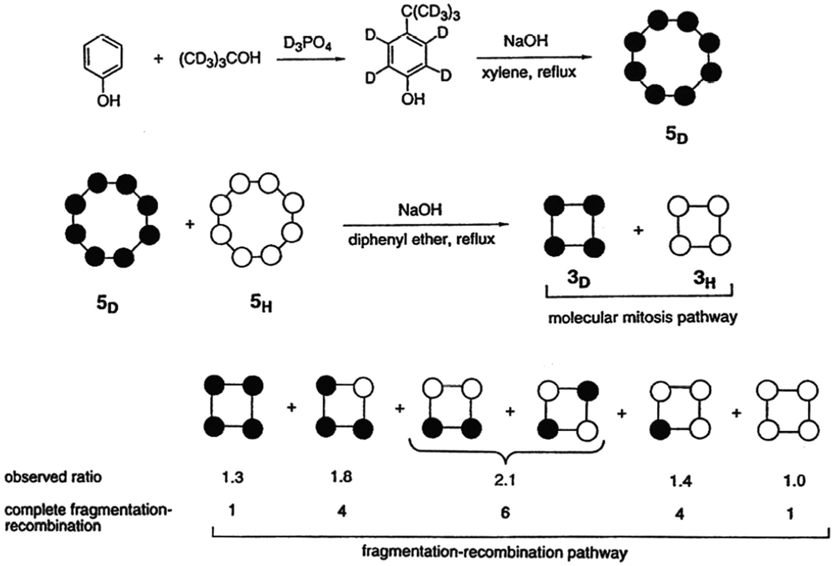
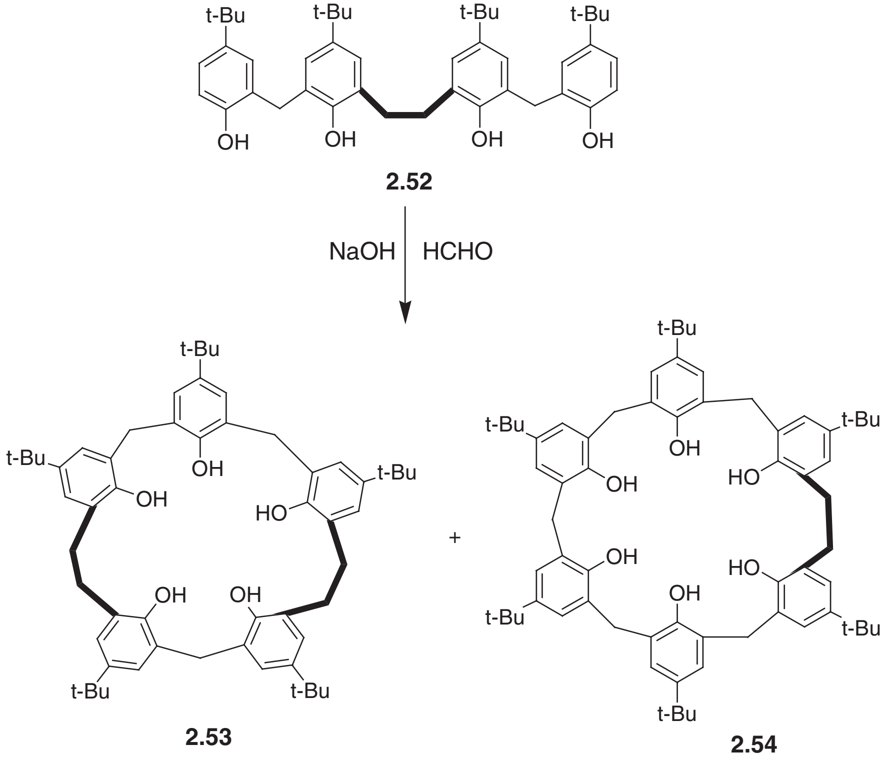


Figure 2.10 Test for molecular mitosis pathway (filled circles are deuterated residues; open circles are proteated residues).

ratio falls between these extremes and, while not completely ruling out molecular mitosis, indicates that fragmentation/recombination must be a major pathway. A further illustration of fragmentation/recombination is seen in the treatment of the linear tetramer **2.52** (containing one ethylene bridge) with HCHO and NaOH to produce a mixture containing 35% of the cyclic pentamer **2.53** and 25% of the cyclic hexamer **2.54** in which the ethylene bridge is conserved in both cases.[129]



The mechanism of formation of the calix[6]arenes is even more conjectural and might involve (a) cyclization of a linear hexamer (the ‘‘pseudocalixarene’’ route), (b) cyclization of an intermolecularly bonded pair of linear trimers (the ‘‘hemicalixarene’’ route), (c) a reversion process from the cyclic octamer or (d) some other pathway. The requirement of a 10-fold increase in the amount of base to shift the product from the calix[8]arene to the calix[6]arene in the Petrolite Procedure and the fact that KOH and RbOH give better yields than LiOH, NaOH and CsOH suggest that a template effect is operative, a phenomenon well documented for crown ether syntheses.[130] The formation of the even numbered calix [4], [6] and [8]arenes may be the result of their stronger

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[129] T. Yamato, M. Yasumatsu, L. K. Doamekpor and S. Nagayama, *Liebigs Ann. Chem.* **1995**, 285.

[130] G. W. Gokel and S. H. Korzeniowski, *Macrocyclic Polyether Syntheses*, Springer, Berlin, **1982**, Chapter 2.

intramolecular hydrogen bonding as compared with that in the odd numbered calix[5] and [7]arenes, as discussed in more detail in Chapter 4.

The outcome of the base-induced condensation of formaldehyde with *p*-substituted phenols is remarkably sensitive to the *p*-substituent and appears to be particularly critical in the formation of the cyclic tetramer. *p*-Cresol and *p*-phenylphenol, for example, react with formaldehyde to form little, if any, cyclic tetramer but significant amounts of larger calixarenes. Attempts to convert *p*-phenylcalix[8]arene to *p*-phenylcalix[4]arene by the base-induced reversion reaction described above fails to yield any of this product. It is conjectured that the ease with which the cyclic tetramer forms, either in the cycloreversion process or in the direct calixarene-forming reaction, is related to the degree to which the *p*-substituents cover the cavity in the preferred cone conformation. Four *tert*-butyl groups nicely cover the cavity, as do four *p*-*tert*-pentyl or four *tert*-octyl groups. But, four isopropyl groups cover it somewhat less well and four methyl groups or four phenyl groups do it rather poorly.

2.5.2 Mechanism of the Acid-catalyzed Reaction

The acid-catalyzed condensation of resorcinol with aldehydes is most logically interpreted in terms of cationic intermediates and electrophilic aromatic substitution reactions, as portrayed in Figure 2.11. A kinetic and molecular

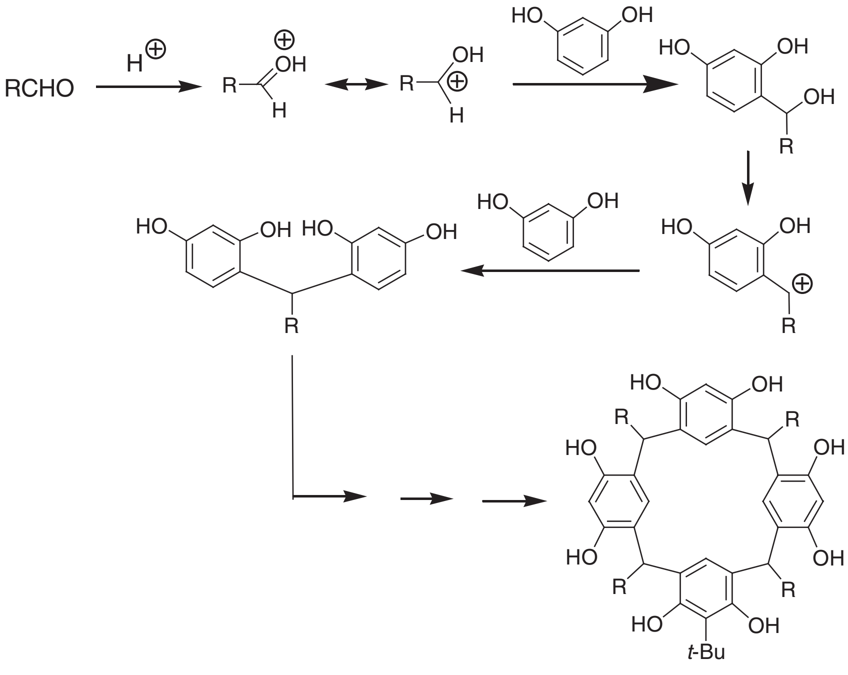

Figure 2.11 Pathway for the acid-catalyzed condensation of resorcinols and aldehydes.

modeling study[131] of the acid-catalyzed reaction of resorcinol and acetaldehyde concludes that (a) ring closure to the calix[4]resorcarene is at least as fast as chain propagation, (b) the macrocyclic products are the thermodynamic sink of the reactions and (c) linear oligomers longer than four aryl units depolymerize fast in comparison with ring opening, thus promoting the formation of the cyclic tetramer. However, reaction with HCHO (from trioxane) yields mixtures containing both calix[4] and calix[6]resorcarenes.[132] Also, it is known that *p-tert*-butylphenol and trioxane yield calixarenes under acid-catalyzed conditions but that the cyclic tetramer is not a major product (while larger cyclic oligomers are preferentially formed, suggesting that propagation of linear oligomers is faster than cyclization to the cyclic tetramer).

2.6 Concluding Remarks

In these first two chapters the early history of phenol-formaldehyde chemistry has been portrayed with particular reference to the events that laid the basis for the experiments that were initiated in the 1970s in several laboratories. Chapter 1 discussed the work from the St Louis laboratory, which focused on the unraveling of the older literature and the development of reliable one-step methods for calixarene synthesis. The present chapter has discussed the contribution form the Mainz laboratory where Kämmerer and Böhmer exploited previously introduced linear stepwise methods and invented new convergent methods for calixarene synthesis. In the next chapter the methods for establishing the structures of calixarenes are discussed, bringing to the fore the research group at Parma, Italy.

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[131] F. Weinelt and H.-J. Schneider, *J. Org. Chem.* **1991**, 56, 5527.

[132] H. Konishi, K. Ohata, O. Morikawa and K. Kobayashi, *J. Chem. Soc. Chem. Commun.* **1995**, 309.

CHAPTER 3

Proving the Baskets: The Characterization and Properties of Calixarenes

> *"It always happens that when man seizes upon a neglected and important idea, people inflamed with the same notion crop up all around"*
>
> Mark Twain, *Life on the Mississippi*

In 1975 Rocco Ungaro of the University of Parma in Italy spent a year at the State University of New York in Syracuse as a research associate with Professor Johannes Smid where he was introduced to the new area of crown ether chemistry. Upon returning to his home laboratory in Parma, Ungaro sought a way to combine this nascent field with his earlier interest in phenol/formaldehyde chemistry. Already aware of the papers by Zinke and Cornforth, he and his colleague Andrea Pochini decided that the "cyclic tetramer" should make good "ordered matrices" for attaching crown-ether-type ligands to produce cation binding compounds. Repeating Cornforth's experiments, they were immediately confronted with the complications discussed in Chapter 1. After a year of frustration in trying to deal with the mixtures that are produced by the Zinke-Cornforth procedure they decided in 1977 to enlist the services of another colleague, Giovanni Andreetti, to take advantage of his expertise as an X-ray crystallographer. The collaboration proved most fruitful, and by the end of the year an X-ray structure of Cornforth's lower-melting compound (LBC) had been solved. However, thinking that no one else in the world could possibly be working on the Zinke–Cornforth compounds, they delayed publishing this result until after the 1978 paper by Gutsche and Muthukrishnan[1] revealed the fallacy of this assumption. Starting, then, with the 1979 publication of the crystal structure of the Cornforth LBC compound[2] the group at the University of Parma proceeded to contribute some of the most important advances in the

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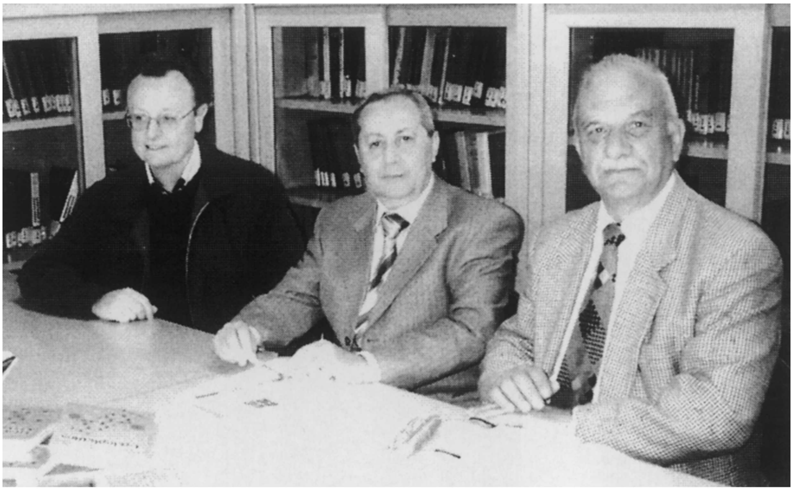
[1] C. D. Gutsche and R. Muthukrishnan, *J. Org. Chem.* **1978**, 43, 4905.

[2] G. D. Andreetti, R. Ungaro and A. Pochini, *J. Chem. Soc. Chem. Commun.* **1979**, 1005.

field of calixarene chemistry. Rocco Ungaro, who has assumed a particularly prominent role in this endeavor, was born in Anzi in Southern Italy, received his advanced degree in 1968 under the guidance of Professor Giuseppe Casnati and has spent most of his professional career at the University of Parma.



Andrea Pochini **Rocco Ungaro** **Giovanni Andreetti**

3.1 Separation and Purification of Calixarenes

For the successful characterization of a compound it is generally necessary to obtain it in pure form. Calixarenes, especially when made by one-step procedures, are often produced as mixtures that require the separation into their components. In some instances, *e.g.* the one-step synthesis of *p*-*tert*-butylcalix[4], [6] and [8]arenes, simple recrystallization suffices. In many other instances, however, chromatographic procedures are necessary, principally HPLC. Figure 3.1 provides an illustrative example in which the many components, ranging from a cyclic tetramer to a cyclic eicosomer, are clearly revealed in the HPLC trace of the product from a *p*-*tert*-butylphenol/formaldehyde reaction.[3] A particularly interesting example of chromatographic separation is the resolution of enantiomers on an enantioselective column.[4] Capillary-zone electrophoresis is another technique, used, for example, in the separation of *p*-sulfanotocalixarenes.[5] A recent procedure employs a diol column used in conjunction with supercritical fluid chromatography.[6]

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[3] D. R. Stewart and C. D. Gutsche, *J. Am. Chem. Soc.* **1999**, 121, 4136.

[4] S. Shinkai, T. Arimura, H. Kawabata, H. Murakami and K. Iwamoto, *Chem. Soc. Perkin Trans 1* **1991**, 2429.

[5] Y. Zhang and I. M. Warner, *J. Chromatogr. A* **1994**, 688, 293.

[6] J. D. Glennon, S. Hutchinson, S. J. Harris, A. Walker, M. A. McKervey and C. C. McSweeney, *Anal. Chem.* **1997**, 69, 2207.

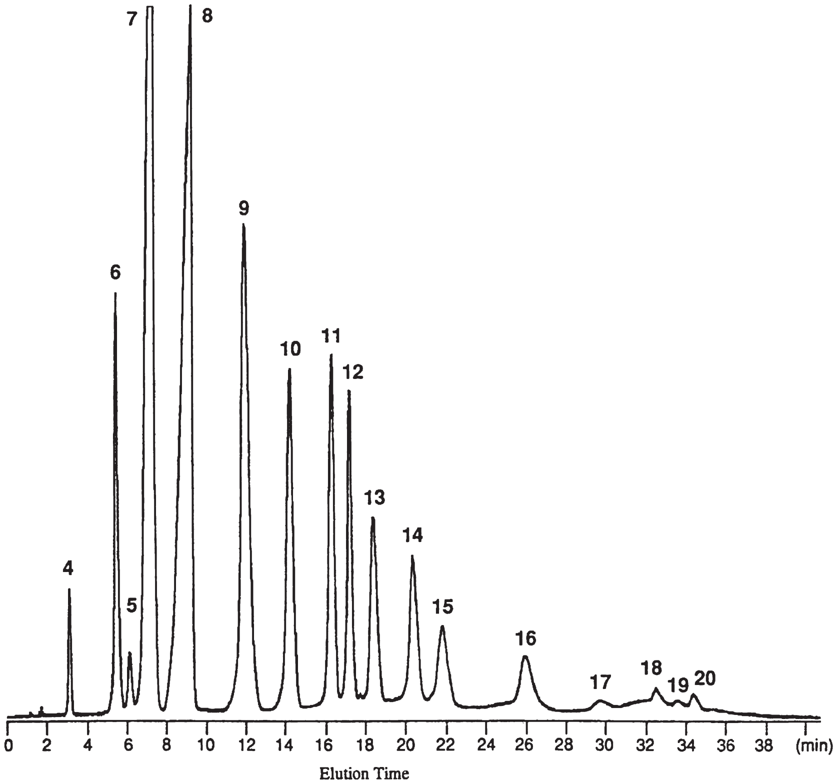

Figure 3.1 HPLC of a *p-tert*-butylcalix[*n*]arene mixture where the numbers above the peaks indicate the value of n.

3.2 X-Ray Crystallography: The Ultimate Proof of Structure

Chemistry, though dealing with materials that generally can be seen and felt, relies on a theory of matter that postulates particles whose existence in most cases must be inferred from indirect observation.[7] With the exception of the scanning tunneling microscope's ability to give a direct view of a few selected atoms and molecules, the closest the chemist can usually come to actually "seeing" molecules is through the wizardry of X-ray crystallography. The way in which this technique has revolutionized our knowledge of the large biomolecules of nature is a well-known and exciting story. Its impact on our knowledge about the structure of smaller molecules, though perhaps less dramatic, is no less important, and in the case of the calixarenes, as with many other "small" molecules, X-ray crystallography provides the conclusive proof

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[7] The atomic and molecular structural theory has been rightly hailed as one of the supreme creations of the human intellect. As David Baltimore (*Daedalus*, **1988**, 117, 335) says "Science as well as art illuminates man's view of himself and his relation to others."

of structure. In the almost four decades since the Parma crystallographic achievement many hundreds of X-ray structures of calixarenes have been obtained, and it has become *de rigueur* to include one or more such structures in current publications in the field. As an historical aside, however, it is worth pointing out that the detailed structures of the calix[4], [6] and [8]arenes were all correctly inferred from existing evidence prior to confirmation by X-ray crystallography.[8]

As already noted, the first example of an X-ray crystallographic structure of a phenol-derived calixarene[9] was the one reported in 1979 by Andreetti, Ungaro and Pochini[2] of the Cornforth LBC compound followed four years later by a structure of Cornforth's LOC compound.[10] Both compounds were shown to possess the cyclic tetrameric structure, as pictured in Figure 3.2 for the LBC compound.

An especially interesting feature of this structure is the presence of a toluene molecule *inside* the cyclic tetramer, calling attention to the ability of calixarenes to form strong inclusion complexes. X-Ray crystallographic confirmation was obtained for *p-tert*-butylcalix[5]arene by the Parma group,[11] but for a number of years *p-tert*-butylcalix[6]arene posed a problem confronting the technology at the time, *viz*. crystals too small. Subsequent improvements in X-ray spectrometers and spectrometry eventually made this a less serious stricture, and Andreetti and coworkers were able eventually to obtain the X-ray structure of the cyclic hexamer[12] as well as the cyclic heptamer.[13] *p-tert*-Butylcalix[8]arene presented a different problem, *viz*. glistening needles that quickly lose their morphology and crumble to a powder. The St Louis group was successful in circumventing this problem by crystallizing the compound from pyridine and maintaining the crystal in a pyridine-saturated atmosphere during the collection of the X-ray reflections by Alexander Karaulov in York, England.[14]

3.3 Physical Properties of Calixarenes

3.3.1 Melting Points

To jump from X-ray crystallography to melting points is to go from one end of the scale of analytical sophistication to the other, from one of the newest

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[8] For example, the structure of *p-tert*-butylcalix[8]arene *via* chemical, osmometric and mass spectral data (R. Muthukrishnan and C. D. Gutsche, *J. Org. Chem.* **1979**, 44, 3962).

[9] X-Ray crystallographic structures of some calix[4]resorcarenes were obtained in the 1960s by Erdtman and coworkers at the Karolinska Institute in Stockholm (H. Erdtman, F. Haglid and R. Ryhage, *Acta. Chem. Scand.* **1964**, 18, 1249; H. Erdtman, S. Högberg, S. Abrahamsson and B. Nilsson, *Tetrahedron Lett*. **1968**, 1679; B. Nilsson, *Acta. Chem. Scand.* **1968**, 22, 732).

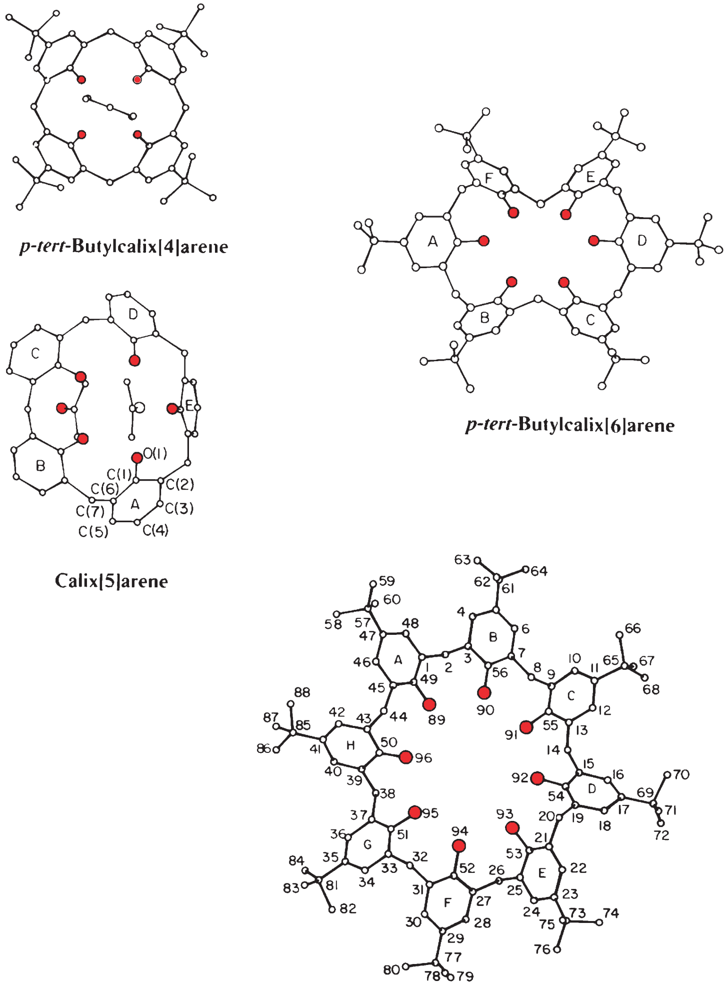
[10] G. D. Andreetti, A. Pochini and R. Ungaro, *J. Chem. Soc. Perkin Trans 2* **1983**, 1773.

[11] M. Coruzzi, G. D. Andreetti, V. Bocchi, A. Pochini and R. Ungaro, *J. Chem. Soc. Perkin Trans 2* **1982**, 1133.

[12] G. D. Andreetti, G. Calestani, F. Ugozzoli, A. Arduini, E. Ghidini, A. Pochini and R. Ungaro, *J. Inclusion Phenom*. **1987**, 5, 123.

[13] G. D. Andreetti, F. Ugozzoli, Y. Nakamoto and S.-I. Ishida, *J. Inclusion Phenom. Molec. Recog. Chem*. **1991**, 10, 241.

[14] C. D. Gutsche, A. E. Gutsche and A. I. Karaulov, *J. Inclusion Phenom*. **1985**, 3, 447.



p-tert-Butylcalix[4]arene

p-tert-Butylcalix[6]arene

Calix[5]arene

p-tert-Butylcalix[8]arene

Figure 3.2 X-ray crystallographic structures of *p-tert*-butylcalixarenes.

techniques to one of the oldest. Melting points, though, have played a significant role in calixarene chemistry, for it was their unusually high values that first attracted Zinke's attention. This is, in fact, a characteristic property of many calixarenes, especially those with free hydroxyl groups where melting points usually are above 250 °C. For example, *p-tert*-butylcalix[4]arene melts at 342–344 °C, *p-tert*-butylcalix[6]arene at 372–374 °C and *p-tert*-butylcalix[8]arene anywhere from 411–412 °C to 418–420 °C. The magnitude and range of the melting point often provides a useful clue to the purity of the calixarene. Alterations in the calixarene structure via derivatization, of course, can greatly affect the melting point, and esters and ethers of calixarenes generally melt lower than the parent compound. For example, the tetramethyl and tetrabenzyl ethers of *p-tert*-butylcalix[4]arene melt at 226–228 °C and 230–231 °C, respectively. But there are exceptions; the tetra-trimethylsilyl ether of *p-tert*-butylcalix[4]arene melts at 411–412 °C and the tetraacetate melts at 383–386 °C.

3.3.2 Solubilities

Another characteristic feature of the calixarenes that caught Zinke's attention is their insolubility in water and aqueous base and their low solubility in organic solvents. In fact, it is this feature that prevented Zinke from obtaining what he considered to be a satisfactory molecular weight, and it is this feature that makes some calixarenes so difficult to isolate, purify and characterize. Fortunately, most calixarenes have sufficient solubility in chloroform, pyridine or carbon disulfide to permit spectral measurements to be made. Conversion of calixarenes to esters or ethers generally increases the solubility in organic solvents, often quite significantly. It has been of particular interest to confer water solubility, and this was first achieved by Ungaro and coworkers,[15] who prepared the tetracarboxymethyl ether of *p-tert*-butylcalix[4]arene (**3.1**), soluble to the extent of 5×10^{-3} to 5×10^{-4} M, depending on the accompanying cation. Calixarenes containing 4–8 aromatic rings and carrying carboxyl groups (**3.2**, **3.3**) or amino groups (**3.5**, **3.6**)[16] in the *para*- positions have solubilities of *ca.* 10^{-3} M in dilute aqueous base or dilute acid, respectively. Considerably more soluble are the sulfonated calixarenes (**3.4**), which were first prepared by Shinkai and coworkers[17] in late 1984 with reported solubilities at least as great as 0.1 M (Figure 3.3).

3.3.3 pK$_a$ Values

The calixarenes are considerably stronger acids than their monomeric phenolic counterparts, but the accurate measurement of their pK values posed some difficulties for the early workers.[18] Using both potentiometric and spectrophotometric methods, Reinhoudt and Shinkai and their respective coworkers measured the pK values in water of calix[4]arenes carrying $SO_2N(CH_2CH_2OH)_2$ or NO_2 groups in the *p*-positions.[19] They compared these values with those of the analogous monomers and trimers, with the results shown in Table 3.1. It is interesting to note that the pK$_1$ values for the linear trimers fall between those of the calix[4]arenes and the monomers and, in the case of the *p*-nitro series, quite close to the former. The unusual ease with which the first

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[15] A. Arduini, A. Pochini, S. Reverberi and R. Ungaro, *J. Chem. Soc. Chem. Commun.* **1984**, 981.

[16] C. D. Gutsche and P. F. Pagoria, *J. Org. Chem.* **1985**, 50, 5795; C. D. Gutsche and I. Alam, *Tetrahedron* **1988**, 44, 4689.

[17] S. Shinkai, K. Araki, T. Tsubaki, T. Arimura and O. Manabe, *J. Chem. Soc. Perkin Trans. 1* **1987**, 2297.

[18] V. Böhmer, E. Schade and W. Vogt, *Makromol. Chem. Rapid Commun.* **1984**, 5, 221; S. Shinkai, K. Araki, H. Koreshi, T. Tsubaki and O. Manabe, *Chem. Lett.* **1986**, 1351.

[19] S. Shinkai, K. Araki, P. D. J. Grootenhuis and D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans. 2* **1991**, 1883.

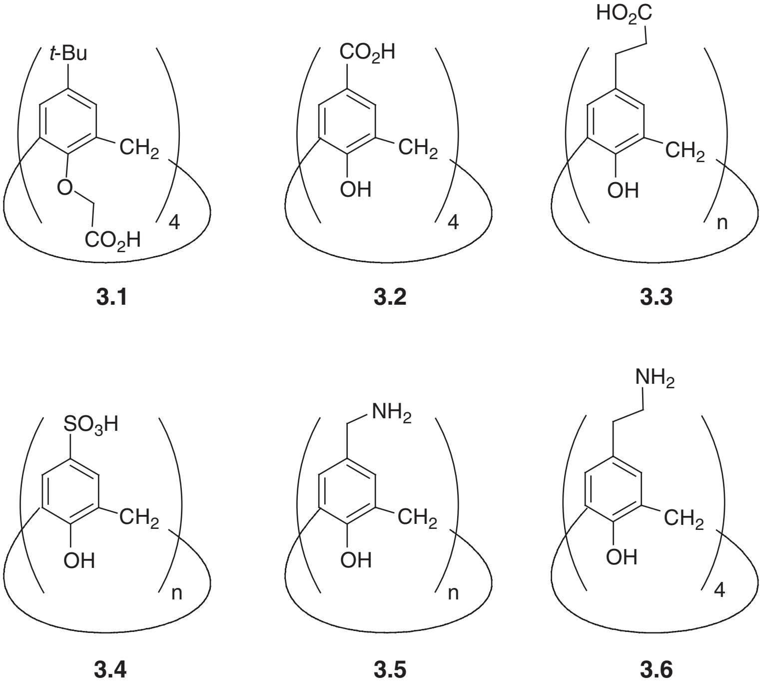

Figure 3.3 Water soluble calixarenes.

Table 3.1 pK values of calix[4]arenes and their linear trimer and monomer counterparts.

Compound	*pK₁*	*pK₂*	*pK₃*	*pK₄*
p-*R*-calix[4]arene[a]	0.8 ± 0.3	9.7 ± 0.1	*ca.* 12.5	> 14
Linear trimer	4.71 ± 0.05	8.27 ± 0.05	11.61 ± 0.1	
Monomer	8.25 ± 0.03			
p-*R*-calix[4]arene[b]	2.9 ± 0.3	10.9 ± 0.1	12.3 ± 0.2	> 14
Linear trimer	3.6 ± 0.1	10.6 ± 0.1	*ca.* 12.5	
Monomer	8.67 ± 0.03			

[a] $R = SO_2N(CH_2CH_2)_2$

[b] $R = NO_2$

dissociation of the calix[4]arenes occurs is attributed to stabilization of the monoanion relative to the parent species. Semi-empirical calculations[20] indicate that the monoanion is strongly hydrogen bonded to its flanking OH groups which, in turn, are stabilized by a bifurcated hydrogen bond with the fourth OH group, as depicted in Figure 3.4. A somewhat analogous stabilization can be achieved with the linear trimers, which accounts for their considerably

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[20] P. D. J. Grootenhuis, P. A. Kollman, I. C. Groenen, D. N. Reinhoudt, G. J. van Hummel, F. Ugozzoli and G. D Andreetti, *J. Am. Chem. Soc.* **1990**, 112, 4165.

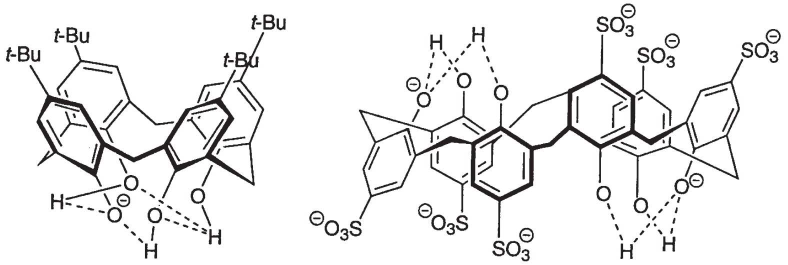

Figure 3.4 Stabilization of calixarene anions.

enhanced acidity. The dissociation of the second proton of the calix[4]arenes, on the other hand, is slightly less facile than that of the corresponding linear trimer. Although calculations indicate that hydrogen bonding still contributes to the stabilization of the dianion,[20] unfavorable electrostatic repulsions appear to be the dominant factor.

Determination of the pK values for the water soluble *p*-sulfonatocalixarenes (*Apndx A-2, p. 445*) has been a particularly thorny problem because of the difficulty in distinguishing between the strongly acidic calixarene OH as well as SO_3H groups. Measurements made in the 1990s give values of 3.26[21] and 3.34[22] for pK_1 and values for pK_2, pK_3 and pK_4 of 12.3, 12.9 and 13.6, respectively. Potentiometric titration (a) of *p*-sulfonatocalix[5]arene[23] gives values of $pK_1 = 4.31$, $pK_2 = 7.63$ and $pK_3 = 10.96$; (b) of *p*-sulfonatocalix[6]arene gives values of $pK_1 = 3.45$[24] (3.44[25]) and $pK_2 = 5.02$[24] (4.76[25]) in a high ionic strength medium; $pK_1=4.16$; $pK_2=5.90$ in a low ionic strength medium; and (c) of *p*-sulfonatocalix[8]arene gives even higher values[24] with $pK_1 = 7.70$ and $pK_2 = 9.10$. The pK_1 in the last case, however, is still somewhat lower than the pK of 8.68 for the OH of *p*-hydroxybenzenesulfonic acid. The enhanced acidity of the calix[6]arene[23] is interpreted in terms similar to those applied to the calix[4]arene, positing two sets of triads with each one forming a monoanion stabilized by adjacent OH groups, as shown in Figure 3.4.

The problem of determining the pK_a values of water insoluble calixarenes has been addressed by Shinkai and coworkers,[26] who used the tetramethylammonium salts of 4-nitrophenol, 2,4-dinitrophenol and 2,4,6-trinitrophenol (picric acid) as the titrants in THF solution. The "apparent pK_1" values for *p-tert*-butylcalix[4], [6] and [8]arene obtained in this fashion are 4.11, 3.62 and

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[21] (a) I. Yoshida, N. Yamamoto, F. Sagara, D. Ishii, K. Ueno and S. Shinkai, *Bull. Chem. Soc. Jpn.* **1992**, 65, 1012.

[22] G. Arena, R. Cali, G. G. Lombardo, E. Rizzarelli, D. Sciotto, R. Ungaro and A. Casnati, *Supramol. Chem.* **1992**, 1, 19.

[23] J. W. Steed, C. P. Johnson, C. L. Barnes, R. K. Juneja, J. L. Atwood, S. Reilly, R. L. Hollis, P. H. Smith and D. L. Clark, *J. Am. Chem. Soc.* **1995**, 117, 11426.

[24] J.-P. Scharff, M. Mahjoubi and R. Perrin, *New J. Chem.* **1991**, 15, 883.

[25] J. L. Atwood, D. L. Clark, R. K. Juneja, G. W. Orr, K. D. Robinson and R. L. Vincent, *J. Am. Chem. Soc.* **1992**, 114, 7558.

[26] K. Araki, K. Iwamoto, S. Shinkai and T. Matsuda, *Bull. Chem. Soc. Jpn.* **1990**, 63, 3480.

4.05, respectively. As a reference point, the pK_a of *p-tert*-butylphenol was determined by this method to be 10.9, while those of a linear dimer, trimer and tetramer are 7.92, 6.9 and 5.3, respectively. The pK_a values for *p*-nitrocalix[8]-arene have been determined to be $pK_1 < 0$, $pK_2 = 2.6$, $pK_3 = 7.2$, $pK_4 = 10.2$ and $pK_{5-8} > 12$.[27] In rather similar fashion the pK values for *p-tert*-butyl-calix[4,6,8]arenes in acetonitrile have been established as:[28] $pK_1 = 19.06$, $pK_2 > 33$ for the cyclic tetramer; $pK_1 = 15.59$, $pK_2 = 23.85$, $pK_3 > 33$ for the cyclic hexamer; $pK_1 = 17.20$, $pK_2 = 20.32$, $pK_3 > 33$ for the cyclic octamer.

The acidities of calix[4]arenes carrying fewer than four OH groups on the *endo* rim have been measured in several systems. By means of 4-nitrophenolate titration in THF the pK_a values for the monomethyl, dimethyl and trimethyl ethers of *p-tert*-butylcalix[4]arene[26] have been determined to be 6.95, 12.2 and 12.5, respectively, although there is some question about the first of these values which ranged downward to 3.98 when picrate was used as the titrant. Picrate titration of the A,C-diamino-*p-tert*-butylcalix[4]arene in THF[29] indicated an apparent pK_a value of 9.17 for the dissociation of the first OH group, *ca.* 5 pK units higher than the value of 4.11 for pK_1 for *p-tert*-butylcalix[4]arene determined in the same fashion. Spectrophotometric titration of the mono-benzoate of *p-tert*-butylcalix[4]arene using hydroxide in ethanol/water[30] gave $pK_1 = 6.84$, $pK_2 = 12.14$ and $pK_3 > 14$.

With one exception, each calixarene discussed above carries an identical substituent in the *p*-positions (*tert*-butyl, SO_3H, $SO_2(NEt_2)_2$ or NO_2). Using the fragment condensation synthesis Böhmer and coworkers prepared calix[4] and [5]arenes carrying a NO_2 group in only one of the *p*-positions (the other *p*-substituents are methyl and/or *tert*-butyl groups). The *p*-nitro group insures that its phenolic unit will be the most easily deprotonated, and it also confers a spectroscopic advantage in the determination of the pK_1 values which are 3.95 for the cyclic tetramer[31a] and 4.02 for the cyclic pentamer[32] in methoxyethanol/water (9:1) solution. Both values are more than 2 pK units lower than those of the corresponding linear trimers carrying a *p*-nitro group on the central phenolic unit, a result that is considered to be consistent with a stabilization of the monoanion *via* two chains of consecutive intramolecular hydrogen bonds.

With the entry of the thiacalixarenes into the calixarene family, these compounds have been subjected to the same range of studies as their methylene analogues, including the measurement of their acidities. Miyano and coworkers[33] have determined the following pK values in aqueous solution: for *p*-sulfonatothiocalix[4]arene $pK_1 = 2.18$, $pK_2 = 8.45$ (overlapping $pK_3 = 11.99$

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[27] J.-C. G. Bünzli and F. Ihringer, *Inorg. Chem. Acta* **1996**, 246, 195.

[28] I. D. Cunningham and M. Woolfall, *J. Org. Chem.* **2005**, 70, 9248.

[29] K. Araki, H. Murakami, F. Ohseto and S. Shinkai, *Chem. Lett.* **1992**, 539.

[30] K. B. Ray, R. H. Weatherhead, N. Pirinccioiglu and A. Williams, *J. Chem. Soc. Perkin Trans 2* **1994**, 83.

[31] (a) M. Backes, V. Böhmer, G. Ferguson, C. Grüttner, C. Schmidt, W. Vogt and K. Ziat, *J. Chem. Soc. Perkin Trans 2* **1997**, 1193; (b) C. Schmidt, M. Kumar, W. Vogt and V. Böhmer, *Tetrahedron* **1999**, 55, 7819.

[32] C. Schmidt, J. M. Kumar, W. Vogt and V. Böhmer, *Tetrahedron* **1999**, 55, 7819.

[33] H. Matsumiya, Y. Terazono, N. Iki and S. Miyano, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1166.

Table 3.2 Dipole moments of calix[4]arenes.

Endo rim	*Exo rim*	*Conformation*	*Dipole moment, D*
OH	*tert*-Bu	Cone	4.19
OPr	NO_2	Cone	13.8
OPr	NO_2	Partial cone	6.7
OPr	NO_2	1,3-Alternate	0.0
OAc	*tert*-Bu	Partial cone	2.57
OAc	*tert*-Bu	1,2-Alternate	2.21
OAc	*tert*-Bu	1,3-Alternate	1.58
OH/OMe	*tert*-Bu	Pinched cone	3.75

and $pK_4 = 11.62$); for *p*-sulfonatosulfonocalix[4]arene pK_1 is too low to measure, $pK_2 = 1.28$ (overlapping $pK_3 = 4.60$ and $pK_4 = 4.42$). The modest acidity-enhancing influence of sulfur bridges (as compared with methylene bridges) and the very strong acidity-enhancing influence of sulfone bridges are clearly expressed in these data.

3.4 Dipole Moments of Calixarenes

A comprehensive study of dipole moments includes data for nine calix[4]arenes[34,35] with examples of each of the four "up-down" conformations, as shown in Table 3.2. As anticipated from simple inspection of molecular models, the sequence of decreasing dipole moment is cone > partial cone > 1,2-alternate > 1,3-alternate.

A computational study[36] affirms the sequence of decreasing dipole moment as cone > partial cone > 1,2-alternate > 1,3-alternate but yields a value of only 0.46 D for *p*-*tert*-butylcalix[4]arene and values of 1.46, 6.4 and 12.6 for the cone conformers of calix[4]arene, *p*-bromocalix[4]arene and *p*-cyanocalix[4]arene, respectively.

3.5 Spectral Properties of Calixarenes

3.5.1 Infrared Spectra

One of the especially distinctive features of the calixarenes is the unusually low frequency at which the stretching vibration of the OH group occurs in the infrared, ranging from 3179 $cm^{-1}$for the cyclic tetramer and 3190 cm^{-1} for the cyclic octamer to 3300 cm^{-1} for the cyclic pentamer, with the other calixarenes falling in between these extremes. This is the result of the very strong

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[34] J. deMendoza, P. Prados, N. Campillo, P. M. Nieto, C. Sánchez, J.-P. Fayet, M. C. Vertut, C. Jaime and J. Elguero, *Recl. Trav. Chim. Pays-Bas* **1993**, 112, 367.

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[36] K. Iwamoto, A. Ikeda, K. Araki, T. Harada and S. Shinkai, *Tetrahedron Lett.* **1993**, 49, 9937.

intramolecular hydrogen bonding[37] in these molecules, sometimes called[38] "circular hydrogen bonding." It is interesting to note that low stretching frequencies are also observed for linear phenol-formaldehyde oligomers,[39] presumably because of the formation of pseudocalixarenes and/or hemicalixarenes (see Figure 2.8, p 55).

The IR "fingerprint" regions for the calixarenes look rather similar to one another, especially between 1500 cm^{-1} and 900 cm^{-1}. In the 900–500 cm^{-1} region the patterns vary to some extent, with certain lines appearing to be characteristic of a particular calixarene, *e.g.* 693 cm^{-1} and 571 cm^{-1} for the cyclic pentamer, 762 cm^{-1} for the cyclic hexamer, 796 cm^{-1} for the cyclic heptamer, and a less-well-resolved set of lines at 600–500 cm^{-1} for the cyclic octamer.

3.5.2 Ultraviolet Spectra

The linear as well as the cyclic oligomers have a pair of absorption maxima at 280 and 288 nm ($CHCl_3$ or dioxane solvent) in the ultraviolet region. In the latter case the ratio of the absorptivities at these two wavelengths is a function of the ring size, ranging from *ca.* 1.3 for the cyclic tetramers to *ca.* 0.75 for the cyclic octamers, as shown in Table 3.3. Although reactions today are generally monitored by means of TLC, HPLC or ^1H NMR measurements, UV has been used on occasion for this purpose. Cornforth and coworkers[40] followed the course of the oxyalkylation of calixarenes by noting the disappearance of

Table 3.3 UV spectra of calix[*n*]arenes ($n = 4$–8).

R Group	*Ring Size*	*280 nm ± 1*	*288 nm ± 1*	*Solvent*	*Ref*
all *tert*-butyl	4	9,800	7,700	$CHCl_3$	41
all methyl	4	10,500	8,300	Dioxane	42c
methyl & *tert*-butyl	5	14,030	14,380	Dioxane	42g
all -*tert*-butyl	6	15,500	17,040	$CHCl_3$	41
methyl & *tert*-butyl	6	16,450	17,330	Dioxane	42f
methyl & *tert*-butyl	7	19,800	20,900	Dioxane	42e
all *tert*-butyl	8	23,100	32,000	$CHCl_3$	41

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[37] S. W. Keller, G. M. Schuster and F. L. Tobiason, *Polym. Mater. Sci. Eng.* **1987**, 57, 906; V. L. Furer, E. I. Borisoglebskaya, V. V. Zverev and V. I. Kovalenko, *Spectrochimica Acta A* **2005**, 62, 483.

[38] W. Saenger, C. Betzel, B. Hingerty and G. M. Brown, *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 883.

[39] T. Cairns and G. Eglinton, *Nature* **1962**, 196, 535.

[40] J. W. Cornforth, E. D. Morgan, K. T. Potts and R. J. W. Rees, *Tetrahedron* **1973**, 29, 1659.

[41] D. R. Stewart. Ph.D. Thesis, Washington University, St Louis, 1995.

[42] (a) H. Kämmerer, G. Happel and F. Caesar, *Makromol. Chem.* **1972**, 162, 179 (b) G. Happel, B. Mathisasch and H. Kämmerer, *ibid.* **1975**, 176, 3317; (c) H. Kämmerer and G. Happel, *ibid.* **1978**, 179, 1199; (d) H. Kämmerer, G. Happel, V. Böhmer and D. Rathay, *Monatsh. Chem.* **1978**, 109, 767; (e) H. Kämmerer and G. Happpel, *Makromol. Chem.* **1980**, 181, 2049; (f) *idem, ibid.* **1981**, 112, 759; (g) H. Kämmerer, G. Happel and B. Mathiasch, *ibid.* **1981**, 182, 1685; (h) H. Kämmerer and G. Happel in *Weyerhauser Science Symposium on Phenolic Resins. 2*, Tacoma, Washington, **1979**. Weyerhauser Publishing Co., Tacoma, **1981**, p. 143.

the absorption at 300 nm (characteristic of the free phenol) and the growth of the absorption at 270–290 nm arising from the ether.

3.5.3 NMR Spectra

When calixarenes re-emerged in the 1970s NMR spectroscopy had become one of the most important analytical tools available to the organic chemist, and the utility of this powerful technique is nicely exemplified by the observation of the difference in the ^{13}C NMR spectra of the linear and cyclic oligomers, as shown in Figure 1.4, p 22. Because of the symmetry of the cyclooligomers their spectra, regardless of ring size, are less complex than those of their acyclic counterparts. In the case of the *p*-*tert*-butyl cyclooligomers the spectra show four resonance lines arising from the aromatic carbons, one line from the methylene carbons and two lines from the *tert*-butyl carbons. While this simple spectrum is not an infallible proof of structure of a calixarene, it does provide a valuable and easily obtained structural clue.

The ^{1}H NMR spectra of the symmetrically substituted calixarenes are similarly uncomplicated such as the one for *p*-*tert*-butylcalix[4]arene at room temperature as illustrated in Figure 3.5. The resonances from the aromatic protons, the *tert*-butyl protons and the hydroxyl protons all are singlets, and that from the CH_2 protons is a pair of doublets at room temperature. As Kämmerer first showed,[42a] however, the pair of doublets pattern changes to a sharp singlet at ca 60 °C as the result of the conformational flexibility of the molecule. On the basis of NOE experiments and the shift induced by pyridine as a solvent, Ungaro and coworkers[43] assigned the higher field doublet to the

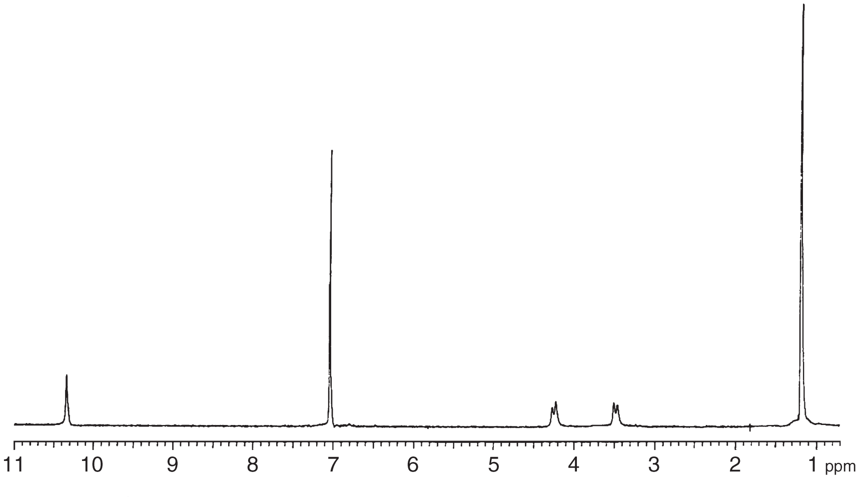

Figure 3.5 ^{1}H NMR spectrum of *p*-*tert*-butylcalix[4]arene at 20 °C in $CDCl_3$.

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[43] A. Arduini, A. Pochini, S. Reverberi and R. Ungaro, *J. Chem. Soc. Chem. Commun.* **1984**, 981.

equatorial protons (closer to the aromatic rings) and the lower field doublet to the axial protons (closer to the hydroxyl groups). Gutsche and coworkers[44] demonstrated that calix[8]arenes behave in a comparable fashion but that calix[6]arenes show only a singlet resonance at room temperature and must be taken to a lower temperature before a splitting pattern emerges. The calix[4] and [8]arenes can be differentiated from one another[45] by the fact that in pyridine solution the calix[4]arene retains a pair of doublets at 0 °C whereas the calix[8]arene shows only a singlet even at temperatures as low as –90 °C. The conformational implications of these data are discussed in the following chapter.

The position of the resonances arising from the hydroxyl groups provides valuable information concerning the shapes of the molecules, a point that is discussed in more detail in the next chapter. For the parent calixarenes listed in Table 3.4 the δ_{OH} value is taken to be a measure of the strength of intra molecular hydrogen bonding, the greater the value the stronger is the hydrogen bond. Thus, intramolecular hydrogen bonding is particularly strong in the calix[4] and [6]arenes, slightly less so in the calix[8]arene and still less so in the calix[5] and [7]arenes. It is interesting to note that for a number of the very large calixarenes ($n > 8$) there are several OH resonances, and a similar situation exists for a calix[6]arene at low temperatures.

^{13}C NMR spectra have been brought to bear on the conformational identification of calix[4]arenes by de Mendoza and coworkers,[46a] who have shown that the resonance arising from the bridge methylene carbon is near δ 31 when the attached aryl groups are in the *syn* orientation (*i.e.* both groups "up" or both groups "down")[46] and near δ 37 when they are in the *anti* orientation (*i.e.* one group "up" and one group "down"). The application of the "de Mendoza rule" has been extended to calix[5]arenes[47] and calix[6]arenes[48] where it appears to be applicable with reasonable accuracy. Another ^{13}C NMR rule has been proposed by Pappalardo and coworkers, which states that the OCH_2 resonances of pyridylmethyl ethers appear at *ca.* $\delta = 71$ when both adjacent aryl moieties are *anti* to one another and at $\delta = 77$ when they are *syn*.[49] An ^{17}O NMR investigation of calix[4]arene and calix[6]arene yields values supporting the stronger hydrogen bonds in the former.[50] The ^{1}H NMR and ^{13}C NMR

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[44] C. D. Gutsche, B. Dhawan, K. H. No and R. Muthukrishnan, *J. Am. Chem. Soc.* **1981**, 103, 3782; *idem*, *ibid.* **1984**, 106, 1891.

[45] C. D. Gutsche and L. J. Bauer, *Tetrahedron Lett.* **1981**, 22, 4763.

[46] (a) C. Jaime, J. de Mendoza, P. Prados, P. M. Nieto and C. Sanchez, C. *J. Org. Chem.* **1991**, 56, 3372; (b) With A,C-diesters in the cone conformation the resonance position is closer to δ 33–34 (J. O. Magrans, J. de Mendoza, M. Pons and P. Prados, *J. Org. Chem.* **1997**, 62, 4518; also *cf.* S. K. Sharma and C. D. Gutsche, *Synthesis* **1995**, 813.

[47] D. R. Stewart, M. Krawiec, R. P. Kashyap, W. H. Watson, W. H and C. D. Gutsche, *J. Am. Chem. Soc.* **1995**, 117, 586.

[48] S. Kanamathareddy and C. D. Gutsche, *J. Org. Chem.* **1994**, 59, 3871.

[49] S. Pappalardo, L. Giunta, M. Foti, G. Ferguson, J. F. Gallagher and B. Kaitner, *J. Org. Chem.* **1992**, 57, 2611.

[50] G. Cerioni, S. E. Biali and Z. Rappoport, *Tetrahedron Lett.* **1996**, 37, 5797.

relaxation times for calix[4], [6] and [8]arenes have been measured[51] as well as the ^{23}Na longitudinal magnetization recovery times for some Na^+ complexes.[52] Solid state ^{13}C NMR measurements (^{13}C CPMAS NMR) on parent calixarenes and some of their ethers[53] generally corroborate the solution state conformations, and similar measurements on complexes of *p*-*tert*-butylcalix[4]arene with alkylbenzenes have been used to establish their structures.[54]

3.5.4 Mass Spectra

Molecular weight determinations of calixarenes have played a crucial role ever since the first report of Zinke in 1941. Restricted in the early days to cryoscopic or ebulloscopic methods, the low solubility of the calixarenes posed a serious problem. As discussed in Chapter 1, this resulted in missed opportunities at correct assignments. With the advent of good osmometers fairly accurate molecular weights could be determined with small amounts of quite insoluble materials, and this technique provided the St Louis group with valuable data in the early 1970s. Today, however, the most generally useful and powerful tool for obtaining molecular weights is the mass spectrometer, enhanced now by a number of new techniques.

The first mass spectral determination of a calixresorcarene was carried out in 1964 by Erdtman and coworkers[60] at the Karolinska Institute in Stockholm, one of the early centers for mass spectrometry. Using the octamethyl ether of C-methylcalix[4]resorcarene, they observed a molecular ion signal at m/e 656, providing confirmation of the cyclic tetrameric structure postulated by Niederl 25 years earlier. When the re-investigation of the phenol-derived calixarenes began in the 1970s mass spectrometry also played a useful role, although sometimes with misleading information. As already discussed in Chapter 1, a case in point is the mass spectrum of *p*-*tert*-butylcalix[8]arene, which shows a strong signal at m/e 648, in exact agreement with a cyclic tetramer. In fact, for several years this datum was accepted as support for a cyclic tetrameric structure of the cyclooligomer produced by the Standard Petrolite Procedure. The appearance of weak signals at m/e greater than 648, however, was

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[60] H. Erdtman, F. Haglid and R. Ryhage, *Acta. Chem. Scand.* **1964**, 18, 1249.

Table 3.4 Melting points, IR stretching frequencies and NMR resonances for O–H bond in calixarenes.

Compound	*mp, °C*	ν_{OH}*, cm*$^{-1}$	δ_{OH}	*Ref*
p-tert-Butylcalix[4]arene	342–344	3160[a]	9.60, 10.34	55, 26
p-Sulfonatocalix[4]arene		3232, 3411	5.52[b]	24
p-tert-Butylcalix[5]arene	310–312	3285	9.64	3
p-tert-Butylcalix[6]arene	380–381	3150	10.2, 10.53	55, 26
p-Sulfonatocalix[6]arene		3393[c]	5.13[b]	24
p-tert-Butylcalix[7]arene	249 (dec 290)	3180	9.60 10.34	3
p-tert-Butylcalix[8]arene	411–412 (418–420)	3230, 3190	9.60	55, 26
p-Sulfonatocalix[8]arene		3242, 3426	4.78[b]	24
p-tert-Butylcalix[9]arene	317–318		9.78	3
p-tert-Butylcalix[10]arene	308–310		9.24	3
p-tert-Butylcalix[11]arene	200–250		9.50	3
p-tert-Butylcalix[12]arene	294–295		9.53	3
p-tert-Butylcalix[13]arene	313–314		9.45	3
p-tert-Butylcalix[14]arene	317–320		9.32	3
p-tert-Butylcalix[15]arene	227–295		9.13	3
p-tert-Butylcalix[16]arene	310–312		9.02	3
p-tert-Butylcalix[17]arene			9.02	3
p-tert-Butylcalix[18]arene			8.98	3
p-tert-Butylcalix[19]arene			9.06	3
p-tert-Butylcalix[20]arene	290–292		8–10	3
Monodeoxy *p-tert*-butylcalix[4]arene			7.5[d]	56
p-tert-Butylhexahomo trioxacalix[3]arene		3369	8.57	57

[a] Values of 3150 cm^{-1} for the solid state spectrum at 300 °K and 3190 and 3140 cm^{-1} for spectra measured in CS_2 and CCl_4, respectively, have been reported.[58]

[b] Value for rapidly exchanging OH/SO_3H in D_2O.

[c] Values of 3165 and 3150 cm^{-1} for spectra measured in CS_2 and CCl_4, respectively, have been reported.[59]

[d] At –90 °C the value is δ 8.8.

disturbing and suggested that something was amiss. Continuing attention to this puzzle eventually led to the preparation of a trimethylsilyl derivative which showed a very strong signal at m/e 1872 (corresponding to a cyclic octamer) along with a slightly weaker signal at m/e 936 (corresponding to a cyclic tetramer). The latter could arise either from a di-cation or from conversion in the ion beam of the cyclic octamer to the cyclic tetramer.

Kämmerer and coworker[42a,c,g,h] reported mass spectral data for many of the *p*-alkylcalixarenes synthesized by the stepwise method, including a calix[7]arene which showed a parent ion at m/e 883, in accord with a cyclic heptamer. They observed[42h] that the cyclic oligomers generally lose the *p*-alkyl groups while conserving their ring structure, whereas the linear oligomers preferentially cleave into their phenolic units. They noted,[43h] however, that a calix[5]arene extruded a phenolic unit and showed the strongest signal at m/e 480, corresponding to the cyclic tetramer. Even the cyclic tetramer, though, can also suffer fragmentation, and signals corresponding to the extrusion of one, two and three phenolic units are observed.

3.6 Concluding Remarks

One of the principal tasks of chemistry is to separate mixtures of chemical species in order to purify and characterize the individual components, because insight into chemical phenomena is usually gained far more easily with pure, well-defined compounds. The phenol-derived calixarenes started life as mixtures, yielding only slowly to complete and correct analysis after many twists and turns along the way. It is instructive to compare calixarene chemistry with cyclodextrin chemistry, where a rather similar situation prevailed. Cyclodextrins, which nature produces as mixtures of cyclooligomers, remained laboratory curiosities for half a century until procedures were developed in the 1950s for their separation, purification and conclusive identification. Once they became readily available they proved to be attractive substances for study, and the literature of these compounds is now so extensive that it constitutes a well-defined sub-discipline of chemistry. Calixarenes have now reached a similar stage of development,[61] the result of the easy availability of pure cyclooligomers which has attracted an army of researchers to the field.

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[61] The calixarenes have been described as "the third generation of supramolecules", following the crown ethers and the cyclodextrins (S. Shinkai, *Tetrahedron* **1993**, 49, 8933).

CHAPTER 4

Shaping the Baskets: Conformations of Calixarenes

"A round man cannot be expected to fit into a square hole right away. He must have time to change his shape"

Mark Twain, *More Tramps Abroad*

Symmetry holds a special fascination for most people and has even been a dominant theme and guiding principle in cultures such as that of ancient Greece. Certainly, some of our fascination with chemistry derives from the symmetry of many of its structures, as witness the beautiful cycles that characterize crown ethers and cyclodextrins. Calixarenes share this beauty, and the name "calixarene" was chosen because of the vase-like shape of the cyclic tetramer in the cone conformation. It turns out, though, that the cyclic tetramer is amoeboid in character and can exist not only as a vase but as several other shapes as well. Calixarenes containing more than four aromatic rings are even more protean in character and can assume an increasingly wider variety of forms. This chapter deals first with the ease with which transformations occur among the available shapes of the parent calixarenes (*i.e.* those molecules containing free intraannular or extraannular OH groups). It then considers calixarenes in which these transformations are constrained in one way or another leading to various conformational consequences.

4.1 Conformational Representation and Nomenclature

The calix[4]arenes were first recognized by Cornforth[1] as being capable of assuming four conformations, with various numbers of aryl groups projecting

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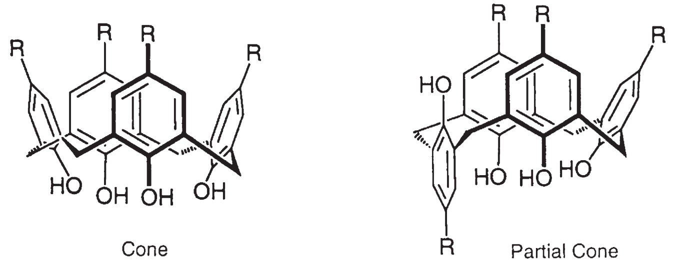
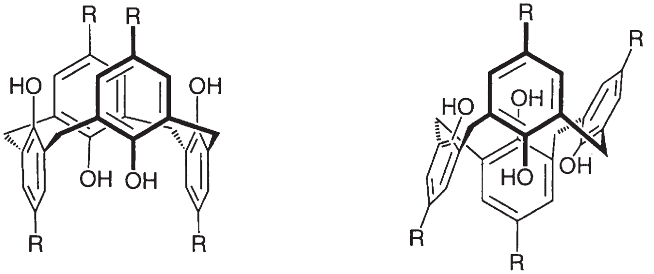
[1] J. W. Cornforth, P. D'Arcy Hart, G.A. Nicholls, R. J. W. Rees and J. A. Stock, *Br. J. Pharmacol.* **1955**, 10, 73.



Cone
u,u,u,u

Partial Cone
u,u,u,d



1,3-Alternate
u,d,u,d

1,2-Alternate
u,u,d,d

Figure 4.1 Conformations of calix[4]arenes.

upward ("u") or downward ("d") relative to an average plane defined by the bridge methylene groups. These conformations were later named by Gutsche[2] as "cone" (u,u,u,u), "partial cone" (u,u,u,d), "1,2-alternate" (u,u,d,d) and "1,3-alternate" (u,d,u,d), as illustrated in Figure 4.1. As the number of aryl groups in the cyclic array escalates, the number of conformations likewise escalates. While calix[5]arenes, like the calix[4]arenes, have only four true "up-down" conformers, calix[6]arenes have eight, calix[8]arenes have sixteen, *etc.* Additionally, with all of the calixarenes there can be departures from the true up/down orientations. For example, the aryl rings can project outward ("o"), and the likelihood of outward projecting aryl residues increases as the flexibility of the system increases. This adds significantly to the total number of possible conformers and to the task of representing them in a simple pictorial (iconographic) or linear fashion. The "up,down,out" designations[3] suffice reasonably well for the calix[4]arenes, the calix[5]arenes, and to some extent the calix[6]arenes, but beyond this point they lose all precision. When applied to calixarene derivatives such as ethers and esters it is necessary for the "up" and "down" designations to accommodate the manner of substitution. To do this a ***reference aryl group*** is chosen by applying the Cahn–Ingold–Prelog priority rules. For example, a *p*-*tert*-Bu-ArOMe ring takes precedence over a *p*-*tert*-Bu-ArOH

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[2] C. D. Gutsche, B. Dhawan, J. A. Levine, K. H. No and L. Bauer, *Tetrahedron* **1983**, 39, 409.

[3] Other designations that have been employed for the up/down orientation of the aryl groups are "+ and –" and "a and b".

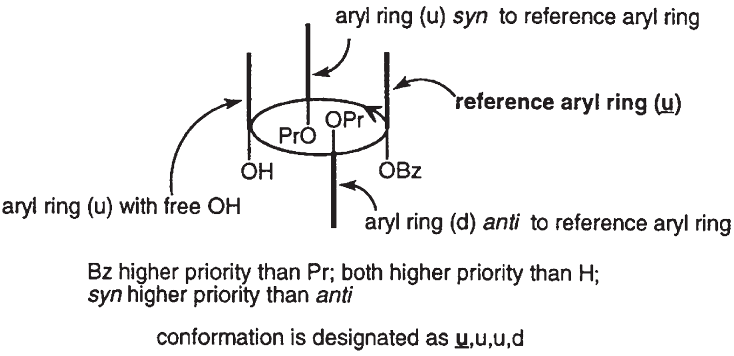

Figure 4.2 "Up/down" designation of an O-substituted calix[4]arene.

ring, a *p-tert*-Bu-ArOH ring takes precedence over a *p*-MeArOH ring, an $ArSO_2$ ring takes precedence over an ArCO ring, *etc*. If two or more aryl rings are identical the one that is flanked by the greater number of higher priority aryl rings is chosen. For example, in the trimethyl ether of *p-tert*-butylcalix[4]arene the ArOMe ring flanked on *both* sides by ArOMe rings is chosen as the reference group. The reference group is indicated by a bold-faced and/or underlined **u** or **d** and in most instances can be arbitrarily assigned an "up" orientation. Since mirror image sequences designate identical constitutions, however, it makes no difference which orientation is chosen unless the absolute configuration of the calixarene is being defined. The other aryl groups in the cyclic array are then designated by proceeding around the ring along the pathway that encounters the groups of higher priority (*i.e.* the "outward exploration" concept of the Cahn–Ingold–Prelog rules). A representative example is depicted in Figure 4.2, where the priority of the rings is established by OBz > OPr > H and the aryl ring *syn* to the reference ring takes precedence over the aryl ring *anti* to the reference ring.

The pictorial depiction of the conformations of calixarenes has been presented in a variety of ways. Representative examples of the pseudo three-dimensional, the iconographic and the linear representations of four of the conformations of a calix[6]arene are shown in Figure 4.3.[4] The iconographic representations, rendered in two dimensions, are derived from the shadow that is projected when light is cast downward from the *exo* rim of the calixarene. A cross-hatched circle denotes a group projecting *toward* the light (a "u" group); a solid circle denotes a group projecting *away* from the light (a "d" group); a circle cross-hatched in the half outside the calixarene ring denotes a group projecting up and outward (a "uo" group); a circle cross-hatched in the half inside the calixarene ring denotes a group projecting up and inward (a "ui" group); a circle solid-filled in the half outside the calixarene ring denotes a group projecting down and outward (a "do" group); a circle solid-filled in the half inside the calixarene

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[4] S. Kanamathareddy and C. D. Gutsche, *J. Am. Chem. Soc.* **1993**, 115, 6572.

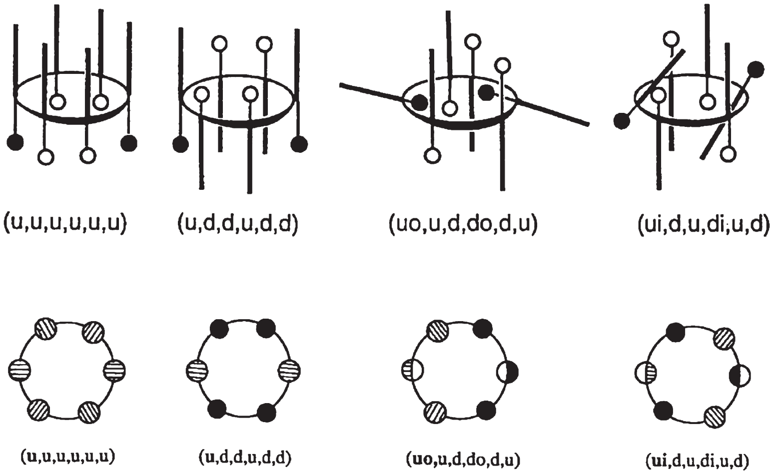

Figure 4.3 Pseudo three-dimensional, iconographic and linear representations of calix[6]arene conformations.

ring denotes a group projecting down and inward (a "di" group); and an unfilled circle denotes a group projecting outward (an "o" group).

The most definitive conformational representation of a calixarene is derived from X-ray crystallography, although even these pictures sometimes fail readily to convey the intended information because of the difficulty of presenting the molecule on the printed page in an orientation suitable for easy visual comprehension. As presaged by Harrowfield and coworkers[5] and then detailed by Ugozzoli and Andreetti,[6] the most critical feature in determining the conformation of a calixarene is the value of the dihedral angles ϕ and χ as defined by the sequences C_1-C_2-C_3-C_4 and C_2-C_3-C_4-C_5, respectively, shown in Figure 4.4. When the two adjacent aryl rings are in the **A**-orientation, the signs of ϕ and χ are the same; when they are in the **B**-orientation, the signs of ϕ and χ are different. For the precise designation of a calixarene conformation the values as well as the signs for all of these dihedral angles must be given. Thus, the four "up/down" conformers of a calix[4]arene can be represented in linear fashion as follows: cone (+ −, + −, + −, + −); partial cone (+ −, + −, + +, − −); 1,2-alternate (+ −, + +, − +, − −); 1,3-alternate (+ +, − −, + +, − −). These can be further refined and, in some cases, condensed by including the Schöenflies point symmetry designation. For example,[7] the symmetrical cone

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[5] J. M. Harrowfield, M. I. Ogden and A. H. White, *Aust. J. Chem.* **1991**, 44, 1237, 1249.

[6] F. Ugozzoli and G. D. Andreetti, *J. Inclusion Phenom. and Molec. Recognit. Chem.* **1992**, 13, 337.

[7] The connection between the "up,down" designations and the Ugozzoli and Andreetti designations is made by focusing on the relative signs as one progresses from one pairwise designation to the next. In a + −, + − sequence the sign changes from − to + and designates an "up" aryl residue (*i.e.* "u"); in a − +, − + sequence the sign changes from + to − and designates a "down" aryl residue (*i.e.* "d"); in a − +, + − sequence the sign remains the same and designates an "up and out" aryl residue (*i.e.* "uo"); in a + −, − + sequence the sign remains the same and designates a "down and out" group (*i.e.* "do").

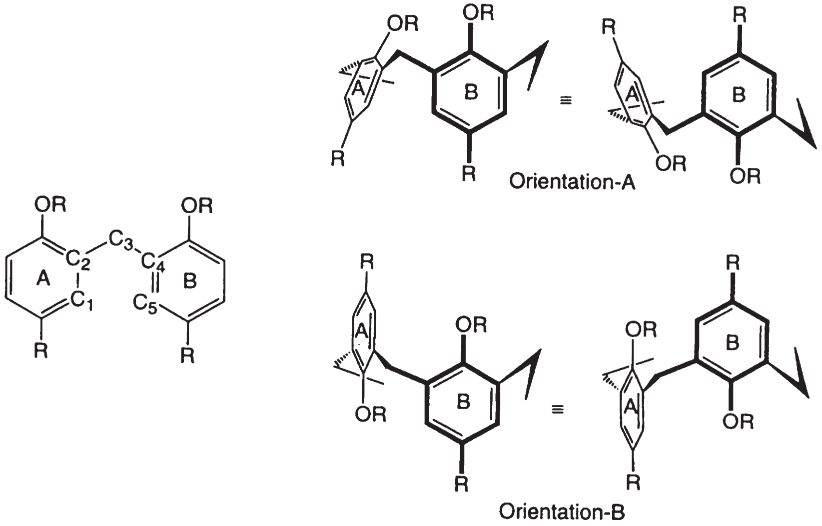

Figure 4.4 Dihedral angles between adjacent aryl groups of a calixarene.

conformation of a calix[4]arene is $C_4 + -$; the distorted cone conformation of a calix[4]arene is $C_2 + -$; the cone conformation of a calix[5]arene lacking symmetry is $C_1 + -, + -, + -, + -, + -$; the pleated loop conformation of *p-tert*-butylcalix[8]arene is $C_4 - +, + -$. In selecting the sequence for the calculations of the *n* pairs of dihedral angles around the macrocyclic ring, the "top side" is defined as containing the maximum number of phenolic oxygens. The sequence of dihedral angles is then obtained by proceeding counterclockwise around the macrocyclic ring. It should be recognized, however, that the "top ring", as defined in this manner, is actually the *endo rim* as defined by the now generally accepted convention (see Figure 1.6, p 26).

4.2 Computational Studies of Calixarene Conformations (*Apndx A-2, p. 280*)

Computational studies of calixarenes have steadily progressed in sophistication and today produce results that are generally in good agreement with experimental values. This was not always the case, however. One of the earliest studies was carried out by the Reinhoudt group[8] and dealt with calculations of structural, energetical and acid-base properties of calix[4]arenes carrying H, Me and *tert*-butyl groups on the *exo* rim and various numbers of OH and OMe groups on the *endo* rim. The results were in generally good agreement with experiment with respect to the relative conformational stabilities, although

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[8] P. D. J. Grootenhuis, P. A. Kollman, I. C. Groenen, D. N. Reinhoudt, G. J. van Hummel, F. Ugozzoli and G. D. Andreetti, *J. Am. Chem. Soc.* **1990**, 112, 4165.

some discrepancies were noted. For example, the stability sequence for the parent calix[4]arene was correctly predicted to be cone > partial cone > 1,2-alternate > 1,3-alternate, but the tetramethyl ether was incorrectly predicted to favor the 1,3-alternate rather than the partial cone conformation. Problems of this sort plagued computational work for several years and inspired studies in which various computational methods were compared, leading one group[9] to declare that "these methods (*i.e.* MM2, AMBER, OPLSA, CHARMm, MOPAC6AM1, MOPAC6PM3, AMPACAM1, AMPACPM3) are ineffective and unreliable computational tools for predicting calixarene conformer stability". The author cautioned "others to refrain from placing too much significance in such computed energies". Happily, the situation has very markedly improved since the time of that publication.

One family of computational studies features molecular mechanics and dynamics calculations as their central focus *per se*,[8,10,11] while another family views these techniques mainly as an adjunct to experimental data[12,13,14,15,16,17] (usually conformation and/or complexation phenomena)[18,19,20] (*Apndx B-12, p. 146*). An extensive study of the conformational energies of the parent calixarenes[21] using the MM3(92) program yielded 4 energy optimized structures for the calix[4]arenes, 10 for the calix[5]arenes, 90 for the calix[6]arenes and 651 for the calix[7]arenes. The lowest energy structure for both the calix[4]arenes and calix[5]arenes was calculated to be the cone conformer, and for the calix[6]arenes and calix[7]arenes the "double cone pinched" conformer. In all of the lowest energy conformers the OH groups form hydrogen bonds with neighboring OH groups and show a regular distance and angle.

A major focus of many of the computational studies of the calixarenes has been on conformational energies, but some attempts have been made to calculate other properties as well. For example, using free energy perturbation

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[9] K. B. Lipkowitz and G. Pearl, *J. Org. Chem.* **1993**, 58, 6729.

[10] (a) T. Harada, J. M. Rudzinski and S. Shinkai, *J. Chem. Soc. Perkin Trans. 2* **1992**, 2109; (b) T. Harada, J. M. Rudzinski, E. Osawa and S. Shinkai, *Tetrahedron* **1993**, 49, 5941; (c) T. Harada, F. Ohseto and S. Shinkai, *ibid.* **1994**, 50, 13377.

[11] I. Thondorf, G. Hillig, W. Brandt, J. Brenn, A. Barth and V. Böhmer, *J. Chem. Soc. Perkin Trans. 2* **1994**, 2259; I. Thondorf and J. Brenn, *ibid.* **1997**, 2293.aq

[12] E. Dahan and S. Biali, *J. Org. Chem.* **1991**, 56, 7269.

[13] J. de Mendoza, P. Prados, N. Campillo, P. M. Nieto, C. Sánchez, J.-P. Fayet, M. C. Vertut, C. Jaime and J. Elguero, *Recl. Trav. Chim. Pays-Bas* **1993**, 112, 367.

[14] P. Neri, M. Foti, G. Ferguson, J. F. Gallagher, B. Kaitner, M. Pons, M. Antónia Molina, L. Giunta and S. Pappalardo, *J. Am. Chem. Soc.* **1992**, 114, 7814.

[15] Z. Goren and S. E. Biali, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1484.

[16] M. Antónia Molina, P. M. Nieto, C. Sánchez, P. Prados, J. de Mendoza and M. Pons, *J. Org. Chem.* **1992**, 57, 6924.

[17] J. K. Moran, E. M. Georgiev, A. T. Yordanov, J. T. Mague and D. M. Roundhill, *J. Org. Chem.* **1994**, 59, 5990.

[18] S. Miyamoto and P. A. Kollman, *J. Am. Chem. Soc.* **1992**, 114, 3668.

[19] P. Guilbaud, A. Varnek and G. Wipff, *J. Am. Chem. Soc.* **1993**, 115, 8298; A. Varnek and G. Wipff, *J. Phys. Chem.* **1993**, 97, 10840; P. Guilbaud and G. Wipff, *J. Inclusion Phenom. and Molec. Recgt.* **1993**, 16, 169.

[20] P. D. Beer, M. G. B. Drew, P. A. Gale, P. B. Lesson and M. I. Ogden, *J. Chem. Soc. Dalton Trans.* **1994**, 3479.

[21] T. Harada and S. Shinkai, *J. Chem. Soc. Perkin Trans. 3* **1995**, 2231.

methods, the relative acidities of *p*-methylcalix[4]arene and an acyclic analogue were calculated.[8] The calixarene was estimated to be the more acidic by 9–11 pK_a units, in qualitative agreement with experimental data (see Section 3.3.3). Dipole moment calculations[22,23] are in quite good agreement with experimentally observed values (see Section 3.5) and correctly predict the sequence to be: cone > partial cone > 1,2-alternate > 1,3-alternate.

4.3 Conformations of Calixarenes in the Solid State

4.3.1 Calix[4]arenes

Calix[4]arenes containing four *endo*-OH groups exist in the cone conformation in the solid state,[24] as previously noted. The first X-Ray structure of a calix[4]arene to show this was that of *p-tert*-butylcalix[4]arene.[25] This observation has since been confirmed with a number of other calix[4]arenes, including those with *p-tert*-octyl,[26] *p*-isopropyl (as a 1:1 toluene complex),[27] *p*-phenyl (as a 1:1 $CHCl_3$ complex),[28] *p*-phenylazo,[29] and *p*-acetyl groups.[30] *p-tert*-Butylcalix[4]arene (as a 1:1 toluene complex) is a cone with almost perfect C_4 symmetry (u,u,u,u), but introduction of four or eight methyl groups onto the positions *meta* to the OH groups[31] causes the cone to change its symmetry from C_4 to approximately C_2 (u,uo,u,uo) to give a conformation variously called "flattened cone", "pinched cone" or "boat".[32] Imposing a bridge between the A,C *p*-positions on the *exo* rim (synthesized by a "2 + 2" convergent synthesis to give **2.21** [$n = 4$–16] on p 45) changes the symmetry in a similar fashion, the magnitude of the change increasing with decreasing values of n.[33] Molecular mechanics calculations[34] on the "annelated" calixarene **2.9** (R^1, $R^2 = H$ on p 43) suggest that it has two conformations nearly equal in energy, one in

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[22] J. de Mendoza, P. Prados, N. Campillo, P. M. Nieto, C. Sánchez, J.-P. Fayet, M. C. Vertut, C. Jaime and J. Elguero, *Recl. Trav. Chim. Pays-Bas* **1993**, 112, 367.

[23] K. Iwamoto, A. Ikeda, K. Araki, T. Harada and S. Shinkai, *Tetrahedron Lett*. **1993**, 49, 9937.

[24] At least one exception has been reported which describes the isolation of two crystalline forms of *p*-hexanoylcalix[4]arene, which, on the basis of CP-MAS ^{13}C NMR spectral measurements, are assigned cone (one C=O resonance) and partial cone (3 C=O resonances) structures (S. Shinkai, T. Nagasaki, K. Iwamoto, A. Ikeda, G.-X He and T. Matsuda, *Bull. Chem. Soc. Jpn*. **1991**, 64, 381).

[25] G. D. Andreetti, R. Ungaro and A. Pochini, *J. Chem. Soc. Chem. Commun*. **1979**, 1005.

[26] G. D. Andreetti, A. Pochini and R. Ungaro, *J. Chem. Soc. Perkin Trans. 2* **1983**, 1773.

[27] M. Ohtsuchi, K. Suzuki, A. E. Armah, Y. Yamagata, S. Fujii, K.-I. Tomita, Z. Asfari and J. Vicens, *Acta. Cryst*. **1993**, C49, 639.

[28] R. K. Juneja, K. D. Robinson, C. P. Johnson and J. L. Atwood, *J. Am. Chem. Soc*. **1993**, 115, 3818.

[29] N. Ehlinger, S. Lecocq, R. Perrin and M. Perrin, *Supramol. Chem*. **1993**, 2, 77.

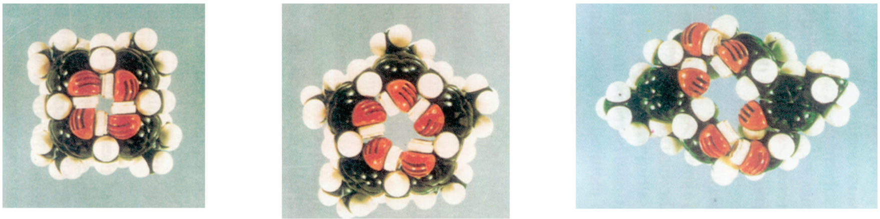
[30] Y. J. Park, K. No and J. M. Shin, *Bull. Korean Chem. Soc*. **1991**, 12, 525.

[31] A. Wolff, V. Böhmer, W. Vogt, F. Ugozzoli and G. D. Andreetti, *J. Org. Chem*. **1990**, 55, 5665; G. D. Andreetti, V. Böhmer, J. G. Jordon, M. Tabatabai, F. Ugozzoli, W. Vogt and A. Wolff, *ibid*. **1993**, 58, 4023; E. Dahan and S. E. Biali, *ibid*. **1989**, 54, 6003.

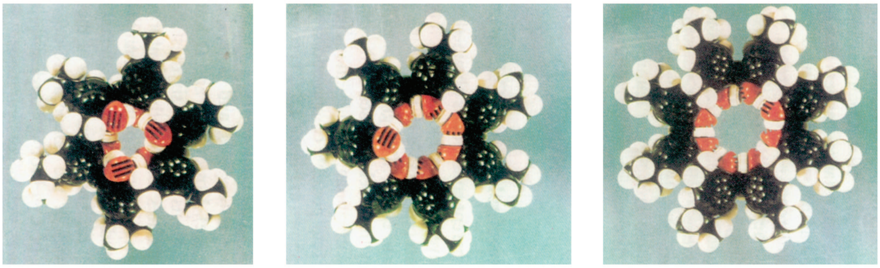
[32] E. Dahan and S. E. Biali, *J. Org. Chem*. **1991**, 56, 7269.

[33] E. Paulus, V. Böhmer, H. Goldman and W. Vogt, *J. Chem. Soc. Perkin Trans. 2* **1987**, 1609.

[34] V. Böhmer, R. Dörrenbächer, M. Frings, M. Heydenreich, D. de Paoli, W. Vogt, G. Ferguson and I. Thondorf, *J. Org. Chem*. **1996**, 61, 549.



p-tert-Butylcalix[4]arene *p-tert*-Butylcalix[5]arene *p-tert*-Butylcalix[6]arene "winged" conformation



p-tert-Butylcalix[6]arene 1,3,5-alternate conformation *p-tert*-Butylcalix[7]arene *p-tert*-Butylcalix[8]arene pleated loop conformation

Figure 4.5 CPK models of the major and minor calixarenes.

which both the *exo* and *endo* portions are cones and the other in which the *endo* part is a cone and the *exo* part is a 1,2-alternate (Figure 4.5).

Calix[4]arenes in which one or more of the OH groups on the *endo* rim are converted to OR groups also frequently exist in the cone conformation in the solid state as, for example, the monomethyl ether,[35] the A,C-dimethyl ether,[8] the trimethyl ether,[8] and the tetramethyl ether[8] of *p-tert*-butylcalix[4]arene. In a number of calix[4]arenes which assume the cone conformation in the solid state, two of the aryl groups are almost parallel to one another while the other two are splayed outward to give the "pinched cone" ("flattened cone") conformation as in the case of the tetrapropyl ether of *p*-A,C-bis(acetamido)calix[4]arene, where both of the pinched cone conformations are present in the solid state, as revealed by X-ray crystallography.[36]

Relatively fewer X-ray structures of calix[4]arenes in the partial cone conformation have been reported, most of them involving tetra-O-substituted compounds such as the tetraethyl[37] and tetrapyridylmethyl[38] ethers of *p-tert*-butylcalix[4]arene. For the tetra-substituted calix[4]arenes, in which two different substituents are attached to the oxygens, two different partial cone

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[35] C. Alfieri, E. Dradi, A. Pochini and R. Ungaro, *Gazz. Chim. Ital.* **1989**, 119, 335.

[36] W. Verboom, R. H. Vreekamp, P. J. Bodewes, S. Harkema and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* **1996**, 115, 402.

[37] (a) K. Iwamoto, K. Araki and S. Shinkai, *J. Org. Chem.* **1991**, 56, 4955; (b) K. Araki, K. Iwamoto, S. Shinkai and T. Matsuda, *Chem. Lett.* **1989**, 1747.

[38] G. Ferguson and J. F. Gallagher, *Acta Crystallographica* **1993**, C49, 1537.

structures are possible depending on which pair of aryl residues are *anti* to one another. In many cases the conformation is more or less distorted from a true partial cone into what is sometimes referred to as a ‘‘flattened partial cone’’ as, for example, the $AlMe_3$ complex of the A,C-dimethyl ether of *p*-*tert*-butylcalix[4]arene,[39] which is described as a ‘‘doubly flattened partial cone’’.

Many examples of 1,3-alternate conformers of calix[4]arenes are known, quite a few of which have been confirmed by X-ray crystallography. Among the earliest are those of 5-allyl-25-methoxy-26,27,28-tribenzylcalix[4]arene[40a] and the $EtAlCl_2$ complex of the tetramethyl ether of *p*-*tert*-butylcalixarene.[40b] It is interesting to note that in the very earliest days of calixarene chemistry in the 1970s, before conformations had been clearly established, it was feared that the calix[4]arenes would always adopt the 1,3-alternate conformation, as was already known to be the case with esters of the calix[4]resorcarenes. Fortunately, this proved unfounded, and the name ‘‘calixarene’’ became a legitimate choice.

Among the four conformations of the calix[4]arenes the least often encountered is the 1,2-alternate. The first reported example[40b] is the complex obtained by treatment of the tetramethyl ether of *p*-*tert*-butylcalix[4]arene with Me_3Al; two more recent examples include the tetraethyl ether[41] and the tetrakis(dimethylthiocarbamoyl) ester of *p*-*tert*-butylcalix[4]arene.[42] Another unusual conformation is that of the $Cr(CO)_6$ complex of the tetra-*n*-propyl ether of calix[4]arene, which is described as a ‘‘bis-roof’’.[43]

Replacement of one or more of the OH groups of *p*-*tert*-butylcalix[4]arene with hydrogens yields a series of OH-depleted calix[4]arenes whose X-ray structures have been determined. The monodeoxy compound (as a pyridine complex)[44] retains the cone conformation in the solid state, whereas the other members of the series assume non-cone conformations, *viz.*1,2-alternate conformations for the A,C-dideoxy compound[44] and the tetradeoxy compound.[44] One, two, three and all four of the OH groups of *p*-*tert*-butylcalix[4]arene have been replaced by SH groups.[42] The monothiol assumes the cone conformation,[42] while the 1,3-dithiol (as a Hg complex),[45] the trithiol[42] and the tetrathiol[46] all assume the 1,3-alternate conformation.

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4.3.2 Calix[5]arenes

X-ray structures of *p*-*tert*-butylcalix[5]arenes have been obtained for the acetone complex,[47] the tetralin complex,[48] the ethyl acetate complex,[49] and the "self" complex.[50] In all of these cases the conformation is a somewhat distorted shallow cone, but when one of the OH groups is replaced by a hydrogen to give a monodeoxycalix[5]arene the conformation changes to a partial cone.[51] Calix[5]arene ethers and esters assume a variety of conformations, depending on the degree and nature of substitution. While the CH_2CO_2Et ether,[52] the 1,2,3-triethers,[53,54] and the monoether[55] all retain a distorted cone conformation (typically u,u,uo,uo,uo), the pentaisopropyl ether is a flattened 1,2-alternate (u,uo,u,d,d) conformation.[55] Several of these compounds show self complexation in which an isopropoxy group or a *tert*-butyl group fills the cavity.

4.3.3 Calix[6]arenes

The conformations of the parent calix[6]arenes have been variously described as distorted cone,[56] compressed cone,[57] pinched cone,[58] double partial cone,[59] winged,[60] 1,2,3-alternate,[61] 1,3,5-alternate and distorted 1,2,3-alternate.[62] A study by Bott and coworkers[61] has shown that the conformation in the solid state is a function of the solvent from which the compound is crystallized. When the solvent (*e.g.* benzene) cannot engage in hydrogen bonding with the OH groups of the calixarene the result is a pinched cone conformation (designated as

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[61] W. J. Wolfgong, L. K. Talafuse, J. M. Smith, M. J. Adams, F. Adeobga, M. Valenzuela, E. Rodriguez, K. Contreras, D. M. Carter, A. Bacchus, A. R. McGuffey and S. G. Bott, *Supramol. Chem.* **1996**, 7, 67.

[62] P. Thuéry, N. Keller, M. Lance, J.-D. Vigner and M. Nierlich, *J. Inclusion Phenom. Molec. Recognit. Chem.* **1995**, 20, 89.

C_2 −+,+−,+−,−+,+−,+− or [uo,u,uo,uo,u,uo]) in which all of the OH groups are intramolecularly hydrogen bonded in a cyclic array. However, when the solvent (*e.g.* acetone, DMSO) can disrupt the intramolecular hydrogen bonding the calixarene assumes a distorted 1,2,3-alternate conformation (designated as C_i +−,−+,−+,−+,+−,+− or [u,u,uo,d,d,do]).

Conversion of all of the OH to OR groups in a calix[6]arene has the same effect as a hydrogen bond breaking solvent, resulting in distorted 1,2,3-alternate conformations.[63] Conversion of only four of the OH groups, however, allows some intramolecular hydrogen bonding to remain, and the solid state conformation becomes u,d,do,d,u,uo (designated by one group of authors as 1,2,4,5-alternate).[14] Conversion of only two OH groups leaves the intramolecular hydrogen bonding even stronger, and the A,C-disubstituted *p*-*tert*-butylcalix[6]arene exists in the pinched cone conformation.[64] The 1,3,5-trimethyl ether has come under particularly close scrutiny, starting with the report from Reinhoudt *et al.*[65] in 1994 and continuing into the present decade.[66] Experimental data as well as theoretical calculations are in agreement with the cone as the most stable conformation in many instances. However, a pentaaluminum complex of calix[6]arene has been shown to exist in the solid state in a conformation in which all six of the oxygen atoms are essentially coplanar,[67] and the solid state structure of calix[6]hexaquinone is best described as a (u,d,o,d,u,o) conformation.[68]

4.3.4 Calix[7]arenes

An X-ray structure of *p*-*tert*-butylcalix[7]arene[69] shows that the molecule adopts a flattened conformation designated as C_i +−,−+,+−,+−,+−,−,− or [u,do,uo,u,u,do,uo]. An X-ray structure of *p*-isopropylcalix[7]arene,[70] on the other hand, shows a conformation that is calculated[20] to be 5.4 kcal/mole less stable and in which two of the phenolic rings are inverted, possibly a consequence of the combined influences of the *para*-substituent and crystal packing forces.

4.3.5 Calix[8]arenes

An early X-ray structure of *p*-*tert*-butylcalix[8]arene crystallized from pyridine showed it to have a "pleated loop" conformation,[71] and rather similar

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[63] R. Ungaro, A. Pochini, G. D. Andreetti and P. Domiano, *J. Inclusion Phenom.* **1985**, 3, 35.

[64] R. G. Janssen, W. Verboom, S. Harkema, G. J. van Hummel, D. N. Reinhoudt, A. Pochini, R. Ungaro, P. Prados and J. de Mendoza, *J. Chem. Soc. Chem. Commun.* **1993**, 506.

[65] J. P. M. van Duynhoven, R. G. Jannsen, W. Verboom, S. M. Franken, A. Casnati, A. Pochini, R. Ungaro, J. de Mendoza, P. M. Nieto, P. M. Prados and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1994**, 116, 5814.

[66] B. Boulet, L. Joubert, B. Cote, C. Bouvier-Capely, C. Cossonnet and C. Adamo, *J. Phys. Chem.* **2006**, 110, 5782.

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[71] C. D. Gutsche, A. E. Gutsche and A. I. Karaulov, *J. Inclusion Phenom.* **1985**, 3, 447.

conformations have been observed for its complexes with calcium and uranyl cations.[72] In another study,[73] however, the X-ray structure of a complex of *p*-*tert*-butylcalix[8]arene with 8 pyridine molecules showed a twisted conformation, similar to the "pinched" conformation suggested in the early 1980s before an X-ray structure had been obtained.[74] Two alkyldiamine complexes of *p*-sulfonatocalix[8]arene crystallize in a pleated loop and inverted double cone conformation, respectively.[75] Complexes of *p*-*tert*-butylcalix[8]arene with various lanthanides[5] also reveal a conformation different from a pleated loop and are approximately described as a 1,2,3,4-alternate structure, Figure 4.6.

4.3.6 Large Calixarenes

Calix[10]arene complexed with acetone assumes a pleated loop conformation, while *p*-*tert*-butylcalix[10]arene complexed with toluene prefers a pinched cone conformation.[77] The conformation of *p*-*tert*-butylcalix[12]arene complexed with 12 molecules of pyridine shows a center of inversion with all of the phenolic groups engaged in hydrogen bonding in a pseudo pleated loop fashion.[78] The preparation of the crystal for this experiment provides a good illustration of the patience often required of X-ray crystallographers, the crystallization time in this instance being a full 180 days. The Perrin group has even succeeded in obtaining the X-ray crystallographic structure of *p*-*tert*-butylcalix[16]arene[79] whose conformation is less easily described than its smaller relatives. However, its structure adheres to the earlier prediction[80] that "calixarenes incorporate as many cone-like and/or pleated loop-like conformational segments as possible", Figure 4.7.

4.4 Conformations of Flexible Calixarenes in Solution

4.4.1 Conformational Mobility of Calix[*n*]arenes

All of the calix[*n*]arenes containing their full complement of free intraannular OH groups are conformationally mobile in solution at room temperature, the degree of mobility varying from one ring system to another.

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[72] J. M. Harrowfield, M. I. Ogden, W. R. Richmond and A. H. White, *J. Chem. Soc. Dalton Trans.* **1991**, 2153; P. Thuéry, N. Keller, M. Lance, J.-D. Vigner and M. Nierlich, *Acta Cryst.* **1995**, C51, 1570; Thuéry, N. Keller, M. Lance, J.-D Vigner, and M. Nierlich, *New J. Chem.* **1995**, 19, 619.

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[78] P. C. Leverd, I. Dumazet-Bonnamour, R. Lamartine and M. Nierlich, *Chem. Commun.* **2000**, 493.

[79] C. Bavoux, R. Baudry, I. Dumazet-Bonnamour, R. Lamartine and M. Perrin, *J. Inclusion Phenom. and Macrocyclic Chem.* **2001**, 40, 221.

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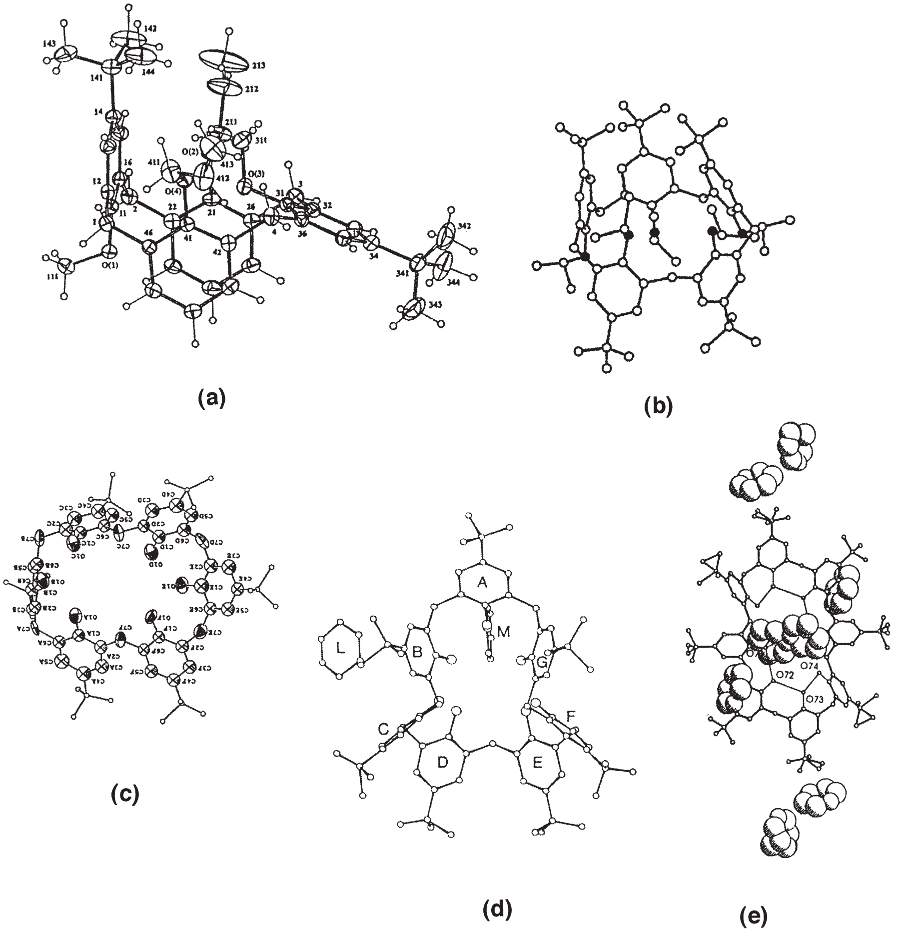
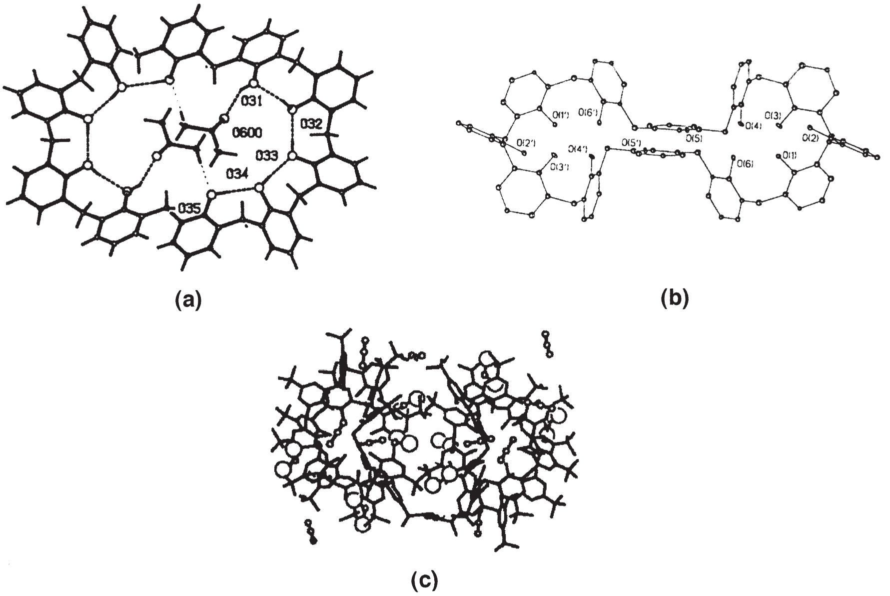


Figure 4.6 Representative examples of X-ray crystallographic structures of the major and minor calixarenes: (a) partial cone conformer of a calix[4]arene;[76] (b) a self-complexed cone conformer of a calix[5]arene;[50] (c) a 1,2,3-alternate conformer of a calix[6]arene;[61] (d) a calix[7]arene with two pyridine molecules;[69] (e) a calix[8]arene with eight pyridine molecules.[73]

4.4.1.1 Conformations of Calix[4]arenes

All four of the conformations for a calix[4]arene shown in Figure 4.1 are accessible by rotations of the aryl groups around the axis that passes through the carbon atoms bonded to the bridging methylene groups. In the days prior to the advent of NMR spectroscopy the magnitude of the barrier to this rotation was overestimated, leading to the postulate of stable conformers. However, as discussed in Chapter 1, the ^{1}H NMR temperature-dependent studies by Kämmerer and coworkers in the 1970s showed that the rate of interconversion is too fast for this to be possible. The applicability of this spectroscopic tool was



(a) (b) (c)

Figure 4.7 X-Ray crystallographic structures of large calixarenes: (a) calix[10]arene complexed with acetone;[77] (b) calix[12]arene;[78] (c) *p-tert*-butylcalix[16]arene.

quickly realized by others,[74,81] and it has become a standard technique for measuring the conformational mobility of calixarenes. With the advent of ever higher field NMR spectrometers coupled with increasingly sophisticated pulse techniques (COSY, NOESY, ROESY *et al.*) it has become one of the most powerful analytical tools available to today's experimenters.

As shown in Figure 4.8, the ^{1}H NMR resonance pattern arising from the methylene protons of a calix[4]arene appears as a pair of doublets at room temperature and as a sharp singlet at higher temperatures (if the spectrum is measured in a non-polar solvent such as $CDCl_3$). This behavior is interpreted in terms of a cone conformation that interconverts slowly on the NMR time-scale at the lower temperature but rapidly at the higher temperature. At the coalescence temperature (where the resonance is a very broad singlet) the rate of interconversion can be calculated to be *ca.* $150\,s^{-1}$ using the relationship $k_{coalescence} = \pi(\Delta\nu^2 + 6J^2)^{1/2}/2^{1/2}$, where $\Delta\nu$ is the difference in chemical shift between the centers of the two doublets arising from the methylene protons and J is the coupling constant. From this value, using the relationship $\Delta G^{\ddagger} = RT \ln(6.62 \times 10^{12}/k_{coalescence})$, the magnitude of the energy barrier in kcal/mole can be calculated. Values of $\Delta G^{\ddagger}$ obtained from the more sophisticated technique of line shape analysis generally agree well with those obtained from the simpler

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[81] C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.* **1985**, 107, 6052.

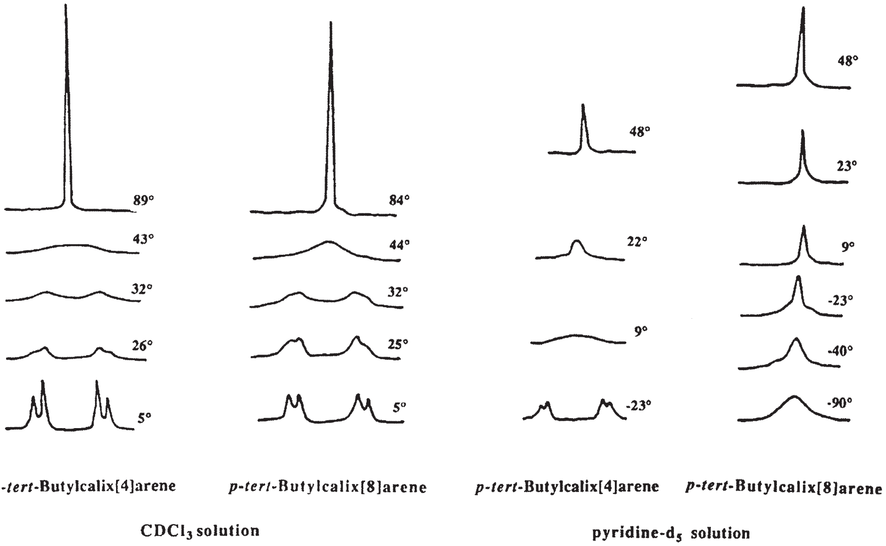

Figure 4.8 Temperature-dependent ^{1}H NMR spectra of *p-tert*-butylcalix[4 and 8]arenes.

method, and they also make possible the assessment of the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values.[10c,82]

As shown in Table 4.1, *p*-substituents including H, alkyl groups, benzoyl and sulfonyl groups have relatively little influence on the conformational mobility. Solvents, on the other hand, can have a significant influence, polar solvents such as pyridine lowering the energy barrier by interfering with the strong intramolecular hydrogen bonding. Likewise, changing the number of OH groups on the *endo* rim lowers the barrier to conformational interconversion.

The subtle question as to whether the cone conformers of calix[4]arenes exist in solution as time-invariant structures with C_4 symmetry or as rapidly interconverting structures with C_2 symmetry, as illustrated in Figure 4.9, has been addressed in some detail.

The first experimental data to suggest rapid interconversion of C_2 structures came from Böhmer's experiments[86] with bridged calix[4]arenes (**2.21** on p 45) in which the ^{1}H NMR resonance for the OH group diminishes from δ10.19 with a 16-methylene bridge to δ 6.93 with a 5-methylene bridge, the result of the increasing distortion imposed on the system by the shorter bridge. Several other experimental observations also appear to support this view, including the effect of Ag^+ on the ^{1}H NMR spectrum[87] as well as the effect of various moieties on

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[82] K. Araki, S. Shinki and T. Matsuda, *Chem. Lett.* **1989**, 581; K. Araki, H. Murakami, F. Ohseto and S. Shinkai, *ibid.* **1992**, 539; T. Harada, F. Ohseto and S. Shinkai, *Tetrahedron* **1994**, 50, 13377.

[83] S. Shinkai, K. Araki, T. Matsuda and O. Manabe, *Bull. Chem. Soc. Jpn.* **1989**, 62, 3856.

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[85] F. Grynszpan and S. E. Biali, *Tetrahedron Lett.* **1991**, 32, 5155.

[86] I. Zetta, A. Wolff, W. Vogt, K. L. Platt and V. Böhmer, *Tetrahedron* **1991**, 47, 1911.

[87] A. Ikeda, H. Tsuzuki and S. Shinkai, *J. Chem. Soc. Perkin Trans. 2*, **1994**, 2073.

Table 4.1 Conformational mobility of calix[4]arenes as influenced by *p*-substituents, *endo* rim substituents and solvent.

p-Substituent	*Endo rim*	*Solvent*	T_c *(°C)*	$\Delta G^{\ddagger}$ *(25 °C) (kcal/mole)*	*Reference*
H	4 OH	$CDCl_3$	36	14.9	81
tert-Butyl	4 OH	$CDCl_3$	60	15.7	81
		C_6D_6	35	15.8	81
		C_5ND_5	15	13.7	81
tert-Octyl	4 OH	$CDCl_3$	30	14.6	81
Phenyl	4 OH	$CDCl_3$	44	15.3	81
Benzoyl	4 OH	$CDCl_3$	33	14.9	81
SO_3Na	4 OH	D_2O		14.1	83
Me_2NCH_2	4 OH	$CDCl_3$	52	15.7	84
tert-Butyl	3 OH, 1 H	$CD_2Cl_2/CDCl_3$	−60	11.6	44
tert-Butyl	2 OH, 2 H	$CDCl_2F$	−71	9.6	85
tert-Butyl	1 OH, 3 H	CD_2Cl_2	−63	9.7	10c
tert-Butyl	4 H	$CDCl_2/CDCl_3$	<-85	<9.5	15

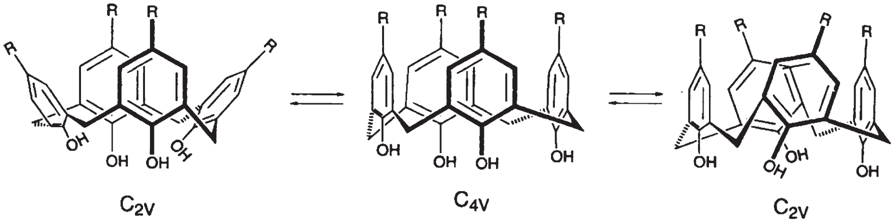

Figure 4.9 Pinched cone-pinched cone interconversion of a calix[4]arene.

the *exo* or *endo* rims.[88] Temperature dependent ^1H NMR measurements give a $\Delta G^{\ddagger}$ of 13.4 kcal/mole for the pinched cone-pinched cone interconversion *via* a transition state with C_4 symmetry[89] comparable to the 14.1 kcal/mole value obtained with the *n*-octyl ether of *p-tert*-butylcalix[4]arene.[88] Upon complexation with Na^+ the system becomes much more rigid, adopting a C_4 symmetry similar to the Na^+ complex of the CH_2CO_2Et ether of *p-tert*-butylcalix[4]arene.[90] Although early molecular dynamics calculations[8] favored a C_4 symmetry, subsequent studies also indicate that the C_2 conformer is favored by *ca.* 0.8 kcal/mole. Similarly, the lowest energy conformers of the larger calixarenes lack complete symmetry; that of calix[5]arene is calculated to be C_1 but approaching C_5 (which is 0.3 kcal/mole less stable), while those of calix[6]arene (calculated to be C_2) and calix[7]arene (calculated to be C_1) are far more stable

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[88] (a) M. Conner, V. Janout and S. L. Regen, *J. Am. Chem. Soc.* **1991**, 113, 9670; (b) A. Arduini, M. Fabbi, M. Mantovani, L. Mirone, A. Pochini, A. Secchi and R. Ungaro, *J. Org. Chem.* **1995**, 60, 1454; (c) J. Scheerder, R. H. Vreekamp, J. F. J. Engbersen, W. Verboom, J. P. M. van Duynhoven and D. N. Reinhoudt, *ibid.* **1996**, 61, 3476.

[89] G. D. Andreetti, V. Böhmer, J. G. Jordon, M. Tabatabai, F. Ugozzoli, W. Vogt and A. Wolff, *J. Org. Chem.* **1993**, 58, 4023.

[90] A. Yamada, T. Murase, K. Kikukawa, T. Matsuda and S. Shinkai, *Chem. Lett.* **1990**, 455.

than their conformers with C_6 and C_7 symmetries, respectively. Another subtle aspect of calix[*n*]arene structure is the question of whether the intramolecular hydrogen bonds are permanently oriented or are engaged in "flip-flop" reorientation. The question has been addressed only for the calix[4]arenes where the computational studies appear to favor permanent orientation.[8] Whether this also prevails for the larger calixarenes, particularly the calix[8]arene in the pleated loop conformation, remains to be explored.

4.4.1.2 Conformational Mobility of Calixarenes Larger than Calix[4]arenes

The conformations adopted by flexible calixarenes in solution depend primarily on the ring size and the substituents on the *endo* rim. The cone conformers are the lowest energy structures for the parent calix[4]arenes and calix[5]arenes, and the "compressed cone" ("double pinched cone") conformers are the lowest energy structures for the parent calix[6]arenes[57] and calix[7]arenes. Whether the parent calix[8]arenes exist in solution as pleated loops, pinched double cones or some other conformer remains uncertain. As with the calix[4]arenes, *p*-substituents play a relatively minor role in conformational mobility of the larger calixarenes. As shown in Figure 4.10, though, solvent can play a more dramatic role as in the case of *p*-*tert*-butylcalix[8]arene where the energy barrier to conformational inversion is lowered from 15.7 kcal/mole in $CDCl_3$ to less than 9 kcal/mole in pyridine-d_5. Not surprisingly, the energy barrier to conformational interconversion generally diminishes as the ring size and concomitant flexibility increase. The change is not uniform, however, and as the data in Table 4.2 show, the conformational stabilities in $CDCl_3$ show peaks at ring sizes four, eight, twelve and sixteen.[80]

4.4.1.3 Conformational Mobility of Oxacalixarenes and Azacalixarenes

The larger annulus of dihomooxacalix[4]arenes as compared with calix[4]arenes leads to greater conformational flexibility and lower rotational barriers with $\Delta G^{\ddagger} = ca.$ 13 kcal/mole.[81] Similarly, the various other oxacalixarenes have lower barriers to conformational interconversion, the general sequence in $CDCl_3$ solution being calix[4]arenes = calix[8]arenes > calix[5]arenes = dihomooxacalix[4]arenes = calix[6]arenes = calix[7]arenes = calix[9]arenes > tetrahomodioxacalix[4]arenes > hexahomotrioxacalix[3]arenes. In pyridine solution the intramolecular hydrogen bonding is disrupted, and the inversion barriers become primarily a function of ring size, with the rotational barriers decreasing in the order: calix[4]arene > calix[5]arene > dihomooxacalix[4]arene > calix[6]arene > tetrahomodioxacalix[4]arene > calix[8]arene > hexahomotrioxacalix[3]arene. N-benzyl-*p*-*tert*-butyldihomoazacalix[4]arene shows a temperature-dependent ^1H NMR spectrum that is ascribed to a major 1,2-alternate

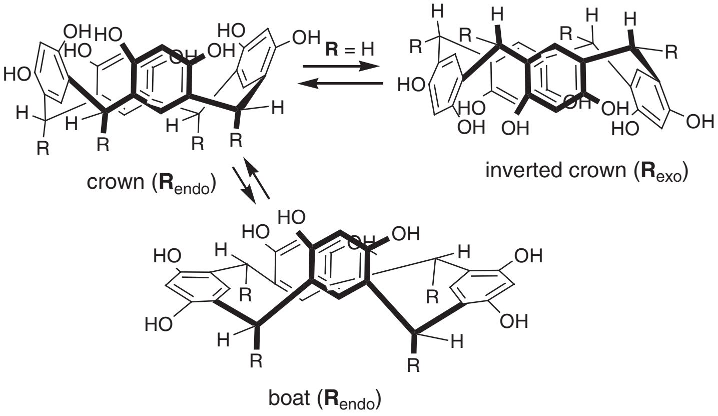

Figure 4.10 Crown and boat conformations of calix[4]resorcarenes.

Table 4.2 Energy barriers of conformational interconversion for *p*-*tert*-butyl-calix[*n*]arenes ($n = 4$–16) in $CDCl_3$.[80]

p-tert-butylcalix[n]arene	T_c (°C)	$\Delta\nu$ (HZ)	k_c (s^{-1})	$\Delta G^{\ddagger}$ (±0.3 kcal/mole)
[4]	65	225	505.3	15.7
[5]	21	180	406.8	13.2
[6]	11	210	472.4	13.1
[7]	14	216	485.5	12.3
[8]	66	246	551.4	15.7
[9]	17	240	538.2	13.4
[10]	−18	255	571.2	11.6
[11]	−37	216	485.5	10.8
[12]	−14	225	505.3	11.9
[13]	−31	270	604.2	11.0
[14]	−29	270	604.2	11.1
[15]	−31	240	538.2	11.1
[16]	0	255	571.2	12.5

conformer accompanied by a small amount of cone conformer,[91] although molecular dynamics calculations indicate the latter to be 10 kcal/mole more stable.

4.4.1.4 Conformational Mobility of Calixresorcarenes (Apndx B-16) and C-Substituted Calixarenes (Apndx D-4)

Calix[4]resorcarenes prepared from aldehydes (except formaldehyde) carry substituents on the bridge methylene groups which add a stereochemical complexity not present in most phenol-derived calix[4]arenes. Five

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[91] H. Takemura, T. Shinmyozu, H. Miura, I. U. Khan and T. Inazu, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 193.

conformations for C-substituted calix[4]resorcarenes have been identified, *viz.* crown (C_{4v}; cone), boat (C_{2v}; pinched or flattened cone), chair (C_{2h}; flattened partial cone), saddle (D_{2d}; 1,3-alternate) and diamond (C_s). Which conformer is obtained from any particular reaction depends, *inter alia*, on the reaction time, the solvent and the aldehyde employed. The four substituents on the methylene bridges can assume an all-*cis* (*ccc*), a *cis*-*cis*-*trans* (*cct*), a *cis*-*trans*-*cis* (*ctc*) or a *trans*-*cis*-*trans* (*tct*) arrangement, thus making possible a rather large number of conformers/stereoisomers. Interconversion among them involves not only changes in the shape of the macrocyclic ring but changes also in the orientation of the substituents on the bridge carbons, *i.e.* the lower energy axial (*endo*) and the higher energy equatorial (*exo*). For example, heating the all-*cis* boat conformer of C-methylcalix[4]resorcarene in HCl/MeOH produces an equilibrium mixture containing 1 part of chair conformer and 4 parts of diamond conformer,[92] indicating the stability sequence to be chair > diamond > boat > crown. Nevertheless, it is possible to isolate crown conformers, as in the case of C-hexylcalix[4]resorcarene, which was obtained as a mixture of the crown (*ccc*), diamond (*cct*) and chair (*ctt*) conformers.[93] The crown conformer (C_{4v} symmetry in the solid state) is a rapidly interconverting pair of boat conformers (C_{2v} symmetry) in solution ($\Delta G^{\ddagger}$ for the pseudorotation of the octa-ester is 15–18 kcal/mole, depending on the ester and the bridge substituent).[94] Chair to completely-inverted-chair transformations, requiring an *endo* to *exo* change for the bridge substituents, is a much higher energy process. In the special case in which the bridges are unsubstituted methylene groups,[95] however, the stability sequence resembles that of the phenol-derived calixarenes, *viz.* cone > partial cone > 1,2-alternate > 1,3-alternate,[96] and a cone-cone interconversion does occur with $\Delta G^{\ddagger} = 12.0$ kcal/mole in $CDCl_3$. This is almost 4 kcal/mole lower than the energy barrier for a calix[4]arene and is attributed to weaker intramolecular hydrogen bonding in the calix[4]resorcarene.

The phenol-derived calixarenes bearing a substituent on one or more of the bridge methylenes share with the resorcinol-derived calixarenes the additional stereochemical complexity that this feature imposes. By means of fragment condensation syntheses or by transformations with preformed calixarenes,[97] calix[4]arenes and calix[5]arenes carrying substituents on one or two of the bridge methylenes have been obtained. In all of these compounds the bridge substituent can assume either an equatorial or an axial orientation. Whereas in the resorcinol-derived calixarenes the preferred

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[92] F. Weinelt and H.-J. Schneider, *J. Org. Chem.* **1991**, 56, 5527.

[93] L. Abis, E. Dalcanale, A. Du Vosel and S. Spera, *J. Chem. Soc. Perkin Trans 2* **1990**, 2075.

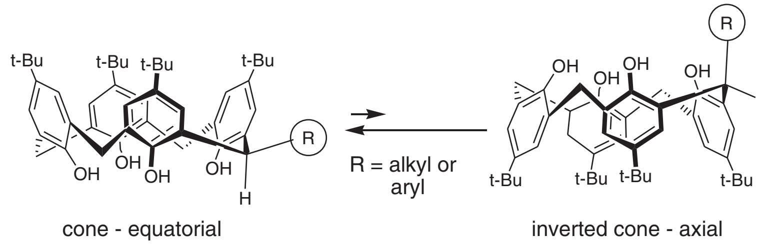
[94] A. G. S. Högberg, *J.Org. Chem.* **1980**, 45, 4498; *idem*, *J. Am. Chem. Soc.* **1980**, 102, 6046.

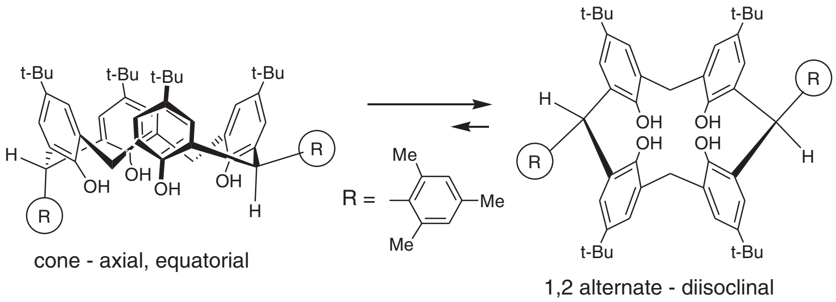
[95] O. M. Falana, E. Al-Farhan, P. M. Keehn and R. Stevenson, *Tetrahedron Lett.* **1994**, 35, 65.

[96] H. Konishi and O. Morikawa, *J. Chem. Soc. Chem. Commun.* **1993**, 34; I. Thondorf, J. Brenn and V. Böhmer, *ibid.* **1998**, 54, 12823; M. Mäkinin, J.-P. Jalkanen and P. Vainiotalo, *Tetrahedron* **2002**, 58, 8591. For the study of calix[4]resorcarenes bearing four OH and four OR groups *cf.* O. Morikawa, E. Iama, T. Oikawa, K. Kobayashi and H. Kohishi, *J. Phys. Org. Chem.* **2006**, 19, 214.

[97] S. Simaan and S. E. Biali, *J. Org. Chem.* **2003**, 68, 3634, 7685.

orientation is axial (*endo*), in the phenol-derived calixarenes it is equatorial (*exo*). For a mono bridge-substituted *p*-*tert*-butylcalixarene the interconversion barrier increases with increasing size of the substituent from R=Me ($\Delta G^{\ddagger} = 15.0$ kcal/mole) to R = *i*-Pr ($\Delta G^{\ddagger} = 17.2$ kcal/mole),[98] and comparable values are observed for the corresponding calix[5]arenes.[99] In the case of A,C disubstitution where the substituents are *cis* to one another the cone diequatorial conformer remains preferred. However, when the substituents are *trans* one of them is forced to occupy an axial position if the calixarene ring remains in the cone conformation.





In most instances it is the power of the circular hydrogen bonding that prevails, and the system remains in this conformation. But, with a sufficiently large substituent (*e.g.* R = mesityl) the advantage of the hydrogen bonding is overcome, and the system adopts a 1,2-alternate diisoclinal conformation.[100]

4.4.1.5 Conformational Mobility of Thiacalixarenes

The thiacalixarenes are conformationally rather similar to their methylene-bridged counterparts both in the solid state and in solution. X-Ray crystallography shows the thiacalix[4]arenes to be a cone,[101] the thiacalix[6]arenes a

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[98] S E. Biali, V. Böhmer, S. Cohen, G. Ferguson, C. Grüttner, F. Grynszpan, E. F. Paulus, I. Thorndorf and W. Vogt, *J. Am. Chem. Soc.* **1996**, 118, 12938.

[99] S. E. Biali, V. Böhmer, I. Columbus, G. Ferguson, C. Grüttner, F. Grynszpan, E. F. Paulus and I. Thondorf, *J. Chem. Soc. Perkin Trans 2* **1998**, 2261.

[100] S. Simaan and S. E. Biali, *J. Org. Chem.* **2004**, 69, 95.

[101] N. Iki, C. Kabuto, T. Fukushima, H. Kumagai, H. Takeya, S Miyanari, T. Miyashi and S. Miyano, *Tetrahedron* **2000**, 56, 1437.

winged cone[102] and the thiacalix[8]arenes a pleated loop.[103] Temperature-dependent ^{1}H NMR spectra show *p*-*tert*-butylthiacalix[4]arene to have a conformational inversion energy barrier of $\Delta G^{\ddagger} = 13.5$ kcal/mole, which is *ca.* 2 kcal/mole lower than that of *p*-*tert*-butylcalix[4]arene due to the larger annulus and weaker hydrogen bonding in the thia compound.[104] The energy barrier for the pinched cone-pinched cone interconversion of the tetrapropyl ether of thiacalix[4]arene in tetrachloroethane-d_2 is also reported to be 13.8 kcal/mole[105a] (<9.8 kcal/mole for the tetrapropyl ether of *p*-*tert*-butylcalix[4]arene) but is dependent on the particular solvent.[105b] Oxidation of the sulfur bridges in *p*-*tert*-butylthiacalix[4]arene adds an oxygen to each of the sulfurs, creating a system rather comparable to a C-substituted calix[4]resorcarene. All four of the stereoisomers of this system have been synthesized.[106]

4.4.1.6 Conformational Mobility of Calixarene Ethers, Deoxycalixarenes, Calixquinones and Calixarenethiols

Whereas all of the parent calixarenes are conformationally flexible in solution at room temperature, space filling molecular models of calix[4]arenes indicate that any group larger than OH should curtail this mobility. Surprisingly, however, OMe groups do not do this, providing another illustration that molecular models are often too "hard" and tend to overestimate conformational inflexibility. In fact, the tetramethyl ether *of p*-*tert*-butylcalix[4]arene has a conformational inversion barrier almost identical with that of the parent compound.[2] And, even ethoxy groups are not quite large enough, for equilibration among the conformers of the tetraethyl ether of *p*-*tert*-butylcalix[4]arene as observed at elevated temperatures.[37b,41] Neither OMe nor OEt groups have much effect in the larger calixarenes where the pentamethyl and pentaethyl ethers of *p*-*tert*-butylcalix[5]arene, for example, have $\Delta G^{\ddagger}$ values that are lower than 9.3 kcal/mole and 11.1 kcal/mole, respectively.[55] With intramolecular hydrogen bonding playing no part in the tetramethyl ether of *p*-*tert*-butylcalix[4]arene, all four conformers are present in equilibrium in $CDCl_3$ solution in the amounts of 85.6% partial cone, 5.5% cone, 6.1% 1,2-alternate and 2.8% 1,3-alternate.[10a] The proportion of cone conformer increases with increasing solvent polarity as the result of the greater dipole moment of the

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[102] N. Iki, N. Morahashi, T. Suzuki, S. Ogawa, M. Aono, C. Kabuto, H. Kumagai, H. Takeya, S. Miyanari and S. Miyano, *Tetrahedron Lett.* **2000**, 41, 2587.

[103] Y. Kondo, K. Endo, N. Iki, S. Miyano and F. Hamada, *J. Inclusion Phenom. Macrocycl. Chem.* **2005**, 52, 45.

[104] T. Sone, Y. Ohba, K. Moriya, H. Kumada and K. Ito, *Tetrahedron* **1997**, 53, 10689; J. Lang, H. Dvořáková , I. Bartošová , P. Lhoták, I. Stibor and R. Hrabal, *Tetrahedron Lett.* **1999**, 40, 373.

[105] (a) M. Cajan, P. Lhoták, J. Lang, Dvořáková, I. Stibor and J. Koca, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1922; (b) J. Matošek, P. Kulhánek, M. Čajan and J. Koča, *J. Phys. Chem. A* **2006**, 110, 861.

[106] N. Morohashi, H. Katagiri, N. Iki, Y. Yamane, C. Kabuto, T. Hattori and S. Miyano, *J. Org. Chem.* **2003**, 68, 2324.

cone conformer compared with those of the other conformers.[23,107,108] With the tetramethyl ether of *p*-sulfonatocalix[4]arene, on the other hand, it is the 1,3-alternate conformer that predominates.[109]

Replacement of two or more of the *endo* rim OH groups with other groups such as H, Me, SH or NH_2 similarly affects the order of conformational stability. For example, molecular mechanics calculations predict the stability sequences for the tetradeoxy compound to be cone > partial cone > 1,3-alternate > 1,2-alternate and that of the tetramethyl compound (Me in place of OH) to be 1,3-alternate $\gg$ partial cone > 1,2-alternate > 1,3-alternate.[10b] The dimethyl ether of calix[4]arenediquinone is conformationally mobile at room temperature, but at $-70\,^\circ C$ it assumes a partial cone conformation in which one of the OMe groups points inward into the calix.[110] The calix[4]arenetetraquinone and calix[6]arenehexaquinone are even more conformationally flexible.[68] Molecular mechanics calculations on *p*-*tert*-butylcalix[4]arenetetrathiol indicates the stability sequence to be 1,3-alternate > partial cone > 1,2-alternate > cone. Conversion of the bridge CH_2 groups to C=O groups produces a conformationally flexible molecule ($\Delta G^{\ddagger} = 15.2$ kcal/mole) which prefers the 1,3-alternate conformation.[111] To study the dynamical behavior of this system in which there are no methylene hydrogens as ^1H NMR "handles", a chiral solvent was employed which renders pairs of enantiotopic protons in the calixarene anisochronous.

4.4.2 Pathways for Cone-cone Interconversion of Calix[4]arenes

The pathway that a calix[4]arene follows in the transformation of its cone conformer (u,u,u,u) to its inverted cone conformer (d,d,d,d) remains somewhat uncertain, although it clearly involves an "*endo* rim through the annulus" pathway (*cf.* Section 4.5.1) One possibility is that the process is concerted (a "continuous chain pathway") without intermediates and with only one transition state. Another possibility is that the process is stepwise (a "broken chain pathway") with 1,3-alternate and/or 1,2-alternate conformers as intermediates. The "continuous chain pathway" is attractive in its postulate that the circular hydrogen bonding remains more or less intact throughout the transformation, in contrast to the "broken chain pathway" in which hydrogen bonds are broken. However, although an Arrhenius plot for the rate of inversion of calix[4]arene[82] may give some support for the "continuous chain pathway", computational studies of *p*-*tert*-butylcalix[4]arene[8,112] provide strong support

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[107] S. Shinkai, K. Iwamoto, K. Araki and T. Matsuda, *Chem. Lett.* **1990**, 1263.

[108] I. C. Groenen, E. Steinwender, B. T. G. Lutz, J. H. van der Maas and D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans 2* **1992**, 1893.

[109] T. Nagasaki, K. Sisido, T. Arimura and S. Shinkai, *Tetrahedron* **1992**, 48, 797.

[110] A. Casnati, E. Comelli, M. Fabbi, Y. Bocchi, G. Mori, F. Ugozzoli, A. M. Manotti Lanfredi, A. Pochini and R. Ungaro, *Recl. Trav. Chim. Pays-Bas* **1993**, 112, 384.

[111] N. Seri, S. Simaan, M. Botoshansky, M. Kaftory and S. E. Biali, *J. Org. Chem.* **2003**, 68, 7140.

[112] (a) S. Fischer, P. D. J. Grootenhuis, L. C. Groenen, W. P. van Hoorn, F. C. J. M. van Veggel, D. N. Reinhoudt and M. Karplus, *J. Am. Chem. Soc.* **1995**, 117, 1611; (b) I. Thorndorf, J. Brenn, W. Brandt and V. Böhmer, *Tetrahedron Lett.* **1995**, 36, 6665.

for the "broken chain pathway" involving a cone → partial cone → 1,2-alternate/1,3-alternate → inverted partial cone → inverted cone sequence. The tetramethyl ether exists preferentially in the partial cone conformation, which undergoes facile transformation to the other conformers[41] for which the energy barriers to rotation have been calculated.[112]

4.5 Conformationally Immobile Calixarenes

4.5.1 Minimum Structural Requirements for Conformational Immobility of Unbridged Calixarene Ethers and Esters

4.5.1.1 Identification of Fixed Conformers

The most conclusive means for establishing the structure of a calixarene in a fixed conformation is X-ray crystallography. A simple and very effective alternative method, used from the earliest days of calixarene chemistry,[2,113] employs ^{1}H NMR spectroscopy. For the three most commonly encountered types of conformationally fixed calixarenes the characteristic ^{1}H NMR spectral patterns are shown in Figure 4.11. A helpful adjunct is the measurement of the magnitude of the chemical shift ($\Delta\delta$) between the high-field and low-field pairs of resonances arising from the methylene protons of a calix[4]arene. As illustrated in Figure 4.12, when the hydrogens project toward the viewer and the aryl rings project away from the viewer, $\Delta\delta$ is generally *ca.* 0.9 ± 0.2 for a system in the cone conformation, and it is zero for a system in the 1,3-alternate conformation if the measurement is made in a non-polar solvent such as $CDCl_3$. Between these extremes, in "flattened" conformations $\Delta\delta$ assumes intermediate values of *ca.* 0.5 ± 0.1, thus providing an indication of the degree to which the system departs from the true cone or the 1,3-alternate conformations. The $\Delta\delta$ values are also dependent on solvent, however, and are generally larger in polar solvents such as pyridine and DMSO than in non-polar solvents. For example, *p*-*tert*-butylcalix[4]arene has a $\Delta\delta = 0.73$ in $CDCl_3$ and a $\Delta\delta = 1.25$ in pyridine-d_5. Still another useful adjunct is the position of the ^{13}C NMR signal arising from the methylene groups, as detailed in Section 3.4.3.

4.5.1.2 Fully Etherified and Esterified Calixarenes

Two pathways are available to a calixarene for conformational inversion. One involves the "*exo* rim through the annulus" and the other involves the "*endo* rim through the annulus", as illustrated in Figure 4.13. If conformational inversion is to be curtailed it is necessary that *both* pathways be precluded, either by the incorporation of sufficiently large groups on the rims or by a bridge across one or both rims. In the case of the calix[4]arenes the "*exo* rim through the annulus" pathway is so hindered that even the *p*-H compound can engage only in "*endo* rim through the annulus" conformational inversion. This

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[113] V. Bocchi, D. Foina, A. Pochini and R. Ungaro, *Tetrahedron* **1982**, 38, 373.

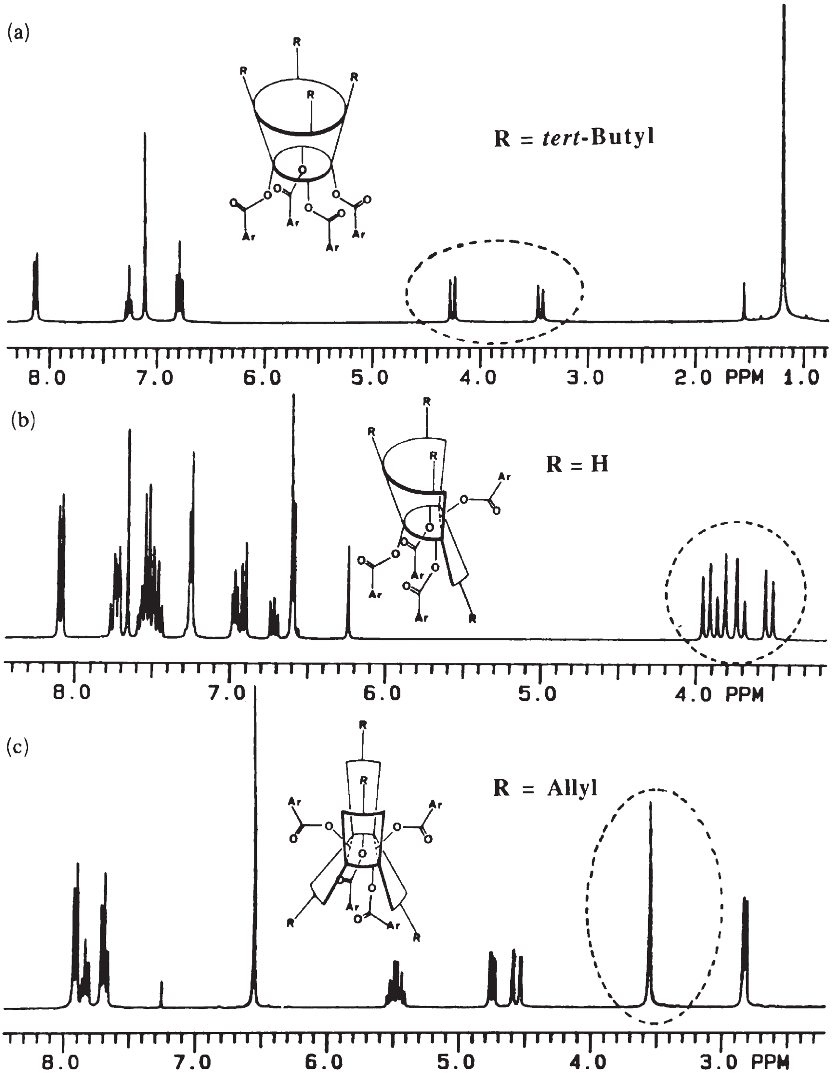

Figure 4.11 ^{1}H NMR spectra at 300 MHz of calix[4]arenes in (a) the cone conformation, (b) the partial cone conformation and (c) the 1,3-alternate conformation. The regions of particular note are circled.

is not true for larger calixarenes, however, where groups even as bulky as *tert*-butyl may not suffice to curtail the "exo rim through the annulus" pathway.

Realizing that only the "*endo* rim through the annulus" pathway is available for the interconversion of calix[4]arene conformers, attention has focused on the minimum size of OR group that is necessary to curtail this pathway. As already discussed, the tetramethyl ether of *p*-*tert*-butylcalixarene is a conformationally flexible molecule, and even the tetraethyl ether can undergo conformational interconversion at higher temperatures.[37a] The tetra-*n*-propyl

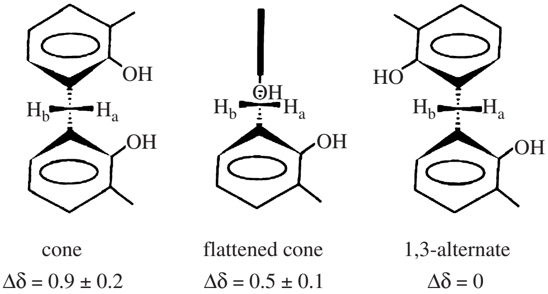

Figure 4.12 Conformational dependence of the chemical shift (Δδ) between the high-field and low-field pairs of resonances of the methylene protons in the calix[4]arenes.

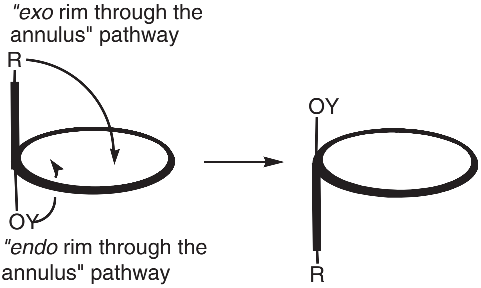

Figure 4.13 Pathways for conformational inversion of calix[*n*]arenes.

ether, however, is conformationally fixed even at elevated temperatures, as are all other tetraethers containing groups larger than *n*-propyl. Tetraacetates and higher esters of calix[4]arenes are similarly conformationally inflexible. In the case of the thiacalixarenes the tetramethyl ether of *p*-*tert*-butylthiacalix[4]arene, containing a somewhat larger annulus than its phenol-derived counterpart, is even more flexible with an energy barrier of $\Delta G^{\ddagger} = 12.43$ kcal/mole.

p-H-Calix[5]arene can undergo conformational inversion by either pathway, but the energy barrier for the "*exo* rim through the annulus" pathway is considerably higher ($\Delta G^{\ddagger} =$ *ca.* 18 kcal/mole[114]) than that for the "*endo* rim through the annulus" pathway. With *p*-*tert*-butylcalix[5]arene, however, only the second pathway is possible, the *tert*-butyl group providing sufficient steric hindrance to preclude the first pathway. As anticipated, larger OR groups are necessary to curtail conformational interconversion of calix[5]arenes than the calix[4]arenes. It has been shown that the threshold size when the substituents are ether groups is slightly beyond *n*-butyl ($\Delta G^{\ddagger}$ of tetra-*n*-butyl ether of *p*-*tert*-butylcalix[5]arene = 15.5 kcal/mole[55]) or CH_2CH_2OEt or CH_2CO_2Et.[114] When they are ester groups the boundary is slightly beyond *n*-butanoyl ($\Delta G^{\ddagger}$ for the

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[114] G. Ferguson, A. Notti, S. Pappalardo, M. F. Parsi and A. L. Speck, *Tetrahedron Lett.* **1998**, 39, 1965.

tetra-*n*-butanoate = 17.5 kcal/mole).[55] Another study showed that the threshold size for OCH_2COR groups is between R = Me and R = *tert*-Bu.[115]

Calix[6]arenes require *para* substituents at least slightly larger than *tert*-butyl to completely curtail conformational transformation *via* the "*exo* rim through the annulus" pathway. This has been demonstrated by placing very large groups (*e.g*. cholesteryl[116] or *p*-phenylbenzyl[117]) on the *endo* rim and finding that slow conformational interconversion still occurs. The barrier to conformational interconversion *via* this "*exo* rim through the annulus" pathway[117] is 21 kcal/mole at 55 °C, appreciably higher than the 15.7 kcal/mole value for the "*endo* rim through the annulus" pathway of *p*-*tert*-butylcalix[4]arene or its tetramethyl ether. It is still low enough, however, to allow slow conformational inversion to occur. For a *p*-H-calix[6]arene the barrier to the "*exo* rim through the annulus" pathway is even lower.[118] Thus, *p*-*tert*-butylcalix[6]arenes carrying large OR substituents can be classed as marginally conformationally flexible. Of course, substituents larger than *tert*-butyl (*e.g*. tert-octyl[119] or adamantyl[120]) should prelude the "*exo* rim through the annulus" pathway. Even though the "*exo* rim through the annulus" pathway is available to *p*-*tert*-butylcalix[6]arenes the barrier is sufficiently high that the threshold sizes of groups necessary to curtail the "*endo* rim through the annulus" pathway can still be established. For example, the hexabenzyl ether of *p*-*tert*-butylcalix[6]arene has been shown to be conformationally flexible *via* this pathway, whereas the hexa *p*-cyanobenzyl ether is not.[121] Inspection of space-filling molecular models shows that it is indeed possible to force a benzylphenoxy moiety through the annulus but not a *p*-cyanobenzylphenoxy moiety. A detailed study of the conformational flexibility of hexa-O-alkylated calix[6]arenes[121] shows the system to be a slowly interconverting mixture of pinched cone and 1,2,3-alternate conformers (energy difference 0.5–1.56 kcal/mole). The special stabilizing effect of methoxyl groups in the 1,3,5-positions has been attributed to their inward orientation to occupy space within the annulus.

The possibility of unbridged calix[7]arenes existing in fixed conformations has yet to be explored, but it is known that the octa-trimethylsilyl ether of *p*-*tert*-butylcalix[8]arene is conformationally flexible with ($\Delta G^{\ddagger} = 13.2$ kcal/mole inversion barrier). It is possible that very large groups on the *exo* and

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[115] S. E. J. Bell, J. K. Browne, V. McKee, M. A. McKervey, J. F. Malone, M. O'Leary and A. Walker, *J. Org. Chem.* **1998**, 63, 489.

[116] (a) H. Otsuka, K. Araki and S. Shinkai, *Chem. Express* **1993**, 8, 479; (b) H. Otsuka, K. Araki, T. Sakaki, K. Nakashima and S. Shinkai, *Tetrahedron Lett.* **1993**, 34, 7275.

[117] J. P. M. van Duynhoven, R. G. Janssen, W. Verboom, S. M. Franken, A. Casnati, A. Pochini, R. Ungaro, J. de Mendoza, P. M. Nieto, P. Prados and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1994**, 116, 5814.

[118] J. C. Iglesias-Sánchez, B. Souto, C. J. Pastor, J. de Mendoza and P. Prados, *J. Org. Chem.* **2005**, 70, 10400.

[119] K. Ohno, M. Yano, K. Inoue, T. Yamamoto, M. Goto, F. Nakashio, S. Shinkai and T. Nagasaki, *Anal. Sci.* **1995**, 11, 893.

[120] I. M. Vatsouro, E. A. Shokova, A. K. Shestakova, A. V. A. Chertkov and V. V. Kovalev, *European J. Org. Chem.* **2006**, 522.

[121] S. Kanamathareddy and C. D. Gutsche, *J. Org. Chem.* **1994**, 59, 3871.

endo rims might curtail conformational flexibility in this system, but this remains to be demonstrated.

4.5.1.3 Partially Etherified and Esterified Calixarenes

It is a seemingly curious fact that partially etherified and esterified calixarenes are often less conformationally flexible than their fully etherified or esterified counterparts. The simplest examples occur with the methyl ethers of calix[4]arenes where the monomethyl, dimethyl and trimethyl ethers have calculated values[122] of $\Delta G^{\ddagger} = 35.1$ kcal/mole, 30.3 kcal/mole and 27.0 kcal/mole, respectively, for conformational inversion, all appreciably higher than the 15.7 kcal/mole value for *p*-*tert*-butylcalix[4]arene. Using the ingenious device of measuring the rate of racemization of the monomethyl- and 1,3-dimethyl ethers of a chiral calix[4]arene (carrying a Me group *meta* to the *endo*-annular carbon of each of the rings), Böhmer and coworkers have provided the experimental values of 24.3 kcal/mole and 23.3 kcal/mole for the inversion barriers for these two members of the methyl ether family.[123] The conformational inflexibility of these ethers is the result of the interplay of intramolecular hydrogen bonding and steric factors in a "cooperative effect".[122] In the parent compound hydrogen bonding is at a maximum, holding the compound firmly in a cone conformation. In the tetramethyl ether hydrogen bonding is non-existent, and only the steric interference arising from the OMe groups determines the conformational mobility. In the partially methylated compounds both hydrogen bonding and steric interference reduce the conformational mobility, the two effects combining to reach a probable maximum at the mono substitution stage. The rate-limiting step in all cases is the reorientation of a MeO-aryl ring. Since a group as small as methyl exerts this "mono substituent effect", it is to be expected that all other substituents will act in like fashion in calix[4]arene systems. The same phenomenon is also observed with the calix[5]arenes and calix[6]arenes, the only difference being that larger OR groups are necessary to achieve similar results. Thus, an OMe group is insufficient in the calix[5]arene, but a single O-*n*-propyl group proves effective in greatly reducing the rate of inversion[55] ($\Delta G^{\ddagger} = 19.9$ kcal/mole)˙. With five O-*i*-Pr groups the system again becomes very flexible ($\Delta G^{\ddagger} = 12.6$ kcal/mole). In the case of the calix[6]arenes a single benzyl group produces a system with inversion barrier $\Delta G^{\ddagger} > 18$ kcal/mole,[121,124] and two *p*-*tert*-butylbenzyl groups produce a system with inversion barrier $\Delta G^{\ddagger} =$ *ca.* 26 kcal/mole.[125] Also, three OMe groups in the 1,3,5 positions of *p*-*tert*-butylcalix[6]arene freeze the conformation into a cone.[126] A careful ^{1}H NMR study of the dynamical properties of a series of

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[122] W. P. van Hoorn, M. G. H. Morshuis, F. C. J. M. van Veggel and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1998**, 102, 1130.

[123] T. Kusano, M. Tabatabai, Y. Okamoto and V. Böhmer, *J. Am. Chem. Soc.* **1999**, 121, 3789.

[124] J. O. Magrans, A. M. Rincon, F. Cuevas, J. López-Prados, P. M. Nieto, M. Pons, P. Prados and J. de Mendoza, *J. Org. Chem.* **1998**, 63, 1079.

[125] P. Neri, C. Rocco, G. M. L. Consoli and M. Piatelli, *J. Org. Chem.* **1993**, 58, 6535.

[126] A. Casnati, P. Minari, A. Pochini and R. Ungaro, *J. Chem. Soc. Chem. Commun.* **1991**, 1413.

phosphorylated and thiophosphorylated *p-tert*-butylcalix[6]arenes[127] shows that at least three processes are at play. Ranked in order of increasing effect on the activation barrier they are: hydrogen bond array reversal, pinched conformer interconversion and macrocyclic ring interconversion.

4.5.1.4 Meta-substituted Calixarenes

Although a calix[4]arene substituted with methyl groups at all of the eight available *meta* positions is conformationally flexible[12] the tetramethyl ether of an octabromo analog is reported[128] to be conformationally stable up to 260 °C in the partial cone conformation.

4.5.2 Conformational Immobilization *via* Bridging

A wide variety of polyfunctional units have been used to bridge the *endo* rim of calix[*n*]arenes ($n = 4$–9) (*Apndx A-2, p. 71, 99, 365*), *endo* rim-bridges generally being synthetically easier to introduce than *exo* rim-bridges. Included among the bridging moieties are $O(CH_2)_nO$,[129] $OCH_2(CH_2OCH_2)_nCH_2O$,[130] $OCH_2NCH_2(CH_2OCH_2)_nCH_2NCH_2O$[131] (which produce the *endo* rim calix crown compounds such as **4.1** and **4.2**), [$-OCH_2CH_2OC(=O)CH_2]_3N$,[132] heterocycles (*e.g.* O-pyridine-O and O-1,10-phenanthroline-O[133]), $O_3P=O$,[134] $OSiR_2O$,[135] O-calixarene-O,[136] O-metallocene-O[137] and O-hemispherand-O.[138] A rather elaborate lower ring bridge is illustrated by compound **4.4** which has been called a "double cavity" calixarene.[139]

Although *exo* rim-bridging is more synthetically demanding, numerous examples have been reported using bridging units similar to some of those

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[127] R. G. Janssen, J. P. M. van Duynhoven, W. Verboom, G. J. van Hummel, S. Harkema and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1996**, 118, 3666.

[128] M. Mascal, R. T. Naven and R. Warmuth, *Tetrahedron Lett.* **1995**, 36, 9361.

[129] J. Wöhnert, J. Benn, M. Stoldt, O. Aleksiuk, F. Grynszpan, I. Thondorf and S. E. Biali, *J. Org. Chem.* **1998**, 63, 3866 (calix[4]arene).

[130] A. Casnati, A. Pochini, R. Ungaro, F. Ugozzoli, F. Arnaud, S. Fanni, M.-J. Schwing, R. J. M. Egberink, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1995**, 117, 1767 (calix[4]arene, $n = 4$); G. M. L. Consoli, F. Cunsolo, C. Geraci, E. Gavuzzo and P. Neri, *Org. Lett.* **2002**, 4, 2649 (calix[8]arene, $n = 4$).

[131] E. Jabin and O. Reinaud, *J. Org. Chem.* **2003**, 68, 3416 (calix[6]arene).

[132] Y. Zhang, H. Yuan, Z. Huang, J. Zhou, Y. Kawanishi, J. Schatz and G. Maas, *Tetrahedron* **2001**, 57, 4161 (calix[6]arene).

[133] S. Konrad, C. Näther and U. Lüning, *European J. Org. Chem.* **2005**, 2330 (calix[5,8]arenes); S. Konrad, M. Bolte, C. Näther and U. Lüning, *ibid.* **2006**, 4717 (calix[6]arene); J. P. W. Eggert, J. Harrowfield, U. Lüning, B. W. Skelton, A. H. White, F. Löffler and S. Konrad, *ibid.* **2005**, 1348 (calix[6]arene).

[134] J. Gloede, S. Ozegowski, B. Costisella and C. D. Gutsche, *European J. Org. Chem.* **2003**, 4873 (calix[9]arene).

[135] P. Sood, H. Zhang and M. Lattman, *Organometallics* **2002**, 21, 4442 (calix[5]arene).

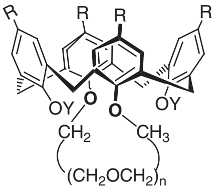
[136] S. Le Gac, X. Zeng, O. Reinaud and I. Jabin, *J. Org. Chem.* **2005**, 70, 1204 (calix[6]arenes).

[137] P. D. Beer and A. D. Keffe, *J. Inclusion Phenom.* **1987**, 5, 499.

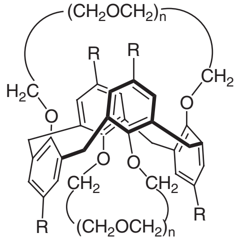
[138] D. N. Reinhoudt, P. J. Dijkstra, P. J. A. Int't Veld, K. E. Bugge, S. Harkema, R. Ungaro and E. Ghidini, *J. Am. Chem. Soc.* **1987**, 109, 4761.

[139] C. D. Gutsche, M. Iqbal, K. C. Nam, K. A. See and I. Alam, *Pure Appl. Chem.* **1988**, 60, 483.

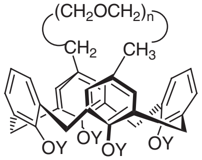
noted above. Several are illustrated in Chapter 2 in compounds **2.9**, **2.10**, **2.13** (calixarene bridge, p 105) and **2.21** ($[CH_2]_n$ bridge, p 45). Others include, *inter alia*, the crown ether and azacrown ether units to produce the corresponding calix crown compounds such as **4.3**, which, along with their *endo* rim counterparts, play a particularly important role in complexation studies (*cf.* Chapter 7). In most cases of bridging, either at the *endo* rim or at the *exo* rim, the system becomes less conformationally mobile and usually cannot undergo complete conformational inversion. Partial inversion is often possible, however, as with compounds **4.1** and **4.3**, in which the non-bridged aryl rings may have the capability of flipping between the up- and down-orientations. Two surprisingly flexible bridged systems are (a) the doubly bridged calix[4]arene **4.5**, which exists as an equilibrium mixture of cone and 1,2-alternate conformers (differing by 0.43 kcal/mole) with a barrier of 18.2 kcal/mole for conformational inversion; and (b) the triply bridged calix[6]arene **4.6**, which is completely flexible above 270 °C.[140]



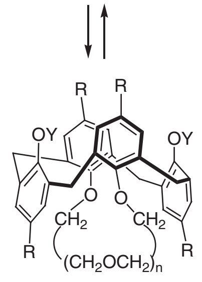
4.1(cone)

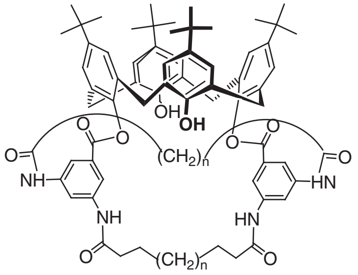


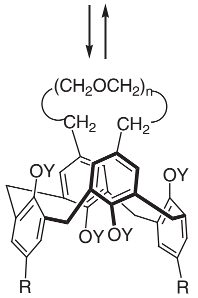
4.2



4.3 (cone)







4.1 (1,3-alternate) **4.4** **4.3 (1,3-alternate)**

An interesting case of partial flexibility occurs in the 1,4-benzylene-bridged calix[6]arene **4.7a**, which assumes a cone conformation when the 1,2,4,5 *endo* rim groups are OH but which upon methylation undergoes a conformational change to a 1,2,3-alternate conformer with the bridging group threaded through the annulus (**4.8a**).[4] In like fashion, conversion of **4.7b** to its tetrabenzyl ether gives a pair of non-interconverting conformers, one a cone (characterized by X-ray crystallography), and the other a 1,2,3-alternate (characterized by ^1H NMR spectroscopy).[141]

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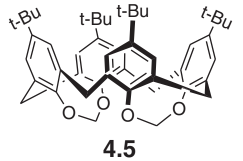
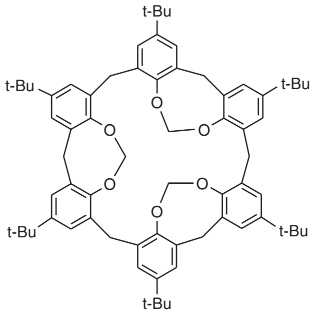
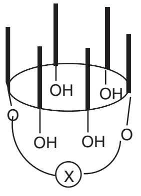
[140] P. Neri, G. Ferguson, J. F. Gallagher and S. Pappalardo, *Tetrahedron Lett.* **1992**, 33, 7403.
[141] T. Saiki, K. Goto and R. Okazaki, *Chem. Lett.* **1996**, 993.



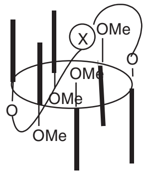
4.5



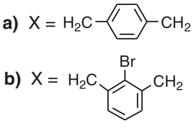
4.6

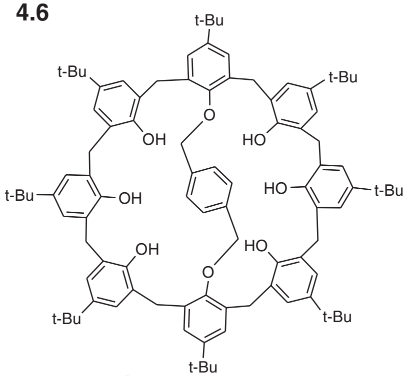


4.7



4.8





4.9

A calix[6]arene bridged on the *exo* rim by triple attachment of a 1,3,5-(methylthiomethyl)-phenyl group at the A,C,E rings has been shown[142] to be a conformationally non-inverting cone conformer that engages in conformational "wobble" between a pinched cone and a regular cone. Conformational control of a calix[6]arene can also be established by multiple *endo* rim bridges[143] as, for example, with a 1,2,4,5 four-point attachment.[144] In the even more flexible calix[8]arene system the imposition of a benzylene moiety between the 1 and 5 *endo* rim positions creates the conformationally restricted molecule **4.9**, in which neither the "*endo* rim through the annulus" pathway nor the "*exo* rim through the annulus pathway" is available for complete conformational interconversion.[145] In this case the bridge has changed the large calix[8]arene cavity to a pair of smaller pseudo calyx[6]arene cavities. Not surprisingly, multiple bridges impose increasingly powerful strictures on conformational mobility, a typical example being a pair of bridges in *p*-*tert*-butylcalix[7]arene[146] to produce a compound that is conformationally stable.

The calix[4]resorcarenes (**4.10**) present a system in which conformational immobilization can be achieved through bridging the OH groups on

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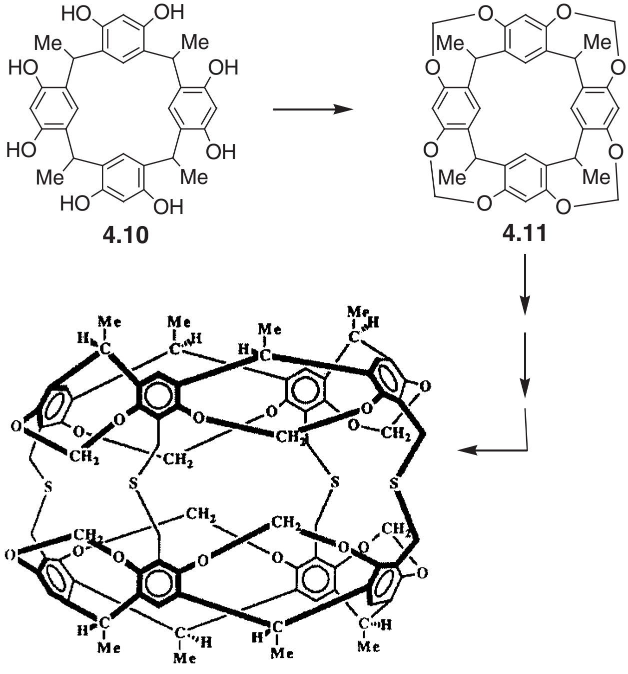
[142] M. Takeshita, S. Nishio and S. Shinkai, *J. Org. Chem.* **1994**, 59, 4032.
[143] H. Galán, J. de Mendoza and P. Prados, *Eur. J. Org. Chem.* **2005**, 4093.
[144] K. C. Nam, Y. J. Choi, D. S. Kim, J. M. Kim and J. C. Chun, *J. Org. Chem.* **1997**, 62, 6441.
[145] F. Consolo, M. Plattelli and P. Neri, *J. Chem. Soc. Chem. Commun.* **1994**, 1917.
[146] M. Martino, C. Gaeta and P. Neri, *Tetrahedron Lett.* **2004**, 45, 3387.

neighboring aryl rings, producing compounds (**4.11**) that Donald Cram named as "cavitands". Cram and coworkers went on to convert the cavitands to the even more complex, spherically shaped compounds (**4.12**), which were named "carcerands". The extraordinarily complete and wide-ranging investigation of these structures (*Apndx A-7, p. 181, 199*) provided part of the basis for the award of the 1987 Nobel Prize in Chemistry to Cram (shared with Charles Pedersen and Jean-Marie Lehn).

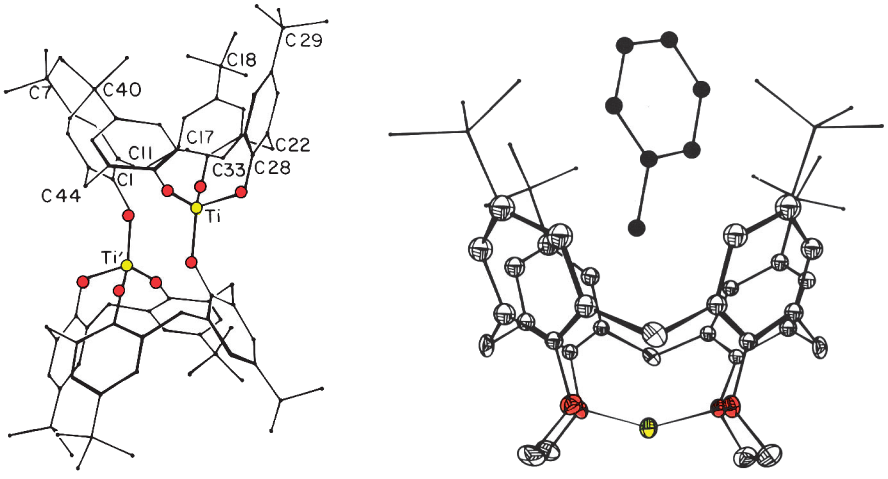


4.10 **4.11**

4.12

4.5.3 Conformational Freezing *via* Oxygen-Metal Bridges

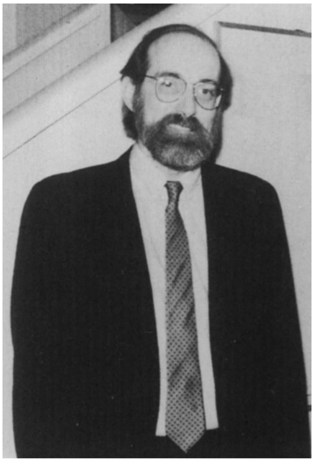
The interaction of calixarenes with certain inorganic compounds produces metal complexes in which the conformation and conformational mobility of the calixarene may be considerably altered. One of the earliest examples, chosen from what has now become a very large number of examples, came from the laboratories of Philip Power and coworkers at the University of California at Davis. They were the first to explore the interaction of calixarenes with transition metal ions in their search for unusual coordination and reactivity patterns in inorganic complexes. In one of the experiments in this study *p*-*tert*-butylcalix[4]arene was treated with $Ti(NMe_2)_4$, which produced a structure that was revealed by X-ray crystallography to contain two titanium atoms sandwiched between a pair of cyclic tetramers, as shown in Figure 4.14. Another early example came from the laboratories of Atwood, who had been introduced



(a) (b)

Figure 4.14 X-ray crystallographic structures of (a) the titanium complex of *p-tert*-butylcalix[4]arene; (b) the toluene/Na$^+$ complex of *p-tert*-butylcalix[4]arene.

to the calixarene field by a lecture by Gutsche at a 1982 conference in Parma that piqued his interest. Following soon thereafter was a publication from his laboratories of an X-ray crystallographic structure of the complex of *p-tert*-butylcalix[4]arene with toluene and Na$^+$, as shown in Figure 4.14. This was the first in what has become a long list of accomplishments in which Atwood has applied his expertise as an X-ray crystallographer to bring new perspectives to the calixarene field. Jerry Atwood, born in Missouri, received his Ph.D. from the University of Illinois in 1964 working with Galen D. Stucky. For the next three decades he was a Professor of Chemistry at the University of Alabama until 1994 when he became chairman of the Department of Chemistry at his home state institution at the University of Missouri-Columbia.



Jerry Atwood

4.6 Factors Governing the Conformational Outcome of Derivatization

4.6.1 O-Tetrasubstitution of Calix[4]arenes

Replacement of the hydrogens of all four of the OH groups of a calix[4]arene with sufficiently large alkyl, acyl or aroyl groups results in conformational immobilization, providing the possibility of isolation of the non-interconverting cone, partial cone, 1,2-alternate and 1,3-alternate conformers. Some useful guidelines for predicting the distribution of conformers in the product have emerged, but accurate predictions are not always assured. The ratio of conformers depends, *inter alia*, on the reaction conditions (temperature, solvent, base), the *p*-substituent of the calix[4]arene and the steric demands and reactivity of the derivatizing reagent. The base in particular can play a pivotal role in the alkylation process. For example, with NaH as the base and *n*-propyl bromide as the alkylating agent, *p*-*tert*-butylcalix[4]arene yields a mixture containing 42% cone, 55% partial cone and 3% 1,3-alternate conformers.[7a] With Cs_2CO_3 as the base, however, the product mixture contains no cone, 34% partial cone, 9% 1,2-alternate and 57% 1,3-alternate conformer.[37a] Similarly, treatment of *p*-*tert*-octyl-calix[4]arene with an excess of $CH_3OCH_2CH_2OTs$ and NaH produces the cone conformer in 81% yield, while with $KOBu^t$ the partial cone conformer is formed in 64% yield.[147] Among the numerous additional examples are (a) the reaction of *p*-*tert*-butylcalix[4]arene with Et_2NCOCH_2Cl or $BrCH_2CO_2Et$, which produces a high yield of cone conformer with Na_2CO_3 as the base[148] but the partial cone with Cs_2CO_3 as the base;[149] and (b) the alkylation with 2-pyridylmethyl chloride and NaH, which gives the cone conformer exclusively, but K_2CO_3 or Cs_2CO_3 produces a mixture that contains only a small amount of cone conformer (9%) along with larger amounts of partial cone and 1,3-alternate conformers.[150]

Other influences affecting the conformational outcome include the *p*-substituent of the calixarene and the leaving group of the alkylating agent. For example, the greater tendency for *p*-H-calix[4]arene to form the 1,3-alternate conformer has been observed with *n*-propyl bromide as the alkylating agent and Cs_2CO_3 as the base.[37a] With the A,C-dipropyl ether of calix[4]arene the ratio of 1,3-alternate to partial cone conformer is 80:20 with *n*-propyl tosylate and 60:40 with *n*-propyl bromide.[151] Another study reported a cone to partial cone ratio of 42:55 with *n*-propyl bromide and 81:15 with *n*-propyl iodide with only a small amount (3–4%) of 1,3-alternate conformer in either case.[37a]

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[147] K. Araki, A. Yanagi and S. Shinkai, *Tetrahedron* **1993**, 49, 6763.

[148] A. Arduini, E. Ghidini, A. Pochini, R. Ungaro, G. D. Andreetti, G. Calestani and F. Ugozzoli, *J. Inclusion Phenom.* **1988**, 6, 119.

[149] K. Iwamoto, K. Fujimoto, T. Matsuda and S. Shinkai, *Tetrahedron Lett.* **1990**, 31, 7169.

[150] S. Pappalardo, *New J. Chem.* **1996**, 20, 465.

[151] W. Verboom, S. Datta, Z. Asfari, S. Harkema and D. N. Reinhoudt, *J. Org. Chem.* **1992**, 57, 5394.

Acylation reactions are also sensitive to the reaction conditions, the *p*-substituent of the calixarene and the particular acylating agent, as illustrated in the following examples. Acylation of *p-tert*-butylcalix[4]arene gives (a) with acetyl chloride/NaH an 89% yield of the cone conformer;[152] (b) with acetic anhydride/H_2SO_4 a 42% yield of the partial cone conformer along with 19% 1,3-alternate and 6% 1,2-alternate;[153] (c) with acetic anhydride/*p*-toluenesulfonic acid a mixture containing 1,3-alternate (36%), 1,2-alternate (15%) and partial cone (3%) conformers.[154] Acylation of *p*-H-calix[4]arene,[155] on the other hand, gives (a) with acetyl chloride/NaH a 2:1 mixture of partial cone and cone conformers; (b) with acetic anhydride/H_2SO_4 a 6:5 mixture of 1,3-alternate and partial cone conformers; (c) with isobutyryl chloride/NaH a 74% yield of cone conformer; (d) with isobutyryl anhydride a 55:13 mixture of partial cone and 1,3-alternate conformers, leading to the conclusion[155] that the *p-tert*-butyl group usually favors the cone conformation in the acylation reaction. Unexpectedly, the 1,2-alternate is the major conformer (43% yield) from *p-tert*-butylcalix[4]arene and N,N-dimethylthiocarbamate/NaH.[42] *p*-Allylcalix[4]arene generally yields the 1,3-alternate conformer upon acylation. A study of the effect of *p*-substituents in the aroylating agents on the conformational outcome[156] showed that electron releasing groups (*i.e.* OMe) increase the amount of 1,3-alternate conformer, while electron withdrawing groups (*i.e.* NO_2) increase the amount of cone conformer. This was interpreted as a competition between conformational inversion and aroylation; lower temperature (which decreases the rate of conformational interconversion) along with more reactive aroylation agents (which compete more effectively with the conformational inversion) favor formation of the cone conformer. With *p*-cyanomethylcalix[4]arene the 1,3 alternate conformer is the major product of aroylation in most cases, two exceptions being with 3,5-dinitrobenzoyl chloride, which produces a mixture of 1,3-alternate and partial cone conformers,[157] and *p*-bromobenzenesulfonyl chloride, which yields the cone conformer.[158]

Like the tetraethyl ethers of calix[4]arenes, the tetraacetates are conformationally stable in solution at room temperature but slowly equilibrate in DMSO-d_6 at 150 °C. Although the conversion of cone to partial cone conformation occurs rapidly (30 min) at this temperature, the overall equilibrium mixture requires a much longer time (384 hrs) to be established and consists of partial cone (18%), 1,2-alternate (43%) and 1,3-alternate (33%) conformations.[153] The authors postulate that the decreasing order of conformer stability

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[152] K. No and H. J. Koo, *Bull. Korean Chem. Soc.* **1994**, 15, 483. It is also reported that under presumably identical conditions the product is 35% tetraacetate in the cone conformation accompanied by 13% of the triacetate and 4% of the monoacetate (S. Akabori, H. Sannohe, Y. Habata, Y. Mukoyama and T. Ishii, *J. Chem. Soc. Chem. Commun.* **1996**, 1467).

[153] S. Akabori, H. Sannohe, Y. Habata, Y. Mukoyama and T Ishii, *J. Chem. Soc. Chem. Commun.* **1996**, 1467.

[154] C. Jaime, J. de Mendoza, P. Pados, P. M. Nieto and C. Sánchez, *J. Org. Chem.* **1991**, 56, 3372.

[155] T. Saiki, K. Goto, N. Tokitoh, M. Goto and R. Okazaki, *Tetrahedron Lett.* **1996**, 37, 4039; T. Saiki, K. Goto, N. Tokitoh and R. Okazaki, *J. Org. Chem.* **1996**, 61, 2924.

[156] M. Iqbal, T. Mangiafico and C. D. Gutsche, *Tetrahedron* **1987**, 43, 4917.

[157] S. K. Sharma and C. D. Gutsche, *Synthesis* **1994**, 813.

[158] S. K. Sharma, I. Alam and C. D. Gutsche, *Synthesis* **1995**, 1089.

is 1,3-alternate > 1,2-alternate > partial cone ≫ cone, which is quite different from that of the tetraalkyl ethers (*cf.* Section 4.2) and is attributed to the greater bulk of an acetyl group compared with an ethyl group.

4.6.2 Mono-, Di- and Tri-O-substitution of Calix[4]arenes

Replacement of the hydrogens of one, two or three of the OH groups of calix[4]arenes with alkyl, acyl or aroyl groups gives products that are generally most stable in the cone conformation but in which the ArOH moieties have the potential for assuming either the "up" or "down" orientation. For example, the possible conformations for the monobenzyl ether of *p*-*tert*-butylcalix[4]arene include one cone, three partial cones, one 1,2-alternate and one 1,3-alternate. In solution the cone conformer is much the most stable, so conformational inversion is not detectable on the ^{1}H NMR time-scale. Further alkylation, acylation or aroylation of a partially O-substituted calix[4]arene ultimately yields a tetra-O-substituted product in which the conformational outcome reflects the flexibility of the ArOH moieties of the intermediates. These pathways have been studied with several alkylating agents, including *n*-propyl bromide,[37a] pyridylmethyl chloride,[150] and benzyl halides.[159]

Although it is difficult to draw hard and fast conclusions from the data in the literature, the following generalizations appear to apply: (a) the tetraalkylation process proceeds in a stepwise fashion, and the products generally are the result of kinetic control; (b) the conformation of the tetraether is mainly but not completely fixed at the trialkylation stage, more so with NaH than with Cs_2CO_3; (c) the "up/down" interconversion of the ArOH moieties occurs less readily with Na^+ as the cation than with Cs^+; thus, in the conversion of a triether (cone conformation) to a tetraether[150] the cone conformation is completely retained with Na^+, partially retained with K^+ and completely inverted to partial cone with Cs^+; (d) strong bases such as NaH favor the formation of tetraethers in the cone conformation; (e) small *p*-substituents in the calixarene favor 1,3-alternate conformers (*e.g.* H *vs.* *t*-Bu[150]); CH_2CN *vs.* the highly branched $C(CH_2C_6H_5)_2CN$).[160]

4.6.3 O-Substitution of Calix[5]arenes and Calix[6]arenes

Calix[5]arenes in which the "*endo* rim through the annulus" pathway for conformational inversion has been curtailed by large substituents frequently adopt a cone conformation. Among the exceptions are (a) the penta-benzyl ether of calix[5]arene, which adopts a 1,2-alternate conformation both in the solid state and in solution; (b) the penta-$CH_2CO_2Bu^t$ and $CH_2CH_2OPr^i$ ethers of *p*-H-calix[5]arene (which can still undergo conformational inversion *via* the *exo* rim through the annulus pathway); and (c) the penta-CH_2CH_2OEt ether of

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[159] C. D. Gutsche and P. A. Reddy, *J. Org. Chem.* **1991**, 56, 4783; S. K. Sharma and C. D. Gutsche, *Tetrahedron* **1994**, 50, 4087.

[160] S. K. Sharma and C. D. Gutsche, *Tetrahedron* **1994**, 90, 4087.

p-tert-butylcalix[5]arene, which adopts partial cone conformations.[114] Calix[6]arenes are completely conformationally stable only when groups larger than *tert*-butyl occupy the *exo* rim positions and groups larger than O-benzyl occupy the *endo* rim positions. Consequently, there have been few if any systematic studies of the conformational implications of this type of substitution, the major attention having been directed to the conformations of the bridged calix[6]arenes.

4.6.4 Calixarene Oxyanions

4.6.4.1 Calix[4]arene Oxyanions

Treatment of calix[4]arenes with *n*-butyllithium in incremental amounts (corresponding to one, two, three and four equivalents per equivalent of calixarene) produces solutions whose UV spectra show a progressive increase in absorptivity at *ca.* 310 nm (characteristic of a phenoxide), up to the addition of the fourth equivalent.[161] The ^{1}H NMR spectrum shows a well-resolved pair of doublets in the δ2.5–5.0 region for the one-equivalent and four-equivalent solutions (characteristic of a cone conformation), a more complex pattern for the three-equivalent solution (characteristic of a partial cone conformation) and a still more complex pattern for the two-equivalent solution. The temperature-dependent ^{1}H NMR spectra indicate that the monoanion is only slightly less flexible than the parent compound, while the tri- and tetra-anions are considerably less flexible (coalescence temperature $>160\,°C$). Complementary data were obtained from the ^{7}Li NMR spectra, which displayed a single resonance for the mono- and tetra-anions, three resonances for the tri-anion and a pattern for the di-anion which could be interpreted as a superposition of the mono- and tri-anions. X-Ray crystallography of the tetra-ion confirms its cone structure.[162]

4.6.4.2 Calix[6]arene Oxyanions

Calix[6]arenes present a conformationally more convoluted system than calix[4]arenes. A study[163] of their oxyanions shows that changes in the ^{1}H NMR spectra occur as incremental amounts of strong base are added, up to six equivalents. A comparison of the temperature-dependent behavior of the lithium and sodium oxyanions indicates that the sodium system is the less conformationally mobile of the two. The X-ray crystallographic structure of a dianion ($HNEt_3^+$ counterion) shows it to be in a distorted 1,2,3-alternate conformation.[164]

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[161] C. D. Gutsche, M. Iqbal, K. C. Nam, K. A. See and I. Alam, *Pure Appl. Chem.* **1988**, 60, 483; K. C. Nam, D. S. Kim and J. M. Kim, *Bull. Korean Chem. Soc.* **1997**, 18, 636.

[162] M. G. Davidson, J. A. K. Howard, S. Lamb and C. W. Lehmann, *Chem. Commun.* **1997**, 1607.

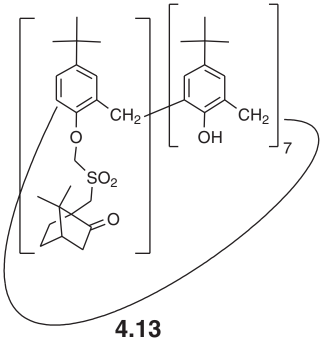
[163] C. D. Gutsche, I. Alam, M. Iqbal, T. Mangiafico, K. C. Nam, J. Rogers and K. A. See, *J. Inclusion Phenom Molec. Recognit.* **1989**, 7, 61.

[164] P. Thuéry, N. Keller, M. Lance, J.-D. Vigner and M. Nierlich, *J. Inclusion Phenom. Molec. Recognit. Chem.* **1995**, 20, 89.

4.7 Chiral Calixarenes (*Apndx B-19*)

The phenomenon of chirality, albeit subtle, is a consequence of shape, and is appropriate, therefore, for inclusion in this chapter. The creation of chirality in calixarenes can be achieved in two ways, *viz*. (a) by attaching a chiral moiety to a calixarene framework or (b) by establishing a dissymmetric or asymmetric set of aryl moieties in the cyclic array of the calixarene framework (often referred to as an inherent chirality).

The first of these, the attachment of a chiral moiety, is generally the easier to accomplish, usually *via* etherification and esterification at the *endo* rim. The earliest example is the camphorsufonyl derivative of *p*-*tert*-butylcalix[8]arene **4.13**[165] reported in 1979. Since that time, many other chiral calixarenes have been made *via endo* rim chemistry, one among the many representative examples being the hexa-cholesteryl ester of *p*-*tert*-butylcalix[6]arene **4.14**.[166] Two examples among the numerous *exo* ring-functionalized calixarenes are the menthone-substituted compounds of calix[5,6, and 8]arene **4.15**[167] and the tetrapropyl ether of *p*-alanylamidocarbonylcalix[4]arene **4.16**.[168] Calix[4]resorcarenes are equally amenable to the attachment of chiral moieties such as compound **4.17** containing proline moieties.[169]



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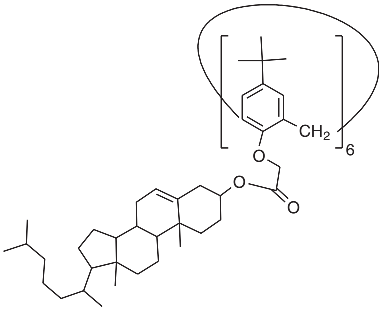

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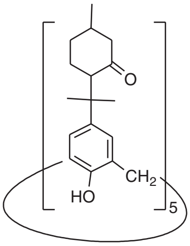

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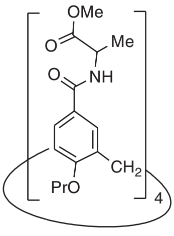
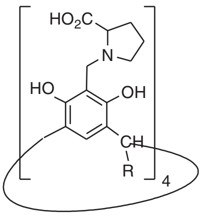


4.16



4.17

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[165] R. Muthukrishnan and C. D. Gutsche, *J. Org. Chem.* **1979**, 44, 3962.

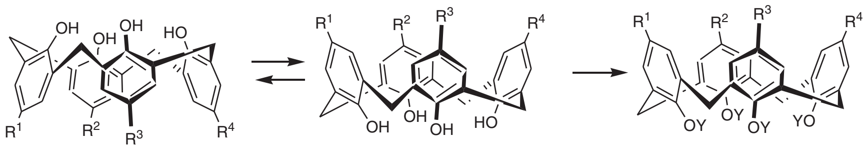
[166] H. Otsuka, K. Araki and S. Shinkai, *Chem. Express* **1993**, 8, 479.

[167] A. Soi, J. Pfeiffer, J. Jauch and V. Schurig, *Tetrahedron Asymm.* **1999**, 177.

[168] F. Sansone, S. Barboso, A. Casnati, M. Fabbi, A. Pochini, F. Ugozzoli and R. Ungaro, *Eur. J. Org. Chem.* **1998**, 5, 897.

[169] R. Yanagiha, M. Tominaga and Y. Aoyama, *J. Org. Chem.* **1994**, 59, 6865.

The synthesis of an inherently chiral calixarene generally presents a greater synthetic challenge than does the attachment of a chiral moiety. To construct an inherently chiral calixarene in the cone conformation *via* substitutions on either the *endo* or *exo* rim it is necessary to establish an ABCD, AABC or ABAC pattern of aryl groups. The earliest example of a calixarene with an AABC pattern is the calix[4]arene **4.18** (R^1, R^2 = *p*-*tert*-butyl, $R^3 = \mathrm{PhCOCH_3}$, $R^4 = \mathrm{PhCO_2H}$).[170] A second example appeared a few years later in which a variety of groups, including Me, *tert*-Bu, phenyl, cyclohexyl and Cl were introduced onto the *exo* rim.[171] In both cases, however, the products were unresolvable mixtures of two rapidly interconverting cone conformers. To create a calixarene capable of optical resolution it is necessary to curtail conformational interconversion. In the case of compounds like **4.18** this is accomplished by placing sufficiently large groups on the *endo* rim to produce **4.19**. *Endo* rim groups, in addition to serving this purpose, can themselves also provide the seat of chirality. For example, the calixarene **4.20** functionalized in an AABC fashion on the *endo* rim has been resolved into optical antipodes by passage through a chiral chromatographic column.[172] Whereas only an ABCD, AABC or ABAC combination of aryl rings in a cone conformer can give rise to a chiral calixarene, other conformers[173] can be less demanding, especially the partial cone which lacks any axes of symmetry higher than C_1. Thus, a partial cone conformer or a 1,2-alternate conformer with an AAAB pattern of aryl rings is chiral and can be resolved if conformationally stable, *e.g.* **4.20** (Y = a group larger than Et). All of the illustrations cited above involve calixarenes in which every aryl group possesses a plane of symmetry. If one or more of the aryl groups is desymmetrized a chiral compound is produced, *e.g.* **4.21**, which, in fact, was the first chiral calixarene to be resolved.[174]



4.18 **4.19**

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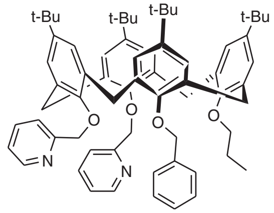
[170] K. H. No and C D. Gutsche, *J. Org. Chem.* **1982**, 47, 2713.

[171] V. Böhmer, L. Merkel and U. Kunz, *J. Chem. Soc. Chem. Commun.* **1987**, 896.

[172] S. Caccamese and S. Pappalardo, *Chirality* **1993**, 5, 159; G. Ferguson, J. F. Gallagher, L. Giunta, P. Neri, S. Pappalardo and M. Parisi, *J. Org. Chem.* **1994**, 59, 42.

[173] K. Iwamoto, H. Shimizu, K. Araki and S. Shinkai, *J. Am. Chem. Soc.* **1993**, 115, 3997; *idem*, *ibid.* **1993**, 115, 12228.

[174] S. Shinkai, T. Arimura, H. Kawabata, H. Murakami, K. Araki, K. Iwamoto and T. Matsuda, *J. Chem. Soc. Chem. Commun.* **1990**, 1734.



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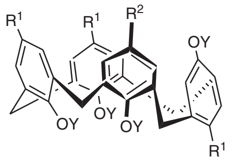

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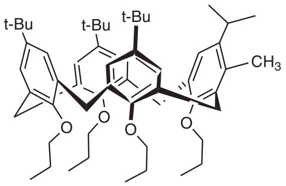
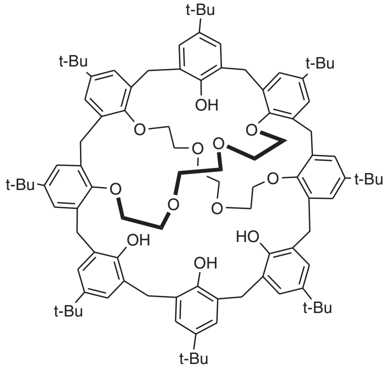


4.21



4.22

As discussed in Section 4.5.2, bridging can provide a powerful way to curtail conformational inversion and provide resolvable chiral compounds. This has been used effectively with the calix[4]arenes, and it becomes a particularly powerful tool with the larger calixarenes where simple etherification or esterification may not suffice to prevent conformational mobility. Thus, *p-tert*-butylcalix[6]arene bridged across the 1,4-positions on the *endo* rim with a 1,10-phenanthroline moiety cannot undergo complete conformational inversion and is rendered chiral by the addition of *p*-tolyl groups at the 2,5-positions on the *endo* rim.[175] Likewise, with the very flexible calix[8]arenes, compound **4.22** for example, is topologically incapable of conformational inversion because of the 1,3 and 2,5 bridges and is amenable to resolution.[176]

4.8 Concluding Remarks

The material in the first four chapters of this book has included a significant amount of historical perspective of the calixarenes, a fairly detailed discussion of methods for their synthesis, a close look at their physical attributes, and a modestly extended discussion of their shape, including both conformational and chiral aspects. The last remaining facet of basic calixarene chemistry yet to be discussed concerns the many ways in which the parent molecules can be converted to functionalized molecules, and this provides the material for the following chapter.

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[175] S. Konrad, M. Bolte, C. Näther and U. Lüning, *Eur. J. Org. Chem.* **2006**, 4717.

[176] C. Caccamese, G. Principato, C. Geraci and P. Neri, *Tetrahedron Asymmetry* **1997**, 8, 1169.

CHAPTER 5

Embroidering the Baskets: Introduction of Functional Groups

"Twirl follows twirl and every synthesis is the thesis of the next series"

Vladimer Nabakov, *Speak, Memory,* 1966

Much of the interest in calixarenes derives from their potential for use in a wide variety of applications. In most cases this depends not only on the basket-like character of the molecules but also on the presence of appropriate functional groups. This chapter presents the various methods for embroidering the calixarene baskets with these functional groups.

5.1 Functionalization Involving the OH Groups (*Apndx A-2, p. 26, 54, 71, 89*)

The phenol-derived and resorcinol-derived calixarenes are already functionalized with OH groups, and these provide excellent handles for affixing other moieties by replacement of either the H or the entire OH.

5.1.1 Esterification

The esters of calixarenes were the earliest derivatives to be prepared. Although most subsequent studies have concentrated more heavily on calixarene ethers, the esters continue to command attention. With acid halides and NaH, acid halides and $AlCl_3$, or acid anhydrides and H_2SO_4 the acylation or aroylation generally involves all of the OH groups if the derivatizing agent is used in excess. Several exceptions have been reported, however, a typical example being the benzoylation of calix[4]arene with benzoyl chloride/NaH which gives the

A,C-diester.[1] A study of the esterification of calix[4]arenes[2] showed that acetylation, propionylation, butyrylation, and isobutyrylation all yield the tetraacylates, although with varied and somewhat unpredictable conformational outcomes. Similarly, the penta-acetate, -propionate, -*n*-butanoate, –isobutanoate, -cyclopropylcarbanoate, -pivaloate, -benzoate and -tosylate of *p*-*tert*-butylcalix[5]arene have been prepared *via* either the acid halide/NaH or the anhydride/H_2SO_2 procedure, again with varied conformational outcomes.[3] While acetylation of the calix[6]arenes goes to completion to form the hexaacetates, aroylation is less likely to do so.[4] Calix[7]arenes remain largely unstudied, but *p*-*tert*-butylcalix[8]arene readily forms the octaacetate.[5]

Esterification studies carried out in the 1990s focused primarily on partial substitution. By using acid halides in the presence of bases weaker than NaH, by using limiting amounts of the esterifying reagent and/or by using bulky esterifying reagents it is often possible to obtain partially substituted calixarenes in selective fashion. The early example of *p*-*tert*-butylcalix[4]arene reacting with benzoyl chloride in the presence of pyridine to give the tribenzoate[6] has been followed by several other studies, one of which reveals the rather complex situation encountered with 3,5-dinitrobenzoyl chloride as the esterifying reagent.[7a] The scheme shown in Figure 5.1 illustrates the effect that seemingly small changes in reaction conditions can have on the outcome of the reaction in which *p*-*tert*-butylcalix[4]arene can be converted directly and/or indirectly to the monoester **5.4**, the *syn*-A,C-diester **5.1**, the *syn*-A,B-diester **5.5**, the *anti*-A,B-diester **5.6**, the *syn*-*anti*-*syn* triester **5.2** or the *syn*-*syn*-*syn*- triester **5.3** simply by changing the relative number of equivalents of reactants, the base (*i.e.* imidazole, 1-methylimidazole and 1-butylimidazole) and the solvent (*i.e.* $CHCl_3$. MeCN). The rearrangement of the *syn*-A,C-diester **5.1** to the *anti*-A,B-diester **5.6** is attributed to a cleavage/reassembly process in which the imidazole may play a cooperative role as nucleophile and proton acceptor/donor. Cesium carbonate promotes a similar rearrangement, and this has been ascribed to a template phenomenon involving the cesium cation.[7b]

Among the larger calixarenes (a) a tetrapivaloate has been prepared from *p*-*tert*-butylcalix[5]arene and pivaloyl chloride/NaH;[3] (b) calix[6]arenes A,B,D,E-tetraesters can be obtained in good yield with aroyl chlorides and 1-methylimidazole[4] or NaH[8] and (c) several heptaaroylates of *p*-*tert*-butylcalix[8]arene have been prepared in 45–80% yields by using a slight excess of aroylating agent in the presence of pyridine.[9]

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[1] C.-M. Shu, W.-C. Liu, M.-C. Ku, F.-S. Tan, M.-L. Yeh and L.-G. Lin, *J. Org. Chem.* **1994**, 59, 3730.

[2] K. No and H. J. Koo, *Bull. Korean Chem. Soc.* **1994**, 15, 483.

[3] D. R. Stewart, M. Krawiec, R. P. Kashyap, W. H. Watson and C. D. Gutsche, *J. Am. Chem. Soc.* **1995**, 117, 586.

[4] J. S. Rogers and C. D. Gutsche, *J. Org. Chem.* **1992**, 57, 3152.

[5] C. D. Gutsche, B. Dhawan, K. H. No and R. Muthukrishnan, *J. Am. Chem. Soc.* **1981**, 103, 3782.

[6] C. D. Gutsche and L.-G. Lin, *Tetrahedron* **1986**, 42, 1633.

[7] (a) K. A. See, F. R. Fronczek, W. H. Watson, R. P. Kashyap and C. D. Gutsche, *J. Org. Chem.* **1991**, 56, 7256; (b) J. A. Lynch, J. J. Mestayer and M. T. Blanda, *J. Supramol. Chem.* **2001**, 1, 139.

[8] S. Kanamathareddy and C. D. Gutsche, *J. Org. Chem.* **1992**, 57, 3160.

[9] G. M. L. Consoli, F. Cunsolo, M. Piatelli and P. Neri, *J. Org. Chem.* **1996**, 61, 2195.

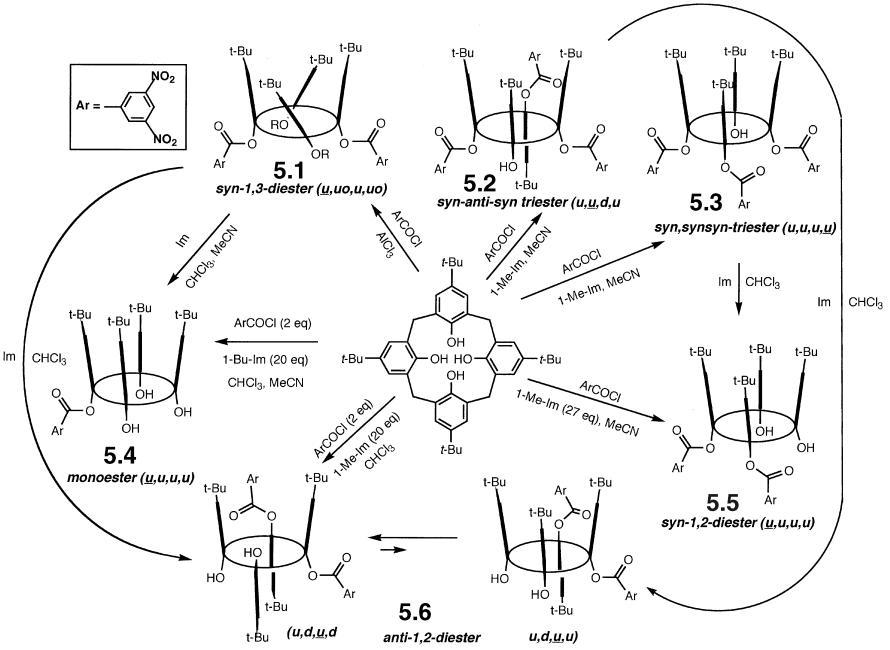

Figure 5.1 Esterification of *p-tert*-butylcalix[4]arene with 3,5-dinitrobenzoyl chloride. For viewing convenience the conformational designations start with the left-hand aryl group and proceed in clockwise fashion around the ring, with the reference group specified with an underlined "u" or "d" (*cf.* Section 4.1).

5.1.2 Etherification

5.1.2.1 With Simple Alkyl Halides

Alkylation has been studied in considerable detail in the calix[4]arene series, and methods have been devised for preparing the mono-, di- (A,B and A,C), tri- and tetra-ethers. Monoethers **5.7a** can be prepared in moderate to good yields by direct alkylation using (a) a strong base such as NaH in toluene[10] or NaOMe in acetonitrile,[11] (b) a weak base such as $Ba(OH)_2$ in DMF,[10] K_2CO_3 in MeCN or CsF in DMF with an excess of alkylating agent[12] or (c) bis(tributyltin)oxide in boiling toluene.[13] The surprising difficulty in avoiding polyalkylation in spite

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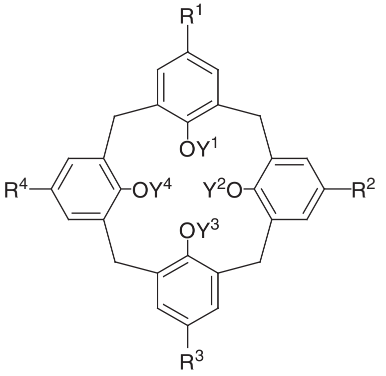
[10] K. Iwamoto, K. Araki and S. Shinkai, *Tetrahedron* **1991**, 47, 4325.

[11] C.-M. Shu, W.-S. Chung, S.-H. Wu, Z.-C. Ho and L.G. Lin, *J. Org. Chem.* **1999**, 64, 2673.

[12] L. C. Groenen, B. H. M. Ruël, A. Casnati, W. Verboom, A. Pochini, R. Ungaro and D. N. Reinhoudt, *Tetrahedron* **1991**, 47, 8379.

[13] F. Santoyo-González, A. Torres-Pinedo and A. Sanchéz-Ortega, *J. Org. Chem.* **2000**, 65, 4409.

of the large gap between pK_1 and pK_2 of the calix[4]arenes (see Section 3.3.3) is attributed to the comparable pK_1 values for the parent calix[4]arene and its monoalkylated counterpart; the proton that is abstracted from the OH group distal to the OR moiety of the monoether leads to a monoanion stabilized by hydrogen bonding to the two flanking OH groups.[12] An alternative to direct alkylation for generating partially alkylated calixarenes involves selective dealkylation of the A,C-diethers **5.7c** or tetraethers **5.7e** with stoichiometric amounts of Me_3SiI.[14] Another alternative takes advantage of the accessibility of the mono-3,5-dinitrobenzoyl ester of calix[4]arene and involves alkylation at the distal ArOH followed by hydrolytic removal of the ester function.[15] Monobenzylation of A,C-*p*-dinitrocalix[4]arene has been achieved with benzyl bromide and Me_3SiK, which gives an 82% yield of **5.7f**, the alkylation occurring preferentially on one of the *p*-nitrophenyl rings.[16] On the other hand, benzoylation of this same calixarene with $AlCl_3$ as the catalyst yields **5.7g**, the aroylation occurring preferentially on the aryl rings lacking the *p*-NO_2 groups.[16]



5.7

a) $Y^1 = R'; Y^{2\text{-}4} = H$

b) $Y^{1,2} = G; Y^{3,4} = H$

c) $Y^{1,3} = G; Y^{2,4} = H$

d) $Y^{1\text{-}3} = G, Y^4 = H$

e) $Y^{1\text{-}4} = G$

G = alkyl, CH_2Ar, CH_2Py, etc

f) $Y^{1,3,4} = H; Y^2 = CH_2Ph; R^{1,3} = H; R^{2,4} = NO_2$

g) $Y^{1,3} = COPh; Y^{2,4} = H; R^{1,3} = H; R^{2,4} = NO_2$

Di-ethers can be either proximal (*i.e.* A,B) or distal (*i.e.* A,C). Distal dialkylation is generally more easily achieved than proximal dialkylation. Under conditions similar to those leading to mono-ethers but with an excess of the alkylating agent, A,C-diethers **5.7c** are produced, often in very high yields.[17,18] Starting with a mono-ether, a second group different from the first

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[14] A. Casnati, A. Arduini, E. Ghidini, A. Pochini and R. Ungaro, *Tetrahderon* **1991**, 47, 2221.

[15] K. C. Nam, J. M. Kim and D. S. Kim, *Bull. Korean Chem. Soc.* **1995**, 16, 186; Y. J. Park, J. M. Shin, K. C. Nam, J. M. Kim and S.-K Kook, *ibid.* **1996**, 17, 643.

[16] S. K. Sharma and C. D. Gutsche, *J. Org. Chem.* **1996**, 61, 2564.

[17] P. J. Dykstra, J. A. J. Brunink, K.E. Bugge, D. N. Reinhoudt, S. Harkema, R. Ungaro, F. Ugozzoli and E. Ghidini, *J. Am. Chem. Soc.* **1989**, 111, 7567; K. No and M. Hong, *J. Chem. Soc. Chem. Commun.* **1990**, 572.

[18] J.-D. van Loon, A. Arduini, L. Coppi, W. Verboom, A. Pochini, R. Ungaro, S. Harkema and D. N. Reinhoudt, *J. Org. Chem.* **1990**, 55, 5639.

can be introduced.[19] Proximal dialkylation leading to A,B-diethers **5.7b** can be carried out by direct alkylation or by selective dealkylation. With direct alkylation a strong base (*e.g.* NaH) is used with a limiting amount of alkylating agent.[20] For example, *p*-*tert*-butylcalix[4]arene treated with 4 equivalents of pyridylmethyl chloride and NaH in DMF gives a 70% yield of the A,B-diether **5.7b** ($R = t$-Bu; $Y = CH_2Py$) accompanied by only small amounts of the mono- and tri-ether.[21] Proximal substitution is the result, in part, of the statistical advantage, but more particularly it is the result of the formation of the trianion of the mono-alkyl precursor in which the anion *proximal* to the ArOR moiety (introduced in the first step) is a stronger nucleophile (*i.e.* conjugate base of a weaker acid) than the oxyanion *distal* to this moiety.[22] Thus, A,C-dialkylation is due to *selective anion formation* at the distal ArOH group, while A,B-dialkylation is due to the *selective reactivity* of the proximal ArO^- group. A selective dealkylation route has been applied in which treatment of the tetramethyl ether of *p*-*tert*-butylcalix[4]arene with 2 equivalents of $TiBr_4$ in $CHCl_3$ gives the A,B-dimethyl ether in good yield.[23]

Trimethylation of *p*-*tert*-butylcalix[4]arene to give **5.7d** ($R = t$-Bu; $Y^{1-3} = Me$) can be accomplished in fair yield with Me_2SO_4 in DMF in the presence of $BaO.Ba(OH)_2$.[24] Higher yields of triether, however, are obtained when the starting material is already partially alkylated. The *syn*-A,B dipyridylmethyl ether of *p*-*tert*-butylcalix[4]arene, for example, produces a high yield of the triether **5.7d** ($R = t$-Bu, $Y^{1-3} = CH_2Py$) in the cone conformation when treated with pyridylmethyl chloride and K_2CO_3 in DMF; the *syn*-A,C analog gives a considerably lower yield of the same triether in the partial cone conformation accompanied by other products.[21] Another approach to the triether as well as the mono- and di-ethers involves protection/de-protection sequences.[10,25]

Tetraalkylation of calix[4]arenes to give **5.7e** is generally carried out with an excess of the alkylating agent in the presence of the strong base NaH, although in some instances the much weaker base K_2CO_3 suffices (*vide supra*). A wide variety of alkyl and aralkyl groups have been introduced in this fashion, ranging in size from Me to naphthylmethyl[26] and even larger. As discussed in Chapter 4,

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[19] G. Ferguson, J. F. Gallagher, A. J. Lough, A. Notti, S. Pappalardo and M. F. Parisi, *J. Org. Chem.* **1999**, 64. 5876; G. Ferguson, J. F. Gallagher, L. Guinta, P. Neri, S. Pappalardo and M. Parsi, *ibid.* **1994**, 59, 42.

[20] J. A. J. Brunink, W. Verboom, J. F. J. Engbersen, S. Harkema and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* **1992**, 111, 511.

[21] (a) S. Pappalardo, *New. J. Chem.* **1996**, 20, 465; (b) L. C. Groenen, B. H. M. Ruël, A. Casnati, P. Timmerman, W. Verboom, S. Harkema, A. Pochini, R. Ungaro and D. N. Reinhoudt, *Tetrahedron Lett.* **1991**, 12, 2675.

[22] K. Araki, K. Iwamoto, S. Shigematsu and S. Shinkai, *Chem. Lett.* **1992**, 1095.

[23] A. Arduini, A. Casnati, L. Dodi, A. Pochini and R. Ungaro, *J. Chem. Soc. Chem. Commun.* **1990**, 1597.

[24] C. D. Gutsche, B. Dhawan, J. A. Levine, K. H. No and L. J. Bauer, *Tetrahedron* **1983**, 39, 409.

[25] Z.-C. Ho, M.-C. Ku, C.-M. Shu and L.-G. Lin, *Tetrahedron* **1996**, 52, 13189; M. P. Oude Wolbers, F. C. J. M. van Veggel, R. H. M. Heeringa, J. W. Hofstraat, F. A. J. Geurts, G. J. van Hummel, S. Harkema and D. N. Reinhoudt, *Liebigs Ann/Recueil* **1997**, 2587.

[26] S. K. Sharma and C. D. Gutsche, *Tetrahedron* **1994**, 50, 4087.

the conformations of the tetra-ethers that are produced[27] depends on (a) the alkylating agent, (b) the *p*-substituent of the calixarene, (c) the reaction conditions, *viz*. the base, solvent and temperature and (d) template effects of the cation accompanying the base.[28] Arylation to give O-Ar ethers has been achieved by the use of the Ullmann reaction with *o*-nitrophenylhalides.[29]

Only a few examples of pentaalkyl ethers of calix[5]arenes have been published.[3,30,31] The mono-ethers that have been made include the methyl, ethyl, *n*-propyl, *n*-benzyl and pyridylmethyl compounds. The 1,2-dimethyl-, 1,3-dimethyl-, 1,2,3-trimethyl, 1,2,4-trimethyl- and tetra-methyl ethers[3] as well as their pyridylmethyl ether counterparts[31] have also been prepared. The calix[6]arenes, on the other hand, have attracted considerable attention. By the use of a combination of direct alkylation methods and by taking advantage of the knowledge gained from the calix[4]arene series all twelve of the methyl ethers[32,33,34] and ten of the twelve pyridylmethyl ethers[35] have been synthesized.[36] Larger alkyl groups, including butyl, octyl[37] and arylmethyl[38] have also been introduced. It was found that with NaH the A,B,D,E-tetraether is the major product, while with Me_3SiOK the A,D-diether is formed preferentially. This is attributed to a cation effect, K^+ forming a complex with the OH groups at the B,C,E,F-rings, leaving the OH groups at the A and D rings more accessible to reaction with the arylmethyl halide.[38]

The calix[8]arenes present an even more complicated case (*Apndx C-12*). In addition to the fully O-substituted calix[8]arenes, which can be obtained by treatment with strong bases and a large excess of derivatizing agent,[39] 27 partially alkylated calix[8]arenes are possible. In spite of this daunting prospect Placido Neri and coworkers have made considerable headway in unraveling the intricacies of this system. The direct methylation has been studied in considerable detail,[40] and procedures have been worked out for generating some of

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[27] M. Iqbal, T. Mangiafico and C. D. Gutsche, *Tetrahedron* **1987**, 43, 4917.

[28] A. Casnati, A. Pochini, R. Ungaro, R. Cacciapaglia and I. Mandolini, *J. Chem. Soc. Perkin Trans 1* **1991**, 2052.

[29] R. Muthukrishnan and C. D. Gutsche, *J. Org. Chem.* **1979**, 22, 3962; S. Chowdhury and P. E. Georghiou, *ibid*. **2001**, 66, 6257.

[30] B. Souley, Z. Asfari and J. Vicens, *Pol. J. Chem.* **1993**, 67, 763.

[31] S. Pappalardo and G. Ferguson, *J. Org Chem.* **1996**, 61, 2407.

[32] R. G. Janssen, W. Verboom, D. N. Reinhoudt, A. Casnati, M. Freriks, A. Pochini, F. Ugozzoli, R. Ungaro, P. M. Nieto, M. Carramolino, I. Cuevas, P. Prados and J. de Mendoza, *Synthesis* **1993**, 380.

[33] (a) H. Otsuka, J. Araki and S. Shinkai, *J. Org. Chem.* **1994**, 59, 1542; (b) *idem*, *Tetrahedron* **1995**, 51, 8757.

[34] A. Casnati, P. Minari, A. Pochini and R. Ungaro, J. *Chem. Soc. Chem. Commun.* **1991**, 1413.

[35] P. Neri and S. Pappalardo, *J. Org. Chem.* **1993**, 58, 1048.

[36] In a study by Janssen *et al.* (ref. 32) showing the critical effect that small changes in reaction conditions can have on the product composition the especially useful A,C,E trimethyl ether (*cf.* **5.26**) was reported in 72% yield, a surprising increase from the previously reported 30% (*cf.* ref 34).

[37] (a) M. D. Conner, V. Janout and S. L. Regen, *J. Am. Chem. Soc.* **1993**, 115, 1178; (b) M. D. Conner, V. Janout, I. Kudelka, P. Dedek, J. Zhu and S. L Regen, *Langmuir* **1993**, 9, 2389.

[38] S. Kanamathareddy and C. D. Gutsche, *J. Org. Chem.* **1992**, 57, 3160.

[39] P. Neri, E. Battocolo, F. Cunsolo, C. Geraci and M. Piatelli, *J. Org. Chem.* **1994**, 59, 3880.

[40] G. M. L. Consoli, F. Cunsolo and P. Neri, *Gazzetta Chimica Ital.* **1996**, 126, 791; P. Neri, G M. L. Consoli, F. Cunsolo, C. Rocco and M. Piatelli, *J. Org. Chem.* **1997**, 62, 4236.

the partially methylated compounds in isolable yield, including the monomethyl ether (33%), A,C-dimethyl ether (52%), A,B,D-trimethyl ether (26%), A,B,C,D-tetramethyl ether (12%) and heptamethyl ether (23%). The major pathways for methylation are attributed to preferential formation of monoanions that are stabilized by hydrogen bonds to two flanking OH groups. The authors suggest, however, that the conformational flexibility of the calix[8]arene ring system might also allow stabilization from a non-flanking OH group, accounting for some of the minor pathways of alkylation.

5.1.2.2 With Functionalized Alkylating Agents

The replacement of the hydrogen of OH with an alkyl group might be considered as reducing the functionality by acting primarily as a protecting group. Alkylating agents of the structure $X(CH_2)_nY$ (X is a leaving group, generally Br or Tosyl; Y is a functional group), however, do introduce additional functionality onto the *endo* rim of calixarenes. Considering C=C and C≡C as proto-functional groups, the simplest examples employ $BrCH_2CH{=}CH_2$ to give allyl ethers **5.8a**[21b,41] and $BrCH_2C{\equiv}CH$ to give propargyl ethers **5.8b**.[42] In the majority of cases the Y of $X(CH_2)_nY$ contains a heteroatom (*e.g.* an OH group as in **5.8c**,[43] an amino group such as **5.8d**,[44] a pyridyl group as in **5.8e**,[21a] a functionalized benzyl group as in **5.8f**,[45] a nitroxo spin-labeled group as in **5.8g**,[46] *etc.*). The most often used reagents, however, are those generated from compounds of the general structure XCH_2COZ to give structures **5.9**, including: (a) ester **5.9a**[47a,b,c] (with R′ ranging from groups

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[41] C. D. Gutsche, J. A. Levine and P. K. Sujeeth, *J. Org. Chem.* **1985**, 50, 5802.

[42] S. Kanamathareddy and C. D. Gutsche, *J. Org. Chem.* **1995**, 60, 6070; W. Xu, J. Vittal, and R. J. Puddephatt, *J. Can. J. Chem.* **1996**, 74, 766.

[43] P. L. H. M. Cobben, R. J. M. Egberink, J. G. Bomer, P. Bergveld, W. Verboom and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1992**, 114, 10573; used, for example, for the attachment of nucleotides to calixarenes (G. M. L. Consoli, G. Granata, E. Galante, F. Cunsolo and C. Geraci, *Tetrahedron Lett.* **2006**, 47, 3245).

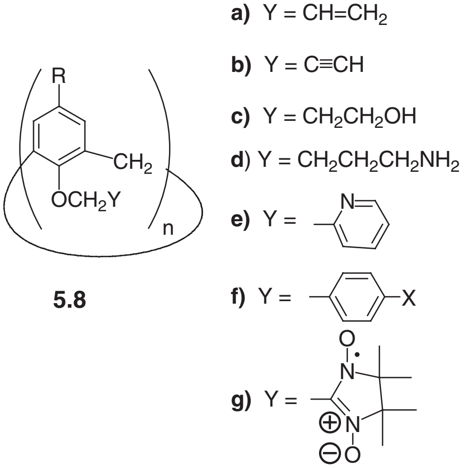
[44] M. Korochkina, M. Fontanella, A. Casnati, A. Arduini, F. Sansone, R. Ungaro, S. Latypov, V. Kataev and V. Alfonsov, *Tetrahedron* **2005**, 61, 5457.

[45] (a) X = NO_2 (Refs. 7, 8, and S. K. Sharma and C. D. Gutsche, *J. Org. Chem.* **1994**, 59, 6030); (b) X = halogen (Ref. 149); (c) X = CN (Ref. 8 and S. Kanamathareddy and C. D. Gutsche, *J. Org. Chem.* **1994**, 59, 3871).

[46] G. Ulrich, P. Turek and R. Ziessel, *Tetrahedron Lett.* **1996**, 48, 8755; also *cf.* X. Hu, Y. Li, H. Yang and Y. Luo, *Tetrahedron Lett.* **2006**, 47, 7463.

[47] (a) R. Ungaro, A. Pochini and G. D. Andreetti, *J. Inclusion Phenom. Molec. Recognit.* **1984**, 2, 199; (b) A. Arduini, A. Pochini, S. Reverberi, R. Ungaro, G. D. Andreetti and F. Ugozzoli, *Tetrahedron* **1986**, 42, 2089; (c) F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. L. Ruhl, M.-J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.* **1989**, 111, 8681; (d) K. Iwamoto and S. Shinkai, *J.Org. Chem.* **1992**, 57, 7066; (e) F. Arnaud-Neu, M.-J. Schwing-Weill, K. Ziat, S. Cremin, S. J. Harris and M. A. McKervey, *New J. Chem* **1991**, 15, 33; (f) F. Arnaud-Neu, G. Barrett, S. Cremin, M. Deasy, G. Ferguson, S. J. Harris, A. J. Lough, L. Guerra, M. A. McKervey, M.-J. Schwing-Weill and P. Schwinte, *J. Chem. Soc. Perkin Trans. 2* **1992**, 1119; (g) G. Barrett, M. A. McKervey, J. F. Malone, A. Walker, F. Arnaud-Neu, L. Guerra, M.-J. Schwing-Weill, C. D. Gutsche and D. R. Stewart, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1475; (h) H. Otsuka, K. Araki, T. Sakaki, K. Nakashima and S. Shinkai, *Tetrahedron Lett.* **1993**, 34, 7275.

as small as Me to as large as pyrenylmethyl,[48] cholesteryl,[47h] α-sialosidyl,[49] and fullereneyl;[50] (b) amides **5.9b**[51] and (c) ketones **5.9c** (Z = alkyl).[47c,52] Compounds such as **5.8a–d** and **5.9** can, in turn, be converted to a wide variety of other functional groups using standard synthesis procedures. Using the Mitsunobu reaction (diethyl azodicarboxylate and PPh_3) O-glycosyl groups have been introduced onto the *endo* rim.[53] Phosphorus-containing moieties have been introduced by treatment of calixarenes, *inter alia*, with Ph_2PCl[54] and with $TsOCH_2P(O)Ph_2$.[55]



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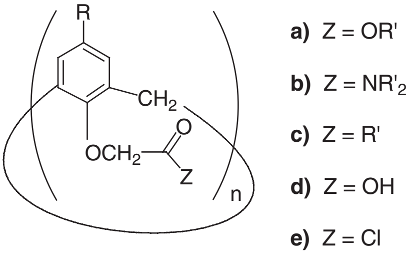

5.9

5.1.3 *Endo* Rim-bridged Calixarenes (*Apndx C-14; D-10, 14, 15*)

The use of *endo* rim bridges to curtail conformational flexibility was discussed in Section 4.5.2 where a number of bridging moieties were listed. Included in

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[48] M. Takeshita and S. Shinkai, *Chem. Lett.* **1994**, 125.

[49] S. J. Meunier and R. Roy, *Tetrahedron Lett.* **1996**, 37, 5469.

[50] A. Ikeda, T. Irisa, T. Hamano, T. Kitahashi, Y. Sasaki, M. Hashizume, J.-I. Kikuchi, T. Konishi and S. Shinkai, *Org. Biomol. Chem.* **2006**, 4, 519.

[51] (a) F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, F. Marques, G. L. Ruhl, M.-J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.* **1989**, 111, 8681; (b) F. Arnaud-Neu, M.-J. Schwing-Weill, K. Ziat, S. Cremin, S. J. Harris and M. A. McKervey, *New J. Chem.* **1991**, 15, 33; (c) C.-K Chang and I. Cho, *Chem. Lett.* **1984**, 4777; (d) *idem*, *J. Chem. Soc. Perkin Trans. 1* **1986**, 211; (e) S.-K. Chang, S.-K. Kwon and I. Cho, *Chem. Lett.* **1987**, 947; (f) G. Calestani, F. Ugozzoli, A. Arduini, E. Ghidini and R. Ungaro, *J. Chem. Soc. Chem. Commun.* **1987**, 344; (g) A. Casnati, P. Minari, A. Pochini, R. Ungaro, W. F. Nijenhuis, F. de Jong and D. N Reinhoudt, *Israel J. Chem.* **1992**, 32, 79.

[52] G. Ferguson, B. Kaitner, M. A. McKervey and E. M. Seward, *J. Chem. Soc. Chem. Commun.* **1987**, 584.

[53] A. Marra, M.-C. Scherrmann, A. Dondoni, A. Casnati, P. Minari, R. Ungaro, A. Casnati and P. Minari, *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 2479.

[54] J. K. Moran and D. Roundhill, *Inorg. Chem.* **1992**, 31, 4213; D. Matt, C. Loeber, J. Vicens and Z. Asfari, *J. Chem. Soc. Chem. Commun.* **1993**, 604.

[55] C. Loeber, D. Matt, A. De Cian and J. Fischer, *J. Organometallic Chem.* **1994**, 475, 297; C. Wieser, D. Matt, J. Fischer and A. Harriman, *J. Chem. Soc. Dalton Trans.* **1997**, 2391.

this list was the polyoxyethylene chain, which gives rise to the prototype of *endo* rim bridged calixarenes, *viz*. the calixcrown ethers. These were first synthesized in the early 1980s by the Parma group[56] and are now represented by many dozens of examples of varying structures, including calixazacrowns in which one or more nitrogen atoms take the place of oxygen atoms (*Apndx A-2, p. 365*). Two such A,C calix[4]crown ethers are illustrated by structures **4.1** and **4.2** (p 105). By employing the alkylation techniques described above (*cf*. Section 5.1.2.1) A,B calix[4]arene crown ethers[57] can also be constructed. A number of calixcrown ethers of the larger calixarenes have also been synthesized[58] (*Apndx A-2, p. 365; B-8*).

As discussed in Section 4.5.2, a wide variety of other types of bridges as well have been employed to span the *endo* rim of calixarenes. The simplest of these is a CH_2 bridge to span adjacent OH groups, as illustrated by structure **4.6** (p 106). Among the many other examples are hemispherand moieties to give **5.10a**,[59] di-glycosyl moieties to give **5.10b**,[60] the metallocene moieties to give **5.11**[61] and a variety of spanners of the general structure Ar-Ar or X-Ar-Z-Ar-X ($X = SO_2$, CO or CH_2, and $Z = CO$ or SO_2) as in **5.12**.[62] Several examples of porphyrins quadruply attached to the *endo* rim of a calix[4]arene have been reported, including **5.13a**,[63] **b**[64] and **c**.[65]

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[56] C. Alfieri, E. Dradi, A. Pochini, R. Ungaro and C. D. Andreetti, *J. Chem. Soc. Chem. Commun.* **1983**, 1075.

[57] (a) A. Arduini, A. Casnati, M. Fabbi, P. Minari, A. Pochini, A. R. Sicuri and R. Ungaro, *Supramolecular Chem.* **1993**, 1, 235; (b) H. Yamamoto, T. Sakaki and S. Shinkai, *Chem. Lett.* **1994**, 469; (c) S. Pappalardo, A. Petringa, M. F. Parisi and G. Ferguson, *Tetrahedron Lett.* **1996**, 37, 3907.

[58] *Calix[5]crown ethers* (D. Kraft, R. Arnecke, V. Böhmer and W. Vogt, *Tetrahedron* **1993**, 49, 6019; F. Arnaud-Neu, B. Arnecke, V. Böhmer, J. C. M. Panni, M. J. Gordon, M.-J. Schwing-Weill and W. Vogt, *J. Chem. Soc. Perkin Trans 2* **1996**, 1855; S. Pappalardo and M. F. Parisi, *J. Org. Chem.* **1996**, 61, 8274; S. Caccamese, A. Noti, S. Pappalardo, M. F. Parisi and G. Principato, *J. Incl. Phenom. Molec Recognit. Chem.* **2000**, 36, 67); *Calix[6]crown ethers* (A. Casnati, P. Jacopozzi, A. Pochini, F. Ugozzoli, R. Cacciapaglia, L. Mandolini and R. Ungaro, *Tetrahedron* **1995**, 51, 591; C. Geraci, M. Piatelli and P. Neri, *Tetrahedron Lett.* **1995**, 36, 5429); *Calix[8]crown ethers* (C. Geraci, M. Piatelli and P. Neri, *Tetrahedron Lett.* **1995**, 36, 5429; C. Geraci, P. Piatelli and P. Neri, *ibid.* **1996**, 37, 3899).

[59] D. N. Reinhoudt, P. J. Dijkstra, P. J. A. in't Veld, K. Bugge, S. Harkema, R. Ungaro and E. Ghidini, *J. Am. Chem. Soc.* **1987**, 109, 4761; P. J. Dijkstra, J. A. J. Brunink, K.-E. Bugge, D. N. Reinhoudt, S. Harkema, R. Ungaro, F. Ugozzoli and E. Ghidini, *ibid.* **1989**, 111, 7567.

[60] A. Dondoni, X. Hu, A. Marra and H. D. Banks, *Tetrahedron Lett.* **2001**, 42, 3295.

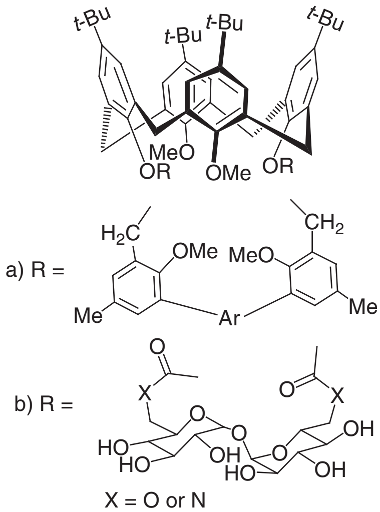
[61] P. D. Beer and A. D. Keefe, *J. Inclusion Phenom. Molec. Recognit. Chem.* **1987**, 5, 499.

[62] J.-D. van Loon, D. Kraft, M. J. K. Ankoné, W. Verboom, S. Harkema, W. Vogt, V. Böhmer and D. N. Reinhoudt, *J. Org. Chem.* **1990**, 55, 5176.

[63] P. A. Gale, J. L. Sessler, V. Lynch and P. I. Sansom, *Tetrahedron Lett.* **1996**, 37, 7881.

[64] N. Kobayashi, K. Mizuno and T. Osa, *Inorg. Chim. Acta* **1994**, 224, 1.

[65] T. Nagasaki, H. Fijishima and S. Shinkai, *Chem. Lett.* **1994**, 989; T. Nagasaki, H. Fijishima, M. Takeuchi and S. Shinkai, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1883.



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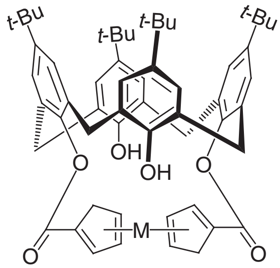

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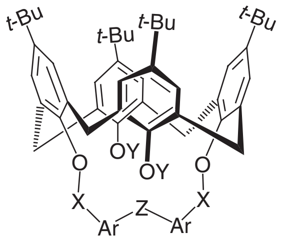

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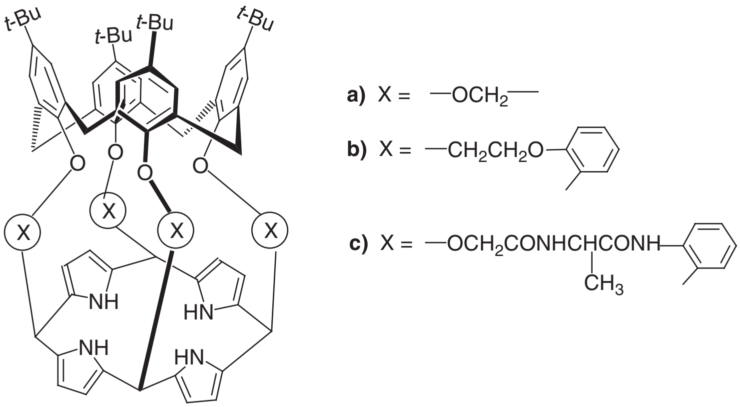

5.13

Among the larger calixarenes considerable attention has been devoted to bridging the *endo* rim of calix[6]arenes with polyethyleneoxy and other spanners. For example, a variety of CH_2ArCH_2 spanners have been introduced to give generally good yields of the A,D-bridged calix[6]arenes, as illustrated by structure **4.7** (p 106), where X is phenylene,[66] durylene,[66] anthralene,[66] or a heterocycle such as a pyridine or a phenanthroline.[67] Spanning of the A,C,E positions of a calix[6]arene has produced a calix[6]azacrown compound.[68] Included among the numerous examples from Neri's laboratory is a doubly spanned *p*-*tert*-butylcalix[7]arene.[69] Calix[8]arenes have been spanned at the *endo* rim with similar bridges to give singly- as well as multiply-bridged compounds including A,E-bridged,[70] A,D-bridged,[71] A,C/E,G-doubly bridged[70] and A,E/C,G doubly bridged.[72] A calix[8]arene spanned with a quadruply attached durylene bridge[73] has been described as having a "fixed pseudo pleated loop" conformation with an architecture reminiscent of the picket fence porphyrins.

Phosphorus, in a number of guises, has been used to build bridges onto the *endo* rims of calixarenes. Phosphate can be singly attached to one or more of the phenolic groups (to give simple esters), doubly attached,[74] triply attached[74,75] as in **5.14** or even quadruply attached[76] as in **5.15**. Treatment of *p*-*tert*-butylcalix[9]arene with PCl_5 engages all nine of the OH groups to produce a triply bridged compound.[77] A number of metals have been attached to the *endo* rim oxygen atoms (in most instances with calix[4]arenes), including,

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[66] S. Kanamathareddy and C. D. Gutsche, *J. Am. Chem. Soc.* **1993**, 116, 6572.

[67] H. Ross and U. Lüning, *Tetrahedron* **1996**, 52, 10879; *idem*, *Tetrahedron Lett.* **1997**, 38, 4539; J. P. W. Eggert, J. Harrowfield, U. Lüning, B. W. Skelton, A. H. White, F Löffler and S. Konrad. *Eur. J. Org. Chem.* **2005**, 1348; S. Konrad, C. Näther and U. Lüning, *Eur. J. Org. Chem.* **2005**, 2330.

[68] I. Jabin and O. Reinaud, *J. Org. Chem.* **2003**, 68, 3416; also, *cf.* Y. Zhang, H. Yuan, Z. Huang, J. Zhou, Y. Kawanishi, J. Schatz and G. Maas, *Tetrahedron* **2001**, 57, 4161.

[69] M. Martino, C. Gaeta and P. Neri, *Tetrahedron Lett.* **2004**, 45, 3387.

[70] F. Cunsolo, M. Piatelli and P. Neri, *J. Chem. Soc. Chem. Commun.* **1994**, 1917.

[71] A. Ikeda, K. Akao, T. Harada and S. Shinkai, *Tetrahedron Lett.* **1996**, 37, 1621; also, *cf.* Y. S. Tsantrizos, W. Chew and L. D. Colebrook, *Tetrahedron Lett.* **1997**, 38, 5411.

[72] G. M. L. Consoli, C. Geraci, P. Neri, G. Bergamini and V. Balzani, *Tetrahedron Lett.* **2006**, 47, 7809.

[73] F. Cunsolo, G. M. L. Consoli, M. Piatelli and P. Neri, *Tetrahedron Lett.* **1996**, 37, 715.

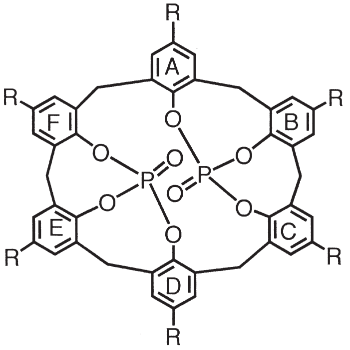
[74] O. Aleksiuk, F. Grynszpan and S. Biali, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 237; J. K. Moran and D. M. Roundhill, *Phosphorus, Sulfur, Silicon* **1992**, 71,7.

[75] F. E. Grynszpan and S. E. Biali, *J. Chem. Soc. Chem. Commun.* **1993**, 13; F. J. Parlevliet, A. Oliver, S. G. J. de Lange, P. C. J. Kamer, H. Kooijman, A. L. Spek and P. W. N. M. van Leeuwen, *J. Chem. Soc. Chem. Commun.* **1996**, 583.

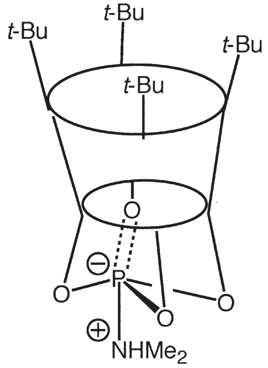
[76] D. V. Khasnis, M. Lattman and C. D. Gutsche, *J. Am. Chem. Soc.* **1990**, 112, 9422; D. V. Khasnis, J. M. Burton, M. Lattman and H. C. Zhang, *J. Chem. Soc. Chem. Commun.* **1991**, 562; D. V. Khasnis, J. M. Burton, J. D. McNeil, C. J. Santini, H. Zhang and M. Lattman, *Inorg. Chem.* **1994**, 33, 2657.

[77] J. Gloede, S. Ozegowski, B. Costisella and C. D. Gutsche, *Eur. J. Org. Chem.* **2003**, 4870.

inter alia, aluminum,[78] tungsten,[79] molybdenum,[80] zirconium,[81] niobium[82] and tantalum.[82]



5.14



5.15

5.1.4 Replacement of OH with H, N and S (*Apndx A-2, p. 110*)

Calixarenes in which one or more of the OH groups are replaced by hydrogen have been of interest for conformational studies (*cf.* Section 4.4.1). One approach for obtaining such molecules makes use of stepwise synthesis routes (*cf.* Section 2.3), but the more often used approach makes use of the reduction of phosphate esters prepared by reaction of the calixarene with $ClP(O)(OEt)_2$. By the use of this procedure[83] the completely dehydroxylated *p-tert*-butylcalix[4]arene **5.16a**,[84] calix[4]arene,[85] *p-tert*-butylcalix[6]arene[86] and *p-tert*-butylcalix[8]arene[84] have been prepared as well as the partially dehydroxylated trihydroxy and A,C-dihydroxy compounds **5.16b** and **5.16 c**.[87] Still another

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[78] M. G. Gardiner, G. A. Koutsantonis, S. M. Lawrence, P. J. Nichols and C. L. Raston, *J. Chem. Soc. Chem. Commun.* **1996**, 2035.

[79] F. Corazza, C. Floriani, A. Chiesi-Villa and C. Rizzoli, *Inorg. Chem.* **1991**, 30, 4465; A. Zanotti-Gerosa, E. Solari, L. Giannini, C. Floriani, A. Chiesi-Villa and C. Rizzoli, *Chem. Commun.* **1996**, 119; B. Xu, P. J. Carroll and T. M. Swager, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2094.

[80] V. C. Gibson, C. Redshaw, W. Clegg and M. R. J. Elsegood, *J. Chem. Soc. Chem. Commun.* **1995**, 2371; F. Corazza, C. Floriani, A. Chiesi-Villa and C. Guastini, *J. Chem. Soc. Chem. Commun.* **1990**, 640; J. A. Acho, T. Ren, J. W. Yun and S. Lippard, *J. Inorg. Chem.* **1995**, 34, 5226.

[81] L. Giannini, E. Solari, A. Zanotti-Gerosa, C. Floriani, A. Chiesi-Villa and C. Rizzoli, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 85.

[82] J. A. Acho, L. H. Doerrer and S. Lippard, *J. Inorg. Chem.* **1995**, 34, 2542.

[83] For a commentary on the mechanism of this reaction, in particular the source of the hydrogen that replaces the OH group, *cf.* F. Grynszpan and S. E. Biali, *J. Phys. Org. Chem.* **1992**, 5, 155.

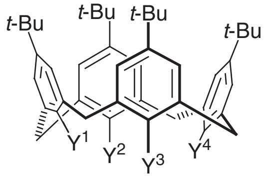
[84] Z. Goren and S. E. Biali, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1484.

[85] J. E. McMurry and J. C. Phelan, *Tetrahedron Lett.* **1991**, 32, 5655.

[86] J.-B. Regnouf de Vains, S. Pellet-Rostaing and R. Lamartine, *Tetrahedron Lett.* **1994**, 35, 8147.

[87] Y. Ting, W. Verboom, L. C. Groenen, J.-D. van Loon and D. N. Reinhoudt, *J. Chem. Soc. Chem. Commun.* **1990**, 1432; Y. Ting, W. Verboom, L. C. Groenen, J.-D. van Loon and D. N. Reinhoudt, *J. Chem. Soc. Chem. Commun.* **1990**, 1432; Y. Fukazawa, K. Deyama and S. Usi, *Tetrahedron Lett.* **1992**, 33, 5803; F. Grynszpan, O. Aleksiuk and S. E. Biali, *J. Org. Chem.* **1994**, 59, 2070.

route involves reactions with calixarene-derived spirodienones (*cf.* Section 5.5.2).



5.16

a) $Y^1 = Y^2 = Y^3 = Y^4 = H$

b) $Y^1 = Y^2 = Y^3 = OH$; $Y^4 = H$

c) $Y^1 = Y^3 = H$; $Y^2 = Y^4 = OH$

d) $Y^1 = NH_2$; $Y^2 = Y^3 = Y^4 = H$

e) $Y^1 = Y^3 = NH_2$; $Y^2 = Y^4 = H$

f) $Y^1 = SH$; $Y^2 = Y^3 = Y^4 = OH$

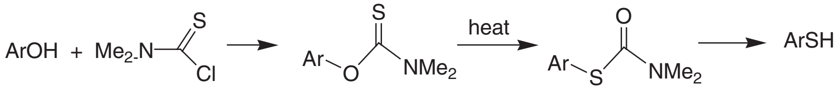
g) $Y^1 = Y^3 = SH$; $Y^2 = Y^4 = OH$

h) $Y^1 = Y^2 = Y^3 = SH$; $Y^4 = OH$

j) $Y^1 = Y^2 = Y^3 = Y^4 = SH$

Replacement of OH with NH_2 has been attempted in a stepwise fashion *via* the A,C-dihydroxy compound, but treatment with NO_2BF_4 results in oxidation (*cf.* Section 5.5.2) rather than nitration.[88] A more successful approach involves treatment of the diphosphate ester with KNH_2 in NH_3, which gives a mixture from which the monoamine **5.16d** and diamine **5.16e** can be isolated in 44% and 8% yield, respectively.[89] The spirodienone approach (*cf.* Section 5.5.2) has also been used to obtain these compounds.

Replacement of OH with SH has been accomplished by means of the Newman–Kwart procedure, which involves the reaction sequence:



The monothio compound **5.16f**,[90] A,C-dithio compound **5.16g**,[90,91] trithio compound **5.16h**[90] and tetrathio compound **5.16i**[90,92] have been prepared as well as the corresponding tetramercapto compound in the thiacalix[4]arenes.[93]

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[88] F. Grynszpan, N. Dinoor and S. E. Biali, *Tetrahedron Lett.* **1991**, 32, 1909.

[89] F. Ohseto, H. Murakami, K. Araki and S. Shinkai, *Tetrahedron Lett.* **1992**, 33, 1217.

[90] C. G. Gibbs and C. D. Gutsche, *J. Am. Chem. Soc.* **1993**, 115, 5338; C. G. Gibbs, P. K. Sujeeth, J. S. Rogers, G. G. Stanley, M. Krawiec, W. H. Watson and C. D. Gutsche, *J. Org. Chem.* **1995**, 60, 8394.

[91] X. Delaigue, J. McB. Harrowfield, M. W. Hosseini, A. De Cian, J. Fischer and N. J. Kyritsaka, *J. Chem. Soc. Chem. Commun.* **1994**, 1579.

[92] X. Delaigue, M. W. Hosseini, N. Kyritsaka, A. De Cian and J. Fischer, *J. Chem. Soc. Chem. Commun.* **1995**, 609.

[93] P. Rao, M. W. Hosseini, A. De Cian and J. Fischer, *Chem. Comm.* **1999**, 2169.

5.2 Modifying the *Exo* Rim of Calixarenes

5.2.1 General Overview

The fragment condensation method for the synthesis of calixarenes (*cf.* Section 2.3.2) is well adapted to functionalizing the *exo* rim, and a variety of groups have been incorporated in this fashion. Although the procedures have been nicely optimized and are exceedingly useful in a variety of applications, they are not readily amenable to the large-scale production of calixarenes. Because the *p*-*tert*-butylcalix[4,6,8]arenes are so easily available *via* the single-step process on any scale of operation, from a few milligrams to many kilograms, the major attention to the introduction of functional groups onto the *exo* rims of calixarenes has been devoted to these starting materials.

It is a fortunate circumstance that the few phenols that provide calixarenes in good yields in the one-step procedures (*viz*. *p*-*tert*-butylphenol, *p*-*tert*-pentylphenol and *p*-*tert*-octylphenol) are the ones from which the *para* substituent can be most easily removed by a reverse Friedel–Crafts reaction, thereby making the *para* positions available for functionalization. The Lewis-acid-catalyzed transalkylation was applied in 1975 to phenols by Tashiro and coworkers.[94] In 1978 the Mainz group[95] adapted the procedure to the calixarenes obtained from the stepwise synthesis, thus setting the stage for its subsequent widespread use in calixarene chemistry. Another fortunate circumstance is that the rate of de-*tert*-butylation depends on the substituents attached to the phenolic oxygens. For example, the A,C-dimethyl ether of *p*-*tert*-butylcalix[4]arene undergoes selective de-*tert*-butylation at the B,D rings,[96] and the tribenzoate loses a single *tert*-butyl group, illustrative of the general phenomenon that *p*-*tert*-butylphenols are usually more easily dealkylated than their corresponding ethers or esters.

With the *p*-positions of the calixarenes made available by de-*tert*-butylation, a wide variety of *p*-functionalization procedures have been explored, as outlined in Figure 5.2. A number of these were developed in the 1980s, including the electrophilic substitution route to give **5.17** (*e.g*. introduction of halogen, NO_2, SO_3H, SO_2Cl, CHO, COR, COAr, CH_2Cl, ArN_2), the *p*-Claisen rearrangement route *via* **5.20** to give **5.22** (and, subsequently, **5.23**), the *p*-quinonemethide route *via* **5.18** and **5.19** to give **5.21** and the acylation route *via* **5.24** or directly to give **5.25**. Current investigations continue to add to and improve upon these and other procedures.

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[94] M. Tashiro, G. Fukata, S. Mataka and K. Oe, *Org. Prep. Proced. Int*. **1975**, 7, 231; see M. Tashiro, *Synthesis* **1979**, 921 for general references.

[95] V. Böhmer, D. Rathay and H. Kämmerer, *Org. Prep. Proced. Int*. **1978**, 10, 113; H. Kämmerer, G. Happel, V. Böhmer and D. Rathay, *Monatsh*. **1978**, 109, 767.

[96] J.-D. van Loon, A. Arduini, W. Verboom, R. Ungaro, G. J. van Hummel, S. Harkema and D. N. Reinhoudt, *Tetrahedron Lett*. **1989**, 30, 2681.

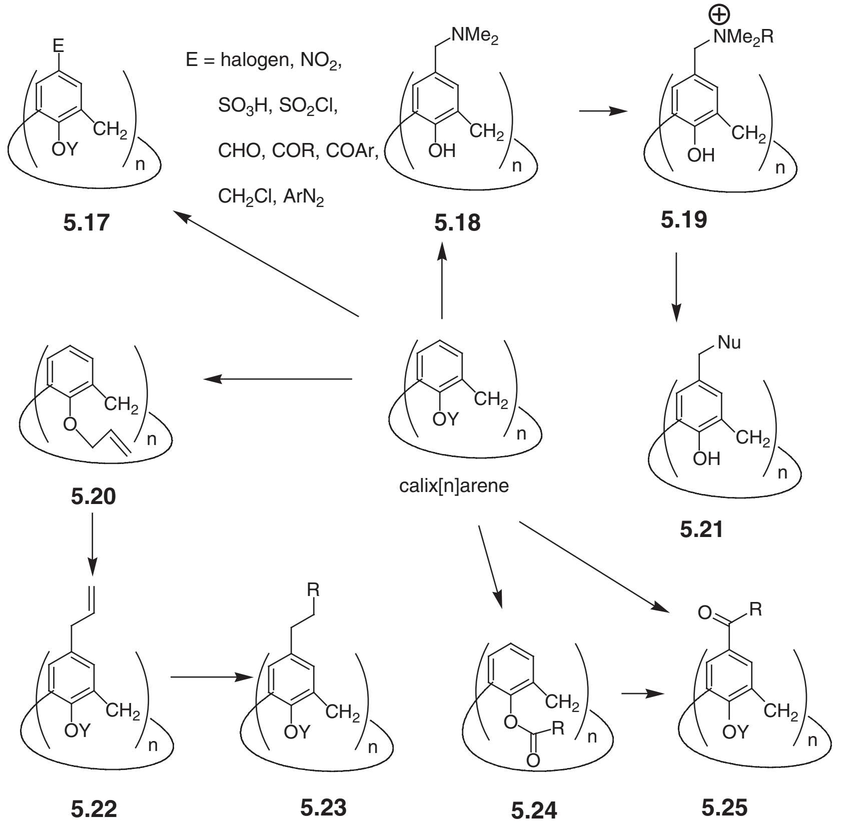

Figure 5.2 *Exo* rim functionalization routes for calix[*n*]arenes.

5.2.2 Halogenation, Nitration, Sulfonation and Diazonium Coupling Routes

Tetra-bromination of the tetramethyl ether of calix[4]arene to give **5.17** (E = Br, Y = OMe) can be effected in high yield with N-bromosuccinimide,[97] while B,D-dibromination of the A,C-dialkyl ether has been carried out with Br_2.[96,98] Iodination to give **5.17** (E = I) has been accomplished in quantitative yield through the use of silver trifluoroacetate and I_2 in $CHCl_3$ and can be carried out

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[97] (a) C. D. Gutsche and P. F. Pagoria, *J. Org. Chem.* **1985**, 50, 5795; (b) F. Hamada, S. G. Bott, G. W. Orr, A. W. Coleman, H. Zhang and J. L. Atwood, *J. Inclusion Phenom.* **1990**, 9, 195; (c) K. Paek, H. Ihm and K. No, *Bull. Korean Chem. Soc.* **1994**, 15, 422.

[98] P. Linnane, D. James and S. Shinkai, *J. Chem. Soc. Chem. Commun.* **1995**, 1997.

selectively by controlling the amount of reagent.[99] Also recommended are the reagents BTMA-ICl_2[100] and ICl.[101]

Halocalixarenes are useful intermediates for the introduction of other moieties into the *p*-positions. Tetra-lithiation, for example, can be effected with *tert*-butyllithium,[102] and the lithium compounds, in turn, can be converted (a) to *p*-carboxylic acids **5.17** ($E = CO_2H$) by carbonation,[97a] (b) to *p*-hydroxy compounds **5.17** ($E = OH$)[103] by treatment with $B(OMe)_3$ followed by oxidation with NaOH-H_2O_2 or to boronic acids **5.17** ($E = B(OH)_2$) by hydrolysis,[104] (c) to *p*-methyl compounds **5.17** ($E = CH_3$) by treatment with MeI,[102] and (d) to *p*-formyl compounds **5.17** ($E = CHO$) by treatment with 4-formylmorpholine[102] or dimethylformamide[105] followed by HCl. Vinyl moieties have been introduced by treatment with $H_2C = CHSnBu_3$ and $Pd(PPh_s)_4$,[37] acetylenic moieties C≡CH and C≡CCH_2OH by treatment with HC≡$CSiMe_3$ followed by desilylation or with HC≡CCH_2OH in the presence of $Pd[P(Ph)_3]_4$[99b] and ethylthio groups by treatment with CuSEt.[99b] Bromination at the carbons nearer the *exo* rim has been achieved if an activating group such as OMe is present in the *p*-position.[106]

Early attempts at direct nitration of calix[*n*]arenes were not very successful, and Shinkai and coworkers resorted first to introducing a sulfonato group in the *p*-position and then replacing it with a nitro group.[107] More recently, however, direct nitration using KNO_3 and $AlCl_3$ in MeCN at 0 °C has been shown to afford high yields of the nitrocalixarenes,[108] although a comparative study of nitration procedures[109] concludes that 100% nitric acid in acetic acid is the preferred reagent. The more interesting and generally more useful procedure, called "ipso" nitration, involves the direct displacement of the *tert*-butyl group, a procedure first employed by Reinhoudt and coworkers.[110] It has the obvious advantage of not having to remove the *tert*-butyl groups in a separate step, and it also makes possible a variety of selective replacements based on the

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[99] (a) P. Timmerman, W. Verboom, D. N. Reinhoudt, A. Arduini, S. Grandi, A. R. Sicuri, A. Pochini and R. Ungaro, *Synthesis* **1994**, 185; (b) A. Arduini, A. Pochini, A. R. Sicuri, A. Secchi and R. Ungaro, *Gazz. Chim. Ital.* **1994**, 124, 129.

[100] B. Klenke and W. Friedrichsen, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3377.

[101] A. Gunji and K. Takahashi, *Synth. Commun.* **1998**, 28, 3933.

[102] H. Ihm and K. Paek, *Bull. Korean Chem. Soc.* **1995**, 16, 71.

[103] K.-S. Paek, H.-J. Kim and S.-K. Chang, *Supramol. Chem.* **1995**, 5, 83.

[104] F. Ohseto, H. Yamamoto, H. Matsumoto and S. Shinkai, *Tetrahedron Lett.* **1995**, 36, 6911.

[105] P. Lhoták and S. Shinkai, *Tetrahedron Lett.* **1996**, 37, 645.

[106] (a) M. Mascal, R. T. Naven and R. Warmuth, *Tetrahedron Lett.* **1995**, 36, 9361; (b) W. Verboom, P. J. Bodewes, G. van Essen, P. Timmerman, G. J. van Hummel, S. Harkema and D. N. Reinhoudt, *Tetrahedron* **1995**, 51, 499; (c) M. Mascal, R. Warmuth, R. T. Naven, R. A. Edwards, M. B. Hursthouse and D. E. Hibbs, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3435.

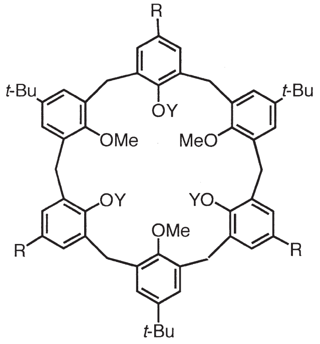
[107] S. Shinkai, T. Usubaki, T. Sone and O. Manabe, *Tetrahedron Lett.* **1985**, 26, 3343.

[108] W.-C. Zhang, Y.-S. Zheng and Z.-T. Huang, *Synthetic Commun.* **1997**, 3763.

[109] S. Kumar, R. Varadarajan, H. M. Chawla, G. Hundal and M. S. Hundal, *Tetrahedron* **2004**, 60, 1001.

[110] (a) W. Verboom, A. Durie, R. J. M. Egberink, Z. Asfari and D. N. Reinhoudt, *J. Org. Chem.* **1992**, 57, 1313; (b) O. Mogck, P. Parzuchowski, M. Nissinen, V. Böhmer, G. Rodicki and R. Rissanen, *Tetrahedron* **1998**, 54, 10053.

fact that nitration occurs more rapidly on (a) rings in which the *endo* rim substituent is OH rather than OR or OCOR,[111] (b) rings containing a *p*-*tert*-butyl rather than a *p*-H[112] and (c) rings containing an *endo* rim OMe rather than certain other groups such as O-imidazolemethyl.[112] As one among many representative examples, compound **5.26** is converted to the trinitro compound **5.27** in 64% yield.[113] The nitrocalixarenes provide extremely useful intermediates for the introduction of other functional groups, generally via the amino calixarenes obtained by reduction with H_2 and Raney Ni,[114] NH_2NH_2 and Raney Ni,[106b] NH_2NH_2 and $FeCl_3$[115a] or $SnCl_2$.[115b] Interesting examples include the introduction of peptide moieties[116] and nucleoside bases in this fashion.[117]



$$\textbf{5.26}\,(R = t\text{-Bu};\ Y = H) \xrightarrow[-15^{\circ}C \text{ to r.t./55 min.}]{HNO_3 \text{ in } CH_2Cl_2} \textbf{5.27}\,(R = NO_2;\ Y = H)$$

$$\textbf{5.29}\,(R = H;\ Y = Me) \xrightarrow[TiCL_4/\,CHCl_3]{Cl_2CHOCH_3} \textbf{5.30}\,(R = CHO;\ Y = Me)$$

One of the earliest of the water soluble calixarenes (*Apndx A-2, p. 441*) was made by direct sulfonation of de-*tert*-butylated calixarenes, and this remains a frequently used procedure,[118] although *ipso* sulfonation can also be effected.[119] The sulfonato calixarenes are important in their own right as water soluble compounds but can also serve as intermediates for additional functionalization,

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[111] K. C. Nam, J. M. Kim and Y. J. Park, *Bull. Korean Chem. Soc.* **1998**, 19, 770; K. C. Nam and D. S. Kim, *ibid.* **1994**, 15, 284; P. D. Beer and J. B. Cooper, *Chem. Commun.* **1998**, 129.

[112] S. Redon, Y. Li and O. Reinaud, *J. Org. Chem.* **2003**, 68, 7004.

[113] (a) A. Casnati, L. Domiano, A. Pochini, R. Ungaro, M. Carramolino, J. O. Magrans, P. M. Nieto, J. Lopez-Prados, P. Prados, J. de Mendoza, R. G. Janssen, W. Verboom and D. N. Reinhoudt, *Tetrahedron* **1995**, 51, 12699; (b) J. de Mendoza, M. Carramolino, F. Cuevas, P. M. Nieto, P. Prados, D. N. Reinhoudt, W. Verboom, R. Ungaro and A. Casnati, *Synthesis* **1994**, 47.

[114] R. A. Jakobi, V. Böhmer, C. Grüttner, D. Kraft and W. Vogt, *New J. Chem.* **1996**, 20, 493.

[115] (a) S. Shinkai, T. Arimura, K. Araki, H. Kawabata, H. Satoh, T. Tsubaki, O. Manabe and J. Sunamoto, *J. Chem. Soc. Perkin Trans 1* **1989**, 2039; (b) D. M. Rudkevich, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.* **1994**, 59, 3683; G. Mislin, E. Graf and M. W. Hosseini, *Tetrahedron Lett.* **1996**, 37, 4503.

[116] M. Lazzarotto, F. Sansone, L. Baldini, A. Casnati, P. Cozzini and R. Ungaro, *Eur. J. Org. Chem.* **2001**, 595.

[117] C.-C. Zeng, Q.-Y. Zheng, Y.-L. Tang and Z.-T. Huang, *Tetrahedron* **2003**, 59, 2539.

[118] S. Shinkai, K. Araki, T. Tsubaki, T. Arimura and O. Manabe, *J. Chem. Soc. Perkin Trans. 1* **1987**, 2297; S. Shinkai, H. Koreishi, K. Ueda, T. Arimur and O. Manabe, *J. Am. Chem. Soc.* **1987**, 109, 6371; S. Shinkai, K. Araki and O. Manabe, *J. Chem. Soc. Chem. Commun.* **1988**, 187; H. M. Chawla, U. Hooda and V. Singh, *Synth. React. Inorg. Met.-Org Chem.* **1996**, 26, 775.

[119] S. Shinkai, H. Kawaguchi and O. Manabe, *J. Polym. Sci.* **1988**, 26, 391.

generally by conversion to sulfonamide or chlorosulfonyl compounds[120] (also obtainable by direct chlorosulfonation[121]).

The first reported calixarene diazo coupling involved the reaction of *p*-nitrophenyldiazonium tetrafluoroborate with calix[4]arene[122] and since that time has found occasional use.[123]

5.2.3 Alkylation (Including Chloromethylation) Route

Friedel-Crafts alkylations of calix[4]arene have been carried out with a variety of alkylating agents using $AlCl_3$,[124] $FeCl_3$,[125] F_3CCO_2H[126] and other similar catalysts to give *p*-alkylcalixarenes. For example, l-hydroxyadamantane with F_3CCO_2H as the catalyst yields the A,B-*p*-di-adamantyl compound at 20–50 °C, the *p*-triadamantyl compound at 60–70 °C or the *p*-tetraadamantyl compound **5.28a** at 80–90 °C.[127] Chloromethylation, the most useful of the Friedel–Crafts alkylation procedures, was introduced in the late 1980s by Ungaro and coworkers,[128] who used a chloromethyl alkyl ether in the presence of a Lewis acid such as $SnCl_4$ to give *p*-chloromethylcalixarenes **5.28b**. Other procedures employ paraformaldehyde with acids (acetic acid, phosphoric acid, conc. HCl)[129] or $SnCl_4$ and trimethylchlorosilane.[57a,113a] The particular virtue of the chloromethyl group comes from its ease of conversion to various other moieties. Reduction with $LiAlH_4$ produces the *p*-methylcalixarene **5.28c**;[130] reaction with MeI gives the next higher homolog **5.28d**;[130b] treatment with aromatic compounds in the presence of BF_3 gives *p*-arylmethylcalixarenes **5.28e**;[130b] displacement with RONa yields ethers **5.28f**;[37b] displacement with $KSCOCH_3$ produces the acetylthio compound **5.28g**,[37b] which can be reduced to the corresponding thiol **5.28h** with $LiAlH_4$; treatment with thiourea yields

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[120] A. Casnati, Y. Ting, D. Berti, M. Fabbi, A. Pochini, R. Ungaro, D. Sciotto and G.G. Lombardo, *Tetrahedron* **1993**, 49, 9815.

[121] Y. Morzherin, D. M. Rudkevich, W. Verboom and D. J. Reinhoudt, *J. Org. Chem.* **1993**, 58, 7602.

[122] S. Shinkai, K. Araki, J. Shibata and O. Manabe, *J. Chem. Soc. Perkin Trans.* **1989**, 195.

[123] (a) S. Shinkai, K. Araki, J. Shibata, D. Tsugawa and O. Manabe, *J. Chem. Soc. Perkin Trans. 1* **1990**, 3333; (b) Y. Morita, T. Agawa, E. Nomura and H. Taniguchi, *J. Org. Chem.* **1992**, 57, 3658; (c) E. Kelderman, L. Derhaeg, W. Verboom, J. F. J. Engbersen, S. Harkema, A. Persoon and D. N. Reinhoudt, *Supramol. Chem.* **1993**, 2, 183; (d) M.-J. Yeh, F.-S. Tang, S.-I. Chen, W.-E. Liu and L.-G. Lin, *J. Org. Chem.* **1994**, 59, 754; (e) C.-M. Shu, T.-S. Yuan, M.-C. Ku, Z.-C. Ho, W.-C. Liu, F.-S. Tang and L.-G. Lin, *Tetrahedron* **1996**, 52, 9805; (f) H. M. Chawla and K. Srinivas, *J. Org. Chem.* **1996**, 61, 8464; F. Oueslati, I. Dumazet-Bonnamour and R. Lamartine, *Tetrahedron Lett.* **2001**, 43, 8177.

[124] Y.-S. Zheng and Z.-T. Huang, *Synth. Commun.* **1997**, 27, 1237.

[125] A. M. Yuldashev, B. T. Ibragimov, S. A. Tallpov and H. L. Gapparov, *J. Structural Chem.* **1996**, 37, 470.

[126] A. N. Khomich, E. A. Shokova and V. V. Kovalev, *Synlett* **1994**, 1027.

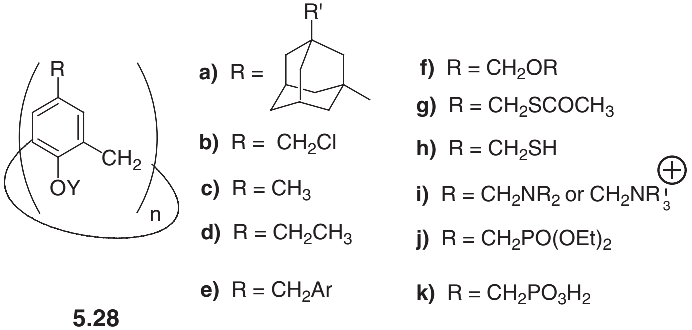
[127] E. A. Shokova, A. N. Khomich and V. V. Kovalev, *Tetrahedron Lett.* **1996**, 37, 543; V.V. Kovalev, E. Shokova, A. Khomich and Y. Luzikov, *New J. Chem.* **1996**, 20, 483.

[128] M. Almi, A. Arduini, A. Casnati, A. Pochini and R. Ungaro, *Tetrahedron* **1989**, 45, 2177.

[129] A. Ikeda and S. Shinkai, *J. Am. Chem. Soc.* **1994**, 116, 3102.

[130] (a) M. Almi, A. Arduini, A. Casnati, A. Pochini and R. Ungaro, *Tetrahedron* **1989**, 45, 2177; (b) A. Arduini, A. Pochini, A. Rizzi, A. R. Sicuri, F. Ugozzoli and R. Ungaro, *Tetrahedron* **1992**, 48, 905.

5.28h directly;[131] treatment with amines[132] yields **5.28i** (including water soluble quaternary amines); and treatment with $P(OEt)_3$ gives **5.28j**, which can be hydrolyzed to the corresponding phosphonic acid **5.28k**.[128]



5.28

5.2.4 Acylation and Aroylation Routes

Treatment of calixarenes with acetyl chloride or benzoyl chloride in the presence of $AlCl_3$ at or below room temperature generally produces esters which can be converted *via* the Fries rearrangement to the *p*-substituted compounds by treatment with $AlCl_3$ at higher temperatures.[133] By carrying out the reaction for longer times at somewhat higher temperature *p*-substitution can be directly effected, perhaps the result of initial O-acylation followed by a Fries rearrangement.[134] A particularly useful acylation involves the introduction of formyl groups onto the *exo* rim of calixarenes[135] using the Gross method[136a] or the Duff method.[136b] An illustrative example of formylation is the conversion of the calix[6]arene **5.29** to the tri-formyl compound **5.30**,[113a] Acyl groups, particularly formyl groups, are useful for conversion to various other functional groups, including oxidation to carboxylic acids,[18,97a] reduction to alcohols,[18] amination to azomethines[137] and conversion to alkenes *via* the Wittig reaction.[123c,138]

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[131] M. T. Blanda and K. E. Griswald, *J. Org. Chem.* **1994**, 59, 4313.

[132] K. Araki, K. Akao, A. Ikeda, T. Suzuki and S. Shinkai, *Tetrahedron Lett.* **1996**, 37, 73.

[133] (a) K. H. No, Y. Noh and Y. Kim, *Bull. Korean Chem. Soc.* **1986**, 7, 442; (b) T. Arimura, S. Shinkai, T. Matsuda, Y. Hirata, H. Satoh and O. Manabe, *Bull. Chem. Soc. Jpn.* **1988**, 61, 3733; (c) K. No and M. S. Hong, *Bull. Korean Chem. Soc.* **1990**, 11, 58; (d) K. L. Hwang, S.-H. Ham and K. No, *Bull. Korean Chem. Soc.* **1992**, 13, 689; (e) K. L. Hwang, S.-H. Ham and K. H. No, *Bull. Korean Chem. Soc.* **1993**, 14, 79.

[134] S. Shinkai, T. Nagasaki, K. Iwamoto, A. Ikeda, G.-X. He, T. Matsuda and M. Iwamoto, *Bull. Chem. Soc. Jpn.* **1991**, 64, 381; Z.-T. Huang and G.-Q. Wang, *Chem. Ber.* **1994**, 127, 519.

[135] (a) V. Arora, H. M. Chawla and A. Santra; (b) A. Sartori, A. Casnati, L. Mandolini, F. Sansone, D. N. Reinhoudt and R. Ungaro, *Tetrahedron* **2003**, 59, 5539; (c) *Ipso* formylation has been reported by H. M. Chawla, N. Pant and B. Srivastava, *Tetrahedron Lett.* **2005**, 46, 7259.

[136] (a) A. Rieche, H. Gross and E. Höft, *Chem. Ber.* **1960**, 93, 88; (b) W. E. Smith, *J.Org. Chem.* **1972**, 37, 3972.

[137] T. Komori and S. Shinkai, *Chem. Lett.* **1992**, 901.

[138] J.-B, Regnouf-de-Vains and R. Lamartine, *Tetrahedron Lett.* **1996**, 37, 6311.

A number of the functionalization reactions discussed in the previous sections of this chapter have also been applied to the thiacalix[4]arenes including the addition of carboxyl, amide, ether, ester, phosphonyl, dansyl and amino groups.[139]

5.2.5 Arylation Reactions

p-Arylcalix[4]arenes, sometimes called "deep cavity calixarenes", are not very readily accessible by the one-step synthesis, so particular interest attends methods for the attachment of *p*-aryl groups to preformed calixarenes. One useful route involves the *p*-bromo compounds **5.17** ($E = Br$; $Y \neq H$) as starting materials, which when treated with BuLi followed by $ArB(OH)_2$ and $Pd(PPh_3)_4$ afford *p*-aryl compounds.[140] A splendid example of the application of this Suzuki type arylation involves the introduction of four 3-benzyloxyphenyl moieties onto the *p*-positions of the tetrabenzyl ether of calix[4]arene to give tetrakis-*p*-3-benzyloxyphenylcalix[4]arene.[141] The Negishi procedure offers an alternative, as exemplified by the preparation of *p*-tetrakis 3-bromophenyl-, 4-methylphenyl- and 4-fluorophenylcalix[4]arene ethers.[142] Still another *p*-arylation route starts with the *p*-iodo compound **5.17** ($E = I$) and entails photolysis in benzene solution.[143] A related deep cavity calixarene can be generated by the reaction of *p*-tetra-formylcalix[4]arene with phenanthrenequinone and ammonium acetate.[144] Employing similar chemistry, alkynyl and phenylalkynyl groups can be added to the *exo* rim,[145] providing another route to *p*-arylation *via* a subsequent Diels–Alder reaction with tetraphenylcyclopentadienone. Calix[4]arenes carrying four *p*-(tetraphenyl)phenyl or four *p*-(pentaphenyl)phenyl moieties have been prepared in this fashion.[146]

5.2.6 Aminomethylation: The *p*-Quinonemethide Route

The *p*-quinonemethide route, introduced in the late 1980s,[147] starts with the reaction of a *p*-H-calixarene with HCHO and a dialkylamine to produce a Mannich base **5.18**. This is followed by methylation to give the quaternary salt

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[139] For a list of references *cf.* Y. Kondo, K. Endo, N. Iki, S. Miyano and F. Hamada, *J. Inclusion Phenom. and Macrocyclic Chem.* **2005**, 52, 45.

[140] (a) A. Arduini, W. M. McGregor, D. Paganuzzi, A. Pochini, A. Secchi, F. Ugozzoli and R. Ungaro, *J. Chem. Soc. Perkin Trans. 2* **1996**, 839; (b) M. S. Wong and J.-F. Nicoud, *Tetrahedron Lett.* **1993**, 34, 8237.

[141] (a) C. A. Gleave and I. O. Sutherland, *J. Chem. Soc. Chem. Commun.* **1994**, 1873. For other examples *cf.* (a) M. S. Wong and J.-F. Nicoud, *Tetrahedron Lett.* **1993**, 34, 8237; (b) T. Haino, T. Harano, K. Matsumura and Y. Fukazawa, *ibid.* **1995**, 36, 5793.

[142] M. Larsen and M. Jørgensen, *J. Org. Chem.* **1997**, 62, 4171.

[143] A. Arduini, A. Pochini, A. Rizzi, A. R. Sicuri and R. Ungaro. *Tetrahedron Lett.* **1990**, 31, 4653.

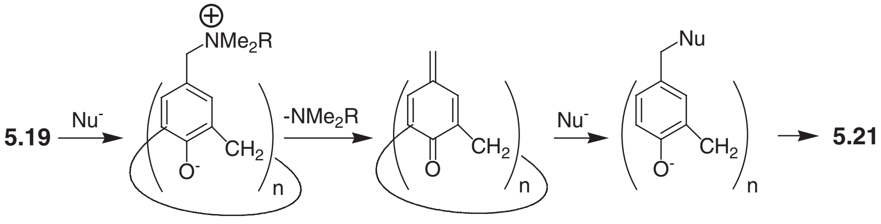
[144] E. Botana, K. Nättinen, P. Prados, K. Rissanen and J. de Mendoza, *Org. Lett.* **2004**, 6, 1091.

[145] G. Dyker, M. Mastalerz and I. M. Müller, *Eur. J. Org. Chem.* **2005**, 3801.

[146] M. Mastalerz, G. Dyker, U. Flörke, G. Henkel, I. M. Oppel and K. Merz, *Eur. J. Org. Chem.* **2006**, 4951.

[147] C. D. Gutsche and K. C. Nam, *J. Am. Chem. Soc.* **1988**, 110, 6153.

5.19, which is then treated with two equivalents of a nucleophile to produce a *p*-CH_2Nu calixarene **5.21**. The name of the process derives from the putative mechanism involving the formation of the highly reactive *p*-quinonemethide **5.32** by extrusion of the NMe_2R moiety from oxyanion **5.31** followed by Michael addition of the nucleophile to give **5.33**. Protonation then yields the product **5.21**. Useful nucleophiles include CN^-, RO^-, N_3^-, H^-, $^-CH(CO_2Et)_2$, $^-CH(NO_2)CO_2Et$ and imidazole. The *p*-cyanomethylcalixarenes **5.21** ($Nu = CN$) have proved to be particularly valuable intermediates for the synthesis of other *p*-substituted calix[4]arenes, yielding (a) carboxymethyl compounds **5.21** ($Nu = CO_2H$ by hydrolysis[148]; (b) aminoethyl compounds **5.21** ($Nu = CH_2NH_2$) by reduction[142]; and (c) aldol condensation products from reactions with aromatic aldehydes.[149]



5.31 **5.32** **5.33**

5.2.7 *p*-Claisen Rearrangement Route

The initial difficulties encountered with the electrophilic substitution reactions of calixarenes prompted Gutsche and coworkers[150] to explore alternative routes, and the most productive of these was the *p*-Claisen rearrangement involving the formation of the O-allyl ethers **5.20** followed by thermal rearrangement to the *p*-allyl compounds **5.22**. When the procedure described in the early papers was employed it was more or less limited to the calix[4]arene series, for only very low yields were obtained with the larger calixarenes. It has since been shown, however, that by carrying out the reaction in the presence of a silylating agent followed by hydrolysis of the resulting O-silyl ether the yields are greatly enhanced, making it a generally applicable procedure.[151] The reactions shown in Figure 5.3 represent a nice example of the selective control

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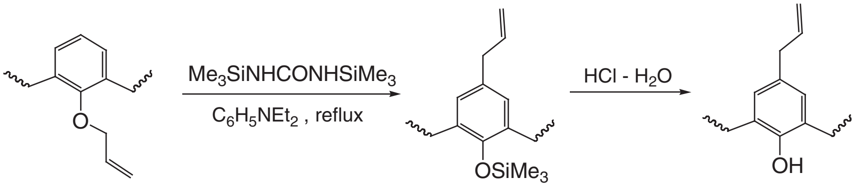
[148] S. K. Sharma, S. Kanamathareddy and C. D. Gutsche, *Synthesis* **1997**, 1268.

[149] S. K. Sharma and C. D. Gutsche, *Synthesis* **1995**, 1089; S. K. Sharma and C. D. Gutsche, *J. Org. Chem.* **1994**, 59, 6030.

[150] C. D. Gutsche and J. A. Levine, *J. Am. Chem. Soc.* **1982**, 104, 2652; C. D. Gutsche, J. A. Levine and P. K. Sujeeth, *J. Org. Chem.* **1985**, 50, 5802.

[151] C. G. Gibbs, J.-S. Wang and C. D. Gutsche, "Calixarenes for Separations", *ACS Symposium Series 757*, G. J. Lumetta, R. D. Rogers and A. S. Gopalan, Eds., **2000**, 313.



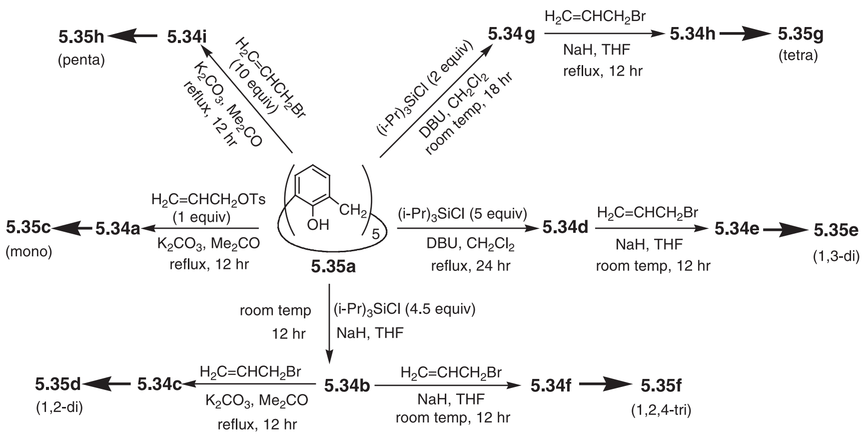


Figure 5.3 Selective functionalization of *exo* rim of calix[5]arene. (cf. p. 138 for structures 5.34 and 5.35)

that can be exerted by the interplay of selective lower-rim functionalization combined with the *p*-Claisen rearrangement (represented by the heavy arrows) leading to six of the seven possible *p*-allylcalix[5]arenes.[151]

The *p*-allyl group is amenable to conversion to a variety of other *p*-functional groups, including photochemically mediated addition of HBr to produce *p*-$CH_2CH_2CH_2Br$[152] and ozonolysis to produce *p*-CH_2CHO from which *p*-CH_2CH_2OH, *p*-CH_2CH_2Br, *p*-$CH_2CH_2N_3$ and *p*-$CH_2CH_2NH_2$ can be generated.[41]

Isomerization of $CH_2CH{=}CH_2$ by treatment with a rhodium catalyst[41] or potassium *tert*-butoxide[18,96] gives $CH{=}CHCH_3$, which can be ozonolyzed to *p*-CHO.[41,96]

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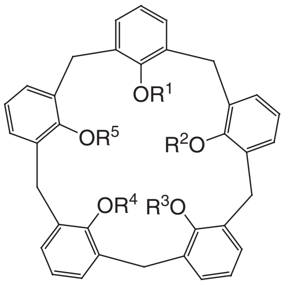
[152] E. M. Georgiev, J. T. Mague and D. M. Roundhill, *Supramol. Chem.* **1993**, 2, 53.



5.34

TIPS = triisopropylsilyl

a) $R^1 = CH_2CH=CH_2$; $R^{2,3,4,5} = H$

b) $R^{1,2,4} = H$; $R^{3,5} = TIPS$

c) $R^{1,2} = CH_2CH=CH_2$; $R^{3,5} = TIPS$; $R^4 = H$

d) $R^{1,3} = H$; $R^{2,4,5} = TIPS$

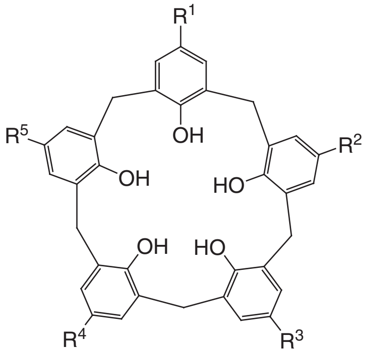
e) $R^{1,3} = CH_2CH=CH_2$; $R^{2,4,5} = TIPS$

f) $R^{1,2,4} = CH_2CH=CH_2$; $R^{3,5} = TIPS$

g) $R^{1,2,3,4} = H$; $R^5 = TIPS$

h) $R^{1,2,3,4} = CH_2CH=CH_2$; $R^5 = TIPS$

i) $R^{1,2,3,4,5} = CH_2CH=CH_2$



5.35

a) $R^{1,2,3,4,5} = H$

b) $R^{1,2,3,4,5} =$ *tert*-Butyl

c) $R^1 = CH_2CH=CH_2$; $R^{2,3,4,5} = H$

d) $R^{1,2} = CH_2CH=CH_2$; $R^{3,4,5} = H$

e) $R^{1,3} = CH_2CH=CH_2$; $R^{2,4,5} = H$

f) $R^{1,2,4} = CH_2CH=CH_2'$ $R^{3,5} = H$

g) $R^{1,2,3,4} = CH_2CH=CH_2$; $R^5 = H$

h) $R^{1,2,3,4,5} = CH_2CH=CH_2$

5.3 Functionalization of the Methylene Bridges

In addition to the functionalization sites at the *endo* and *exo* rims of calixarenes a third potential site is the methylene group between the flanking aryl residues. Treatment of the acetates of *p*-*tert*-butylcalix[4,6,8]calixarenes (**5.40**, $R = COCH_3$) with CrO_3 was reported in 1985 to yield products (**5.39**) in which one or more of the $ArCH_2Ar$ methylene groups is converted to a carbonyl group.[153] A more recent study confirmed the formation of the monooxo compound from *p*-*tert*-butylcalix[4]arene and showed that under more

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[153] A. Ninagawa, K. Cho and H. Matsuda, *Makromol. Chem.* **1985**, 186, 1379.

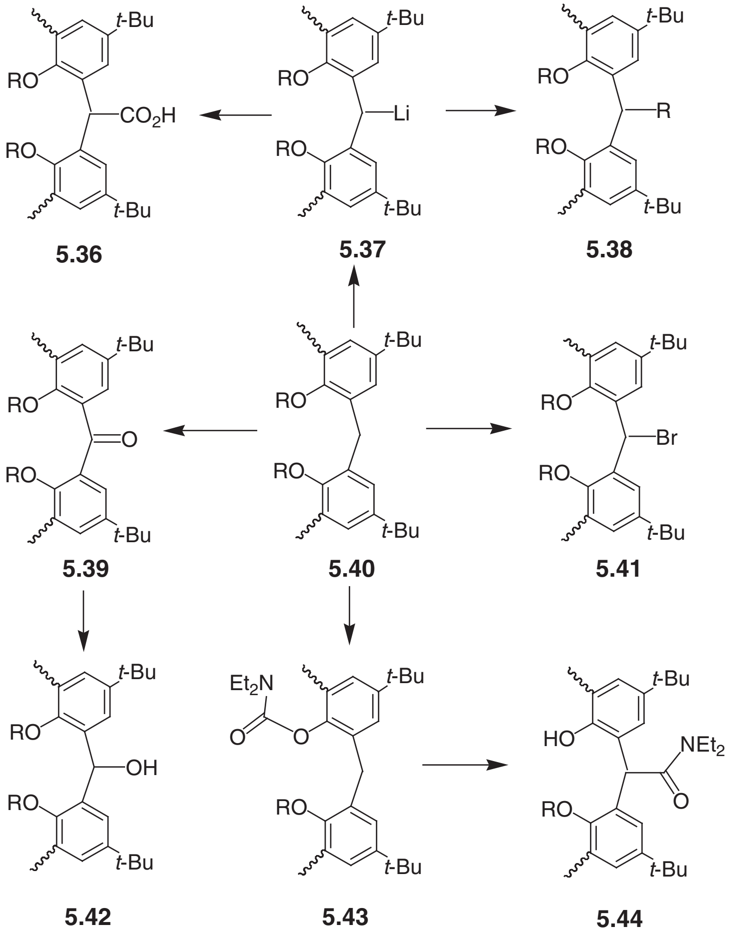

Figure 5.4 Functionalization of methylene groups of calix[*n*]arenes.

strenuous conditions a 90% yield of the tetraoxo compound can be obtained, which upon reduction with $NaBH_4$ can be converted to the corresponding alcohol **5.42**.[154] The methylene groups of the tetramethyl ether of *p*-*tert*-butylcalix[4]arene can be brominated (by action of N-bromosuccinimide) to yield **5.41**[155] or lithiated (by treatment with *n*-butyllithium) to yield **5.37** and, subsequently, alkylated (*via* RX) to **5.38** or carbonated (*via* CO_2) to **5.36**,[156] as shown in Figure 5.4. Another approach involves the Fries rearrangement of the

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[154] G. Görmar, K. Seiffarth, M. Schulz, J. Zimmermann and G. Flämig, *Makromol. Chem.* **1990**, 191, 81.

[155] (a) B. Klenke, C. Näther and W. Friedrichsen, *Tetrahedron Lett.* **1998**, 39, 8967; (b) S. Kumar, H. M. Chawla and R. Varadarajan, *Tetrahedron Lett.* **2002**, 43, 7073.

[156] P. A. Scully, T. M. Hamilton and J. L. Bennett, *Org. Lett.* **2001**, 3, 2741.

carbamate **5.43** to the amide **5.44**.[157] Still other approaches include the fragment condensation synthesis (see Section 2.3.2) and the use of spirodienone compounds (see Section 5.5.2).

5.4 *Exo* Rim-Bridged Calixarenes

Some of the most interesting embroidering of calixarenes involves bridge building at the *exo* rim. Although the earliest success was achieved by fragment condensations, as discussed in Section 2.3.2, most examples involve the addition of the bridge to the already constructed calixarene framework. A number of these start from an A,C *p*-diaminocalix[4]arene, obtained by reduction of the *p*-di-nitrocalix[4]arene, and proceed to yield compounds such as **5.45**.[158,159h] Spanners with the general structure CH_2-R-CH_2 can be introduced *via* chloromethylation or formylation procedures.[159] An ethylene bridge can be introduced *via* an intramolecular McMurry coupling reaction of a *p*-*bis*-formylcalix[4]arene.[160] An interesting example of a doubly bridged calix[4]arene obtained from *p*-carboxymethylcalix[4]arene (*via* the *p*-quinonemethide route) is the bis anhydride **5.46**, which can be converted to the selectively functionalized compounds **5.47** by treatment with various nucleophiles.[161] Although the great majority of *exo* rim-spanned calixarenes are found in the cyclic tetramer family, there are some examples in the cyclic hexamer family such as the triply spanned calix[6]arene **5.48**, obtained from the reaction of the *p*-1,3,5-tris-chloromethylcalix[6]arene with 1,3,5-tris-thiomethylbenzene.[162] A calix[8]arene spanned by four bridges has also been reported.[163]

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[157] O. Middel, Z. Greff, N. J. Taylor, W. Verboom, D. N. Reinhoudt and V. Snieckus, *J. Org. Chem.* **2000**, 65, 667.

[158] For examples of other spanners for *p*-aminocalix[4]arenes *cf.* (a) B. R. Cameron and S. J. Loeb, *J. Chem. Soc. Chem. Commun.* **1996**, 2003; (b) D. M. Rudkevich, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.* **1994**, 59, 3683; (c) P. D. Beer, P. A. Gale and D. Hesek, *Tetrahedron Lett.* **1995**, 36, 767; (e) D. M. Rudkevich, W. Verboom and D. N. Reinhoudt, *Tetrahedron Lett.* **1994**, 35, 7131; (f) *idem*, *J. Org. Chem.* **1995**, 60, 6585.

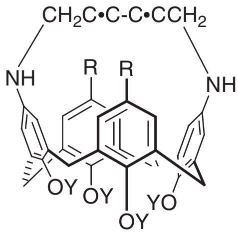
[159] (a) A. Arduini, S. Fanni, G. Manfredi, A. Pochini, R. Ungaro, A. R. Sicuri and F. Ugozzoli, *J. Org. Chem.* **1995**, 60, 1448; (b) A. Arduini, S. Fanni, A. Pochini, A. R. Sicuri and R. Ungaro, *Tetrahedron* **1995**, 51, 7951; (c) J.-D. van Loon, L. C. Groenen, S. S. Wijmenga, W. Verboom and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1991**, 113, 2378; (d) S. Kanamathareddy and C. D. Gutsche, *J. Org. Chem.* **1995**, 60, 6070; (e) A. Arduini, M. Cantoni, E. Graviani, A. Pochini, A. R. Secchi, R. Ungaro and M. Vicenti, *Tetrahedron* **1995**, 51, 599; (f) A. Arduini, A. Casnati, M. Fabbi, P. Minari, A. Pochini, A. R. Sicuri and R. Ungaro, *Supramol. Chem.* **1993**, 1, 235; (g) A. Arduini, G. Manfredi, A. Pochini, A. R. Sicuri and R Ungaro, *J. Chem. Soc Chem. Commun.* **1991**, 936; (h) A. Arduini, W. M. McGregor, A. Pochini, A. Secchi, F. Ugozzoli and R. Ungaro, *J. Org. Chem.* **1996**, 61, 6881; (i) R. Seangprasertkij, Z. Asfari, F. Arnaud, J. Weiss and J. Vicens, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, 14, 141.

[160] P. Lhoták and S. Shinkai, *Tetrahedron Lett.* **1996**, 37, 645.

[161] S. K. Sharma and C. D. Gutsche, *J. Org. Chem.* **1999**, 64, 3507.

[162] M. Takeshita, S. Nishio and S. Shinkai, *J. Org. Chem.* **1994**, 59, 4032.

[163] H. M. Chawla and K. Srinivas, *Tetrahedron Lett.* **1994**, 35, 2925; *idem*, *J. Chem. Soc. Chem. Commun.* **1994**, 2593.



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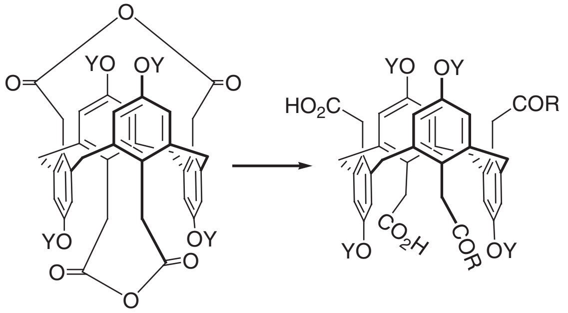
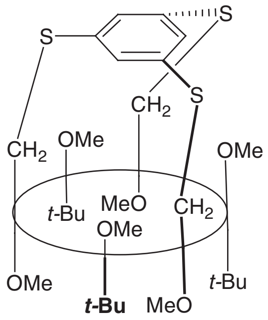


5.46 **5.47**



5.48

5.5 Oxidation of Calixarenes (*Apndx A-2, p. 266*)

5.5.1 Calixquinones

The first detailed publication of a calixquinone described three multi-step conversions of *p-tert*-butylcalix[4]arene to the tetraquinone **5.49a**.[164] One sequence involves the Fries rearrangement of the tetraacetate to the *p*-tetraacetyl compound followed by esterification, Baeyer–Villiger oxidation, hydrolysis to the hydroquinone and oxidation to the tetraquinone. A second sequence involves a Hoffmann rearrangement to the *p*-tetraacetylamino compound followed by oxidation. A third sequence involves the synthesis of the *p*-phenyldiazo compound followed by reduction to the aminophenol and oxidation. A one-step procedure using chlorine dioxide has been used to make all three of the quinones **5.49a-c**.[165] Similarly, thallium trifluoroacetate converts *p-tert*-butylcalix[4]arene directly to the quinone **5.49a**, although it fails with the larger calixarenes.

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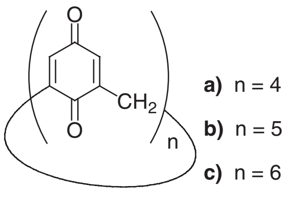
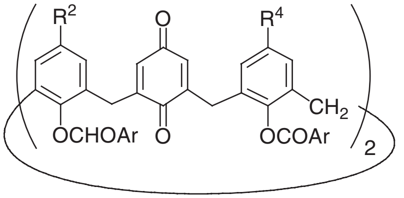
[164] Y. Morita, T. Agawa, Y. Kai, N. Kanehisa, N. Kasai, E Nomura and H. Taniguchi, *Chem. Lett.* **1989**, 1349; Y Morita, T. Agawa, E. Nomura and H. Taniguchi, *J. Org. Chem.* **1992**, 57, 3658.

[165] P. A. Reddy, R. Kashyap, W. H. Watson and C. D. Gutsche, *Isr. J. Chem.* **1992**, 32, 89.



5.49

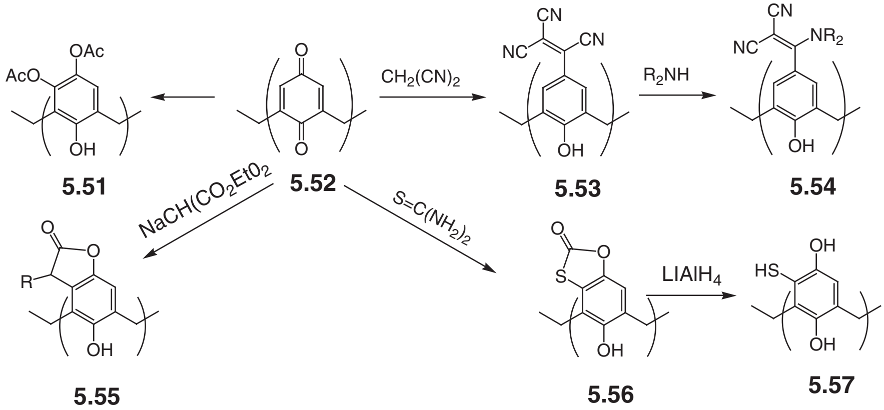


5.50

By using one or another of the various techniques for the selective removal of groups along with the introduction of protecting groups discussed elsewhere in this chapter, mono-, di- and tri-calix[4]quinones can be prepared.[166]

In addition to the calix[6]quinones **5.49c**, Tl(OCOCF)$_3$ oxidation of the A,B,D,E-tetrakis(*p*-nitrobenzoate) of *p-tert*-butylcalix[6]arene yields the A,D bisquinone **5.50** in 49% yield;[165] oxidation of the A,C,E-trimethyl ether yields the A,C,E-triquinone;[113a] and oxidation of an A,E bridged calix[8]arene followed by removal of the bridge yields an A,E-diquinone.[167]

The reactions of the mono- and diquinone of calix[4]arene have been studied in some detail.[168] The diquinone, for example, reacts with acetic anhydride to give **5.51** and with 2 equivalents of malononitrile (pathway involves carbonyl addition, 1,6-conjugate addition, HCN elimination) to give a 68% yield of the tricyano compound **5.53**, which, when treated with a secondary amine, affords dicyanoamines **5.54**. The monoquinone undergoes 1,4-conjugate addition with a variety of nucleophiles to give, *inter alia*, compounds **5.51**, **5.55**, **5.56** and **5.57**.



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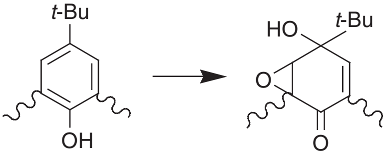
[166] K. C. Nam, D. S. Kim and S. Yang, *Bull. Korean Chem. Soc.* **1992**, 13, 105; K. Toth, B. T. Lan, J. Jeney, M. Horváth, I. Bitter, G. Grün, B. Auai and L. Toke, *Talanta* **1994**, 41, 104; H. Yamamoto, K. Ueda, K. R. A. Samankumara Sandanyake and S. Shinkai, *Chem. Lett.* **1995**, 497; H. Yamamoto, K. Ueda, H. Suenaga, T. Sakaki and S. Shinkai, *Chem. Lett.* **1996**, 39; P. D. Beer, Z. Chen, P. A. Gale, J. A. Heath, R. J. Knubley, M. I. Ogden and M. G. B. Drew, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 343; P. D. Beer, Z. Chen and P. A. Gale, *Tetrahedron* **1994**, 50, 931; Z. Chen, P. A. Gale, J. A. Heath and P. D. Beer, *J. Chem. Soc. Faraday Trans.* **1994**, 90, 2931.

[167] R. Ferro, C. Tedesco, C. Gaeta and P. Neri, *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, 52, 85.

[168] P. A Reddy and C. D. Gutsche, *J. Org. Chem.* **1993**, 58, 3245.

Base-promoted direct addition of O_2 to *p-tert*-butylcalix[4]arene yields products in which a single ring or a pair of distal rings have been oxidized to epoxyquinol rings:[169]



5.5.2 Spirodienones (*Apndx A-2, p. 270*)

Although strong oxidizing agents convert the phenolic rings of calixarenes to quinones, as discussed above, Silvio Biali and coworkers serendipitously[170] discovered that milder oxidizing agents produce compounds in which one or more of the phenolic rings of the calixarenes are converted to a spirodienone moiety. Using trimethylphenylammonium tribromide instead of the intended monobromide (as a phase transfer catalyst), *p-tert*-butylcalix[4]arene was transformed to the spirodienone **5.58** ($n = 4$).[171] With a larger amount of oxidant the product was a mixture of two A,B-di-spirodienones **5.59** (R,S and R,R/S,S diastereoisomers) and one of the possible A,C-di-spirodienones **5.60** (R,S).[172] The larger calixarenes behave in similar fashion.[173] Mild oxidation yields the mono-spirodienones **5.58** ($n = 5,6,8$); more strenuous oxidation yields the A,C-di-spirodienone from *p-tert*-butylcalix[5]arene, the A,B,E- and A,C,E-tri-spirodienones from *p-tert*-butylcalix[6]arene and the A,C,E,G-tetra-spirodienone (1–2% yield) from *p-tert*-butylcalix[8]arene. Biali has ingeniously exploited his discovery by demonstrating that the calix-spirodienones can engage in reactions that lead to a variety of altered calixarenes, including (a) *p-tert*-butylcalixarenes in which one or two of the *endo* rim hydroxyl groups (A,B and A,C) are replaced by H (or D),[171a] Me,[174] or NH_2[175] and (b) *p-tert*-butylcalix[4]arenes with an R group (D, halogen, alkyl, OR, SR, N_3) on one or two of the methylene bridges[176] (*cf.* **5.16b,c,d,e**). Photolysis of a spirodienone

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[169] C. Gaeta, F. Troisi, M. Martino, E. Gavuzzo and P. Neri, *Org. Lett.* **2004**, 6, 3027.

[170] S. E. Biali, *Synlett No. 1* **2003**, 1.

[171] (a) O. Aleksiuk, F. Grynszpan and S. E. Biali, *J. Chem. Soc. Chem. Commun.* **1993**, 11; (b) A. M. Litwak and S. E. Biali, *J. Org. Chem.* **1992**, 57, 1943.

[172] A. M. Litwak, F. Grynszpan, O. Aleksiuk, S. Cohen and S. E. Biali, *J. Org. Chem.* **1993**, 58, 393.

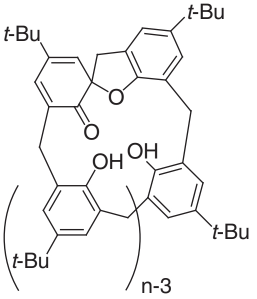
[173] (a) F. Grynszpan and S. E. Biali, *J. Chem. Soc. Chem. Commun.* **1994**, 2545; (b) F. Grynszpan and S. E. Biali, *J. Org. Chem.* **1996**, 61, 9512; (c) F. Grynszpan, O. Aleksiuk and S. E. Biali, *Pure Appl. Chem.* **1996**, 68, 1249.

[174] J. M. Van Gelder, J. Brenn, I. Thondorf and S. E. Biali, *J. Org. Chem.* **2997**, 62, 3511.

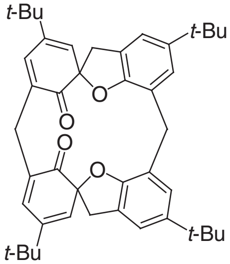
[175] O. Aleksiuk, S. Cohen and S. E. Biali, *J. Am. Chem. Soc.* **1995**, 117, 9645; S. Simaan and S. E. Biali, *Org. Lett.* **2005**, 7, 1817.

[176] K. Agbaria and S. E. Biali, *J. Am. Chem. Soc.* **2001**, 123, 12495; S. Simaan, K. Agbaria and S. E. Biali, *J. Org. Chem.* **2002**, 67, 6136; S. Simaan and S. E. Biali, *ibid.* **2003**, 68, 3634; *idem*, *J. Phys. Org. Chem.* **2004**, 17, 752.

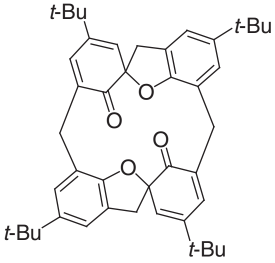
with 300 nm irradiation produces a compound containing a spirocyclic cylopentenone unit, a trisubstituted phenol and a benzofuran moiety.[177]



5.58



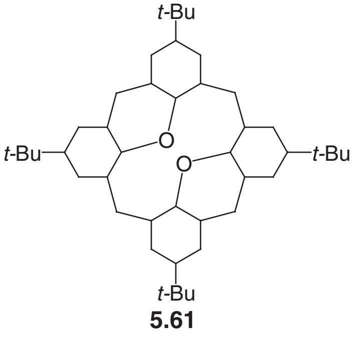
5.59



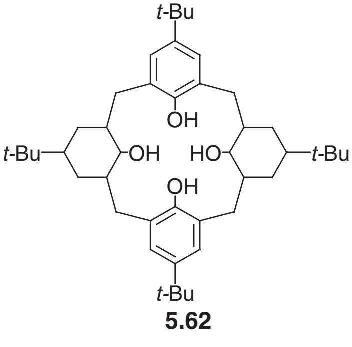
5.60

5.6 Reduction of Calixarenes (*Apndx A-2, p. 273*)

Calix[4]arene undergoes reduction with Raney-Ni-PrOH and H_2 at 1450 p.s.i. to give a mixture of stereoisomeric perhydro calix[4]arene diethers **5.61** (*via* intramolecular dehydration of proximal OH groups) from which the *trans*-*syn*-*trans* isomer was isolated in 15% yield and its structure verified by X-ray crystallography.[178] Subsequent work showed that under milder conditions, using PdC catalyst at 600 p.s.i. and 100 °C, partially reduced compounds are produced in which either a single ring or two distal rings (**5.62**) are present as cyclohexanol moieties.[179] With the same catalyst at 250 °C complete reduction occurs with the removal of all of the oxygen functions. With $RhCl_3$ as the hydrogenation catalyst a slightly different pathway is followed, yielding a product in which one of the rings in the cyclic array has been reduced to a cyclohexanone moiety.[180]



5.61



5.62

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[177] R. L. Varma, V. B. Ganga and E. Suresh, *J. Org. Chem.* **2007**, 72, 1017.

[178] F. Grynszpan and S. E. Biali, *J. Chem. Soc. Chem. Commun.* **1996**, 195.

[179] I. Columbus and S. E. Biali, *J. Am. Chem. Soc.* **1998**, 120, 3060.

[180] A. Bilyk, J. M. Harrowfield, B. W. Skelton and A. H. White, *Ana. Quim. Int. Ed.* **1997**, 93, 363; I. Columbus, M. Haj-Zaroubi and S. E. Biali, *J. Am. Chem. Soc.* **1998**, 120, 11806.

5.7 Selective Functionalization

Selective functionalization of calixarenes is of central importance for the construction of compounds to serve in various capacities such as polyfunctional ion binders, molecular complexing agents and enzyme mimics. Many examples of selective functionalization have already been presented in the preceding sections, and only one additional example is included at this point as a good representative of the present state of the art. It comes from the European consortium of calixarene chemists and involves a sequence of reactions that rely solely on *exo* rim selectivities. Starting with the tetrapropyl ether **5.63**, prepared by etherification of *p*-*tert*-butylcalix[4]arene, a pair of nitro groups were introduced on the A and C rings by treatment with HNO_3 at room temperature[181] to give **5.64**; then a single iodine atom was added using 1 equiv of CF_3CO_2Ag/I_2 to yield **5.65**, and this was treated with phthalimide followed by NH_2NH_2 cleavage to produce the chiral compound **5.66**[100a] with four different substituents on the *exo* rim, as illustrated in Figure 5.5.[182]

In contrast to the example just presented, many routes for selective functionalization on the *exo* rim take advantage of the relative ease with which selective functionalization on the *endo* rim can be effected. Procedures have

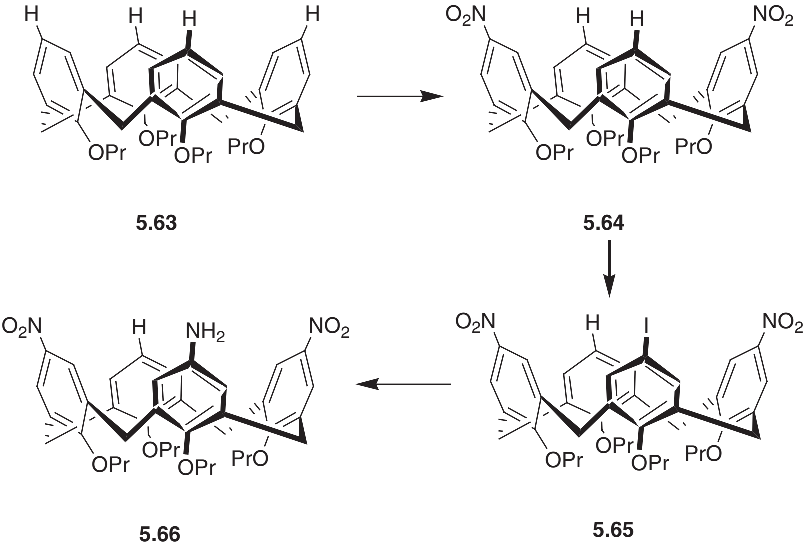

Figure 5.5 Selective *exo* rim functionalization of calix[4]arene.

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[181] E. Kelderman, L. Derhaeg, G. J. T. Heesink, W. Verboom, J. F. J. Engbersen, N. F. van Hulst, A. Persoons and D. N. Reinhoudt, *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 1075.

[182] For an example of selective functionalization of calix[6]arenes *cf*. J. de Mendoza, M. Carramolino, F. Cuevas, P. M. Nieto, P. Prados, D. N. Reinhoudt, W. Verboom, R. Ungaro and A. Casnati, *Synthesis* **1994**, 47.

been described in Section 5.1 for preparing mono-, di-, tri- and tetraethers and esters of calix[4]arenes, and comparably selective procedures have been devised for some of the larger calixarenes. The great virtue of selective esterification and etherification is that they create a significant difference in the reactivity at the *p*-positions, which renders the ArOH moieties more susceptible to electrophilic substitution. This makes possible the selective removal of *tert*-butyl groups and, in turn, the selective introduction of other groups by one or another of the methods discussed in Section 5.2.

5.8 Concluding Remarks

In the first edition of this book multi-calixarenes were few enough in number to fit comfortably in its Chapter 5. In the interim, however, this facet of calixarene chemistry has expanded so rapidly that it is now expedient to devote a separate chapter to describe these larger structures that are bringing calixarenes into the new world of nanochemistry.

CHAPTER 6

Combining the Baskets: Multi-Calixarenes

So pleas'd at first the towering Alps we try,
Mount o'er the vales, and seem to tread the sky
Th' eternal snows appear already past,
And the first clouds and mountains seem the last:
But those attain'd we tremble to survey
The growing labours of the lengthen'd way
Th' increasing prospect tires our wand'ring eyes
Hills peep o'er hills, and Alps on Alps arise!

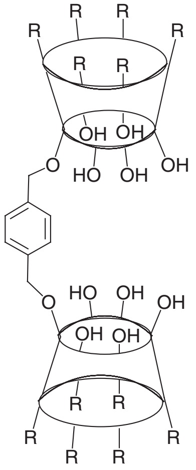
Alexander Pope, *Essays on Criticism II*

Life has evolved from single-celled microbes to multi-celled flora and fauna. Businesses have evolved from very small enterprises to very large corporations. In like fashion, calixarenes are evolving from simple single-calixarene compounds to complex multi-calixarene compounds as "Alps on Alps arise". That this is a fairly recent phenomenon is indicated by the publication dates of many of the references in this chapter. Whereas in Chapters 1–5 there is a heavy concentration on publications appearing from the 1980s to the late 1990s which is the period during which the basic features of the field were being discovered and consolidated, a significant number of the references in this chapter are more current.

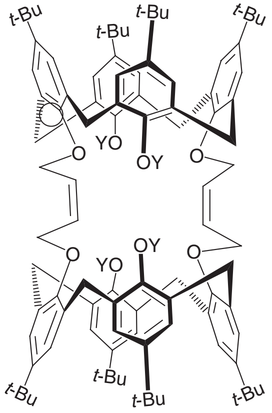
6.1 Calixarenes Intermolecularly Bridged by Covalent Bonding (*Apndx A-2, p. 130*)

6.1.1 Bridging *via* the *Endo* Rims

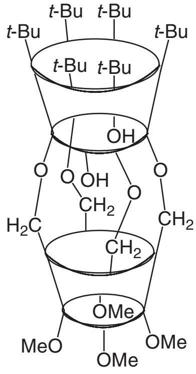
Calixarene units have been joined one to another at their *endo* rims by a variety of spanners to produce singly spanned structures (*e.g.* **6.1**[1]) or multiply spanned structures (*e.g.* **6.2**[2], **6.3**[3] and **6.4**[4]).



6.1



6.2



6.3

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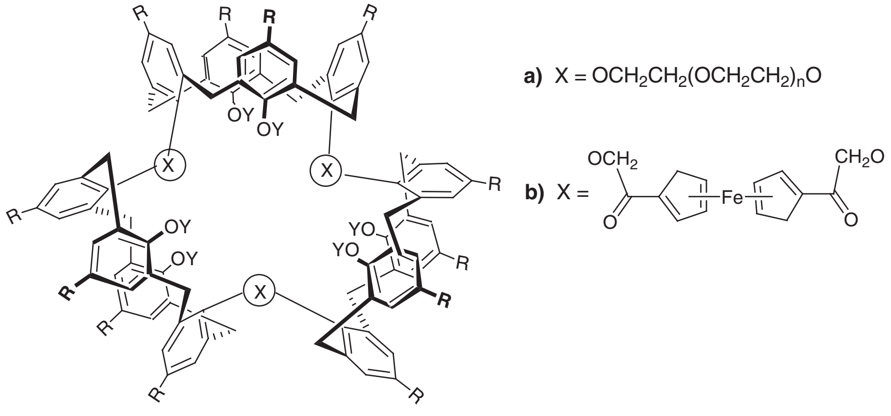
[1] S. Kanamathareddy and C. D. Gutsche, *J. Org. Chem.* **1994**, 59, 3871.

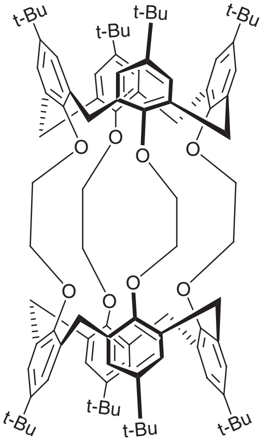
[2] J. Wang and C. D. Gutsche, *J. Am. Chem. Soc.* **1998**, 120, 12226.

[3] A. Arduini, A. Pochini, A. Secchi and R. Ungaro, *J. Chem. Soc. Chem. Commun.* **1995**, 879.

[4] D. Kraft, J.-D. van Loon, M. Owens, W. Verboom, W. Vogt, M. A. McKervey, V. Böhmer and D. N. Reinhoudt, *Tetrahedron Lett.* **1990**, 31, 4941; P. D. Beer, A. D. Keefe, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc. Dalton Trans* **1990**, 3675.



6.4



6.5

Compounds like **6.3** have acquired the name "calix[*n*]tube" (*Apndx A-1, p. 109, 135; D-1*), an early example of which is the calix[4]tube **6.5** reported[5] in 1997 from the reaction of *p-tert*-butylcalix[4]arene with its tetra-tosyloxyethyl ether. In this family compound **6.2** is classed as a "calix[4]semitube". With calix[4]arenes in the 1,3-alternate conformation extended calix[4]tubes (nanotubes) (**6.6**) can be constructed.[6] The joining of a pair of *p-tert*-butylcalix[6]arenes with three $CH_2CH_2NRCH_2CH_2$ spanners provides a good example of a calix[6]azatube.[7]

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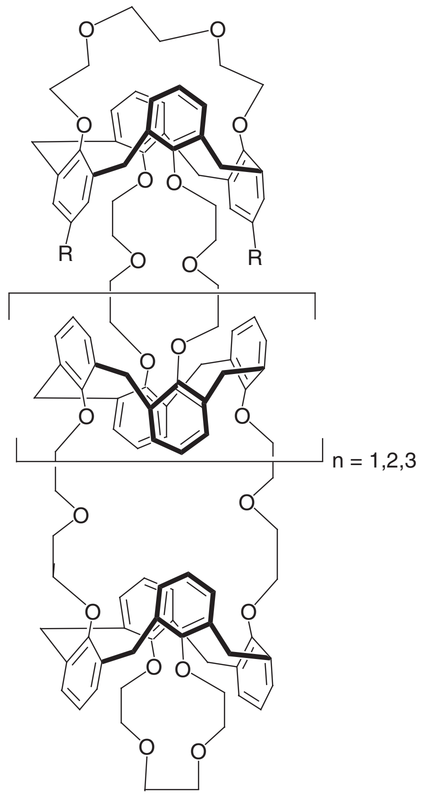
[5] P. Schmitt, P. D. Beer, M. G. B. Drew and P. D. Sheen, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1840; S. E. Matthews, P. Schmitt, V. Felix, M. G. B. Drew and P. D. Beer, *J. Am. Chem. Soc.* **2002**, 124, 1341.

[6] S. K. Kim, W. Sim, J. Vicens and J. S. Kim, *Tetrahedron Lett.* **2003**, 44, 805; S. K. Kim, J. Vicens, K.-M. Park, S. S. Lee, W. Sim and J. S. Kim, *ibid.* **2003**, 44, 993.

[7] S. Le Gac, X. Zeng, O. Reinaud and I. Jabin, *J. Org. Chem.* **2005**, 70, 1204.

Other combinations include calix[4]-calix[*n*]tubes (hybrid tubes),[8] calix[4]semitube quinones,[9] thiacalix[4]tubes[10] and trimeric arrays.[11]



6.6

6.1.2 Bridging *via* the *Exo* Rims

A variety of calixarenes joined one to another *via* bridges attached at the *exo* rims have been made. Compound **6.7** obtained by a double tandem Claisen rearrangement of the corresponding *endo* rim-bridged calix[4]arene,[12] is one of numerous examples in which the bridge contains only carbon atoms.[13] Another

---

[8] A. Notti, S. Occhipinti, S. Pappalardo, M. F. Parisi, J. Pisagatti, A. J. P. White and D. J. Williams, *J. Org. Chem.* **2002**, 67, 7569.

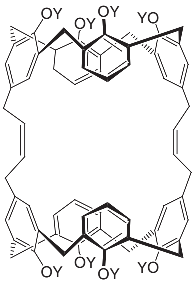
[9] R. P. A. Weber, A. Cowley and P. D. Beer, *Dalton Trans.* **2003**, 3922; N. Kerdpaiboon, B. Tomapatanaget, O. Chailapakul and T. Tuntulani, *J. Org. Chem.* **2005**, 70, 4797.

[10] S. E. Matthews, V. Felix, M. G. B. Drew and P. D. Beer, *New J. Chem.* **2001**, 25, 1355.

[11] M. Makha, P. J. Nichols, M. J. Hardie and C. L. Raston, *J. Chem. Soc. Perkin Trans 1* **2002**, 354.

[12] J. Wang and C. D. Gutsche, *J. Am. Chem. Soc.* **1998**, 120, 12226.

[13] For another example (a multiple *ansa* compound) *cf*. A. Siepen, A. Zett and F. Vögtle, *Liebigs Ann.* **1996**, 757.



6.7

set of examples includes -N = CH-X-CH = N- bridges, where X can be phenyl, pyridyl, thiophenyl, furanyl, *etc*.[14] Compound **6.8**, similar to **6.6**, is another interesting example of a calix[4]arene in the 1,3-alternate conformation joined at the *exo* rims to form an extended calix[4]tube.[15] It is also possible to directly join calixarenes at their *exo* rims by means of oxidative coupling using ferric chloride to produce bis-calix[4,5,6,8]arenes **6.9**.[16]

A strategy used by Reinhoudt[17] and others for constructing artificial receptor molecules as biochemical mimics makes use of medium-sized molecules as platforms to which functional groups can be attached. Included among such platforms are calix[4]arenes, calix[4]resorcarenes, cyclodextrins, and porphyrins which have been combined in various ways to give, for example, compound **6.10** derived from a calix[4]arene and a calix[4]resorcarene[18] (heralded as "an organic molecule with a rigid cavity of nanosize dimensions"). The advantageous use of Cs_2CO_3 in combination with NaH in creating some of the intermolecular links in these compounds is a good example of a template effect as well as an illustration of the importance of preorganization. From the reaction of a calix[4]arene with chloromethyl methyl ether and a $ZnCl_2$ catalyst a macrocycle containing five calixarene units joined to one another by methylene groups was isolated in 4% yield.[19]

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[14] G. T. Hwang and B. H. Kim, *Tetrahedron* **2002**, 58, 9019.

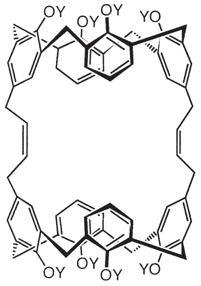
[15] A. Ikeda and S. Shinkai, *J. Chem. Soc. Chem. Commun.* **1994**, 2375.

[16] P. Neri, A. Bottino, F. Consulo, M. Piatelli and E. Gavuzzo, *Angew. Chem. Intl. Ed. Engl.* **1998**, 37, 166; A. Bottino, F. Consulo, M. Piatelli, D. Garozzo and P. Neri, *J. Org. Chem.* **1999**, 64, 8018; J. Wang, S. G. Bodige, W. H. Watson and C. D. Gutsche, *ibid.* **2000**, *65*, 8260.

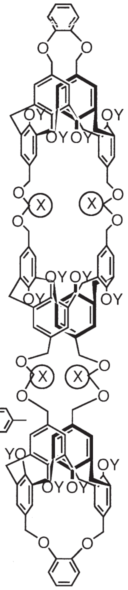
[17] P. Timmerman, H. Boerrigter, W. Verboom and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* **1995**, 114, 10; A. M. A. van Wageningen, W. Verboom and D. N. Reinhoudt, *Pure & Appl. Chem.* **1996**, 68, 1273.

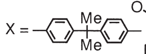
[18] P. Timmerman, W. Verboom, F. C. J. M. van Veggel, W. P. van Hoorn and D. N. Reinhoudt, *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1292; P. Timmerman, K. G. A. Nierop, E. A. Brinks, W. Verboom, F. C. J. M. van Veggel, W. P. van Hoorn and D. N. Reinhoudt, *Chem. Eur. J.* **1995**, 1, 132.

[19] J.-M. Liu, Y.-S. Zheng, Q.-Y. Zheng, J. Xie, M.-X. Wang and Z.-T. Huang, *Tetrahedron* **2002**, 5, 3729.

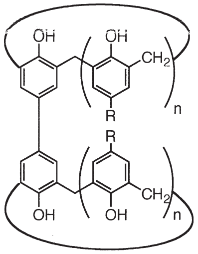


6.7





6.8



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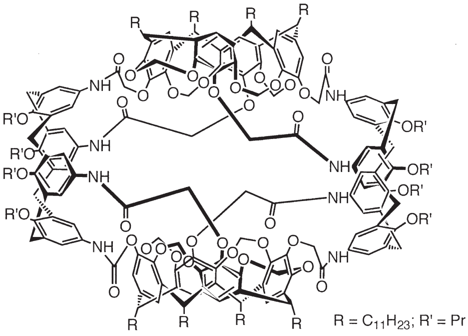

R = $C_{11}H_{23}$; R' = Pr

6.10

6.1.3 Multi-Calixarenes and Calixarene Dendrimers (*Apndx A-1, p. 21, 89*)

The first calixarene-based dendrimer was reported by Newcome and coworkers in 1991 who attached $[(HOCH_2)_3CNHCO]_3CCH_2$ groups to each of the four *p*-positions of calix[4]arene. Since then several other examples have been published in which the calixarene serves as the central unit to which other types of moieties are attached.[20] A second type of calixarene-based dendrimer are those in which calixarenes are both the central unit as well as the appendages.[21] A "second generation" dendrimer in this category[22] is schematically illustrated by **6.11**. A third type employs the calixarenes only as appendages with a different kind moiety serving as the central unit.[23] An interesting approach to both of these last two types employs calixarenes carrying one or two alkyne moieties in the *p*-position (**6.12**), which can engage in a cyclotrimerization reaction to yield the tris-calixarene **6.13** and the pentakis-calixarene **6.14**.[24]

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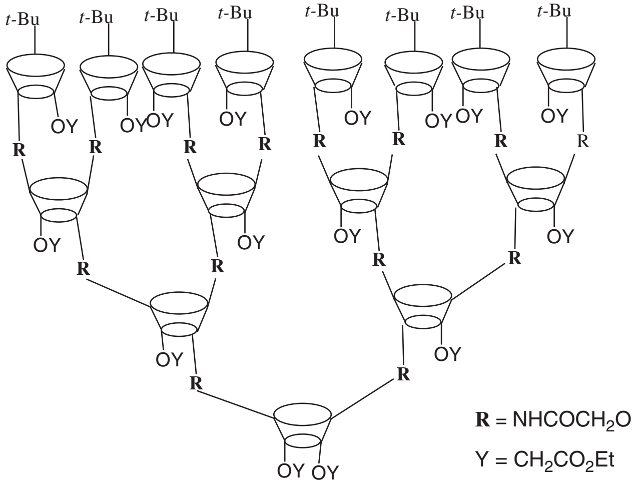
[20] T. Nagasaki, S. Tamagaki and K. Ogino, *Chem. Lett.* **1997**, 26, 717; R. Roy and J. M. Kim, *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 369.

[21] P. Lhotak and S. Shinkai, *Tetrahedron* **1995**, 51, 7681; O. Mogck, P. Parzuchowski, M. Nissinen, V. Böhmer, G. Rokicki and K. Rissanen, *Tetrahedron* **1998**, 54, 10053; F. Szemes, M. G. B. Drew and P. D. Beer, *Chem. Commun.* **2002**, 1228.

[22] J.-H. Bu, Q.-Y. Zhang, C.-F. Chen and Z.-T. Huang, *Tetrahedron* **2005**, 61, 897.

[23] N. Cheriaa, R. Abidi and J. Vicens, *Tetrahedron Lett.* **2005**, 46, 1533.

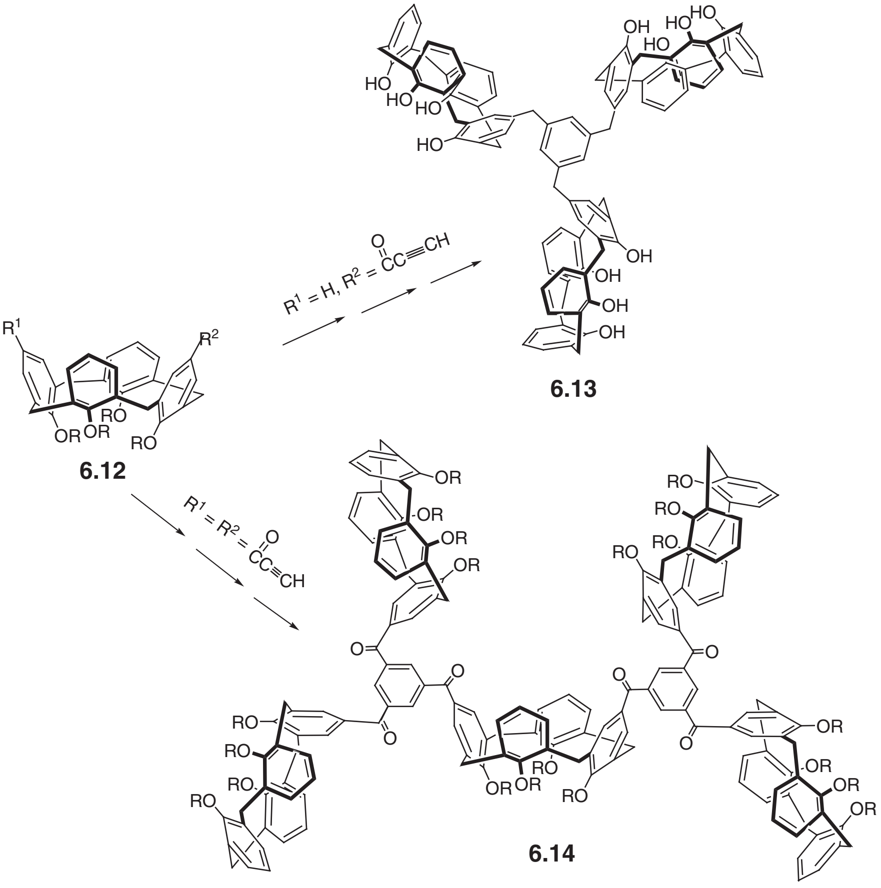
[24] J. Wang and C. D. Gutsche, *J. Org. Chem.* **2002**, 67, 4423.



$\mathbf{R}$ = $NHCOCH_2O$

Y = CH_2CO_2Et

6.11



6.12

6.13

6.14

6.2 Calixarenes Intermolecularly Bridged by Non-covalent Bonding (*Apndx A-2, p. 155*)

"Self assembly" is an integral aspect of the physical world; electrons, neutrons, and other subatomic particles assemble into atoms; atoms assemble into molecules; molecules react with one another to reassemble into new molecules and molecules assemble reversibly with themselves and/or with other molecules *via* intermolecular non-covalent forces to form supramolecular arrays. The term "self assembly", however, seems to have been selected to describe only the last of these phenomena and is currently a topic of great interest in chemistry as well as biology. The calixarenes, not surprisingly, are among the many types of molecules that have been chosen by the chemists for investigating this phenomenon.

6.2.1 Dimeric Assemblies of Calixarenes (*Apndx A-1, p. 21; A-2, p.155; A-4, p.203; B-4, B-5*)

Intermolecularly associated dimers derived from the calixarenes were first studied in the early 1990s by Reinhoudt and coworkers[25] who synthesized ethoxyethyl ethers of calix[4]arenes **6.15a,b** carrying and two pyridone moieties on the *exo* rim, and they showed that **6.15a** forms a dimer with $K_{assoc} = 100\ M^{-1}$. At about the same time, Atwood and coworkers[26] published an X-ray structure of a dimer formed from two molecules of Na_4(pyridinium)[calix[4]arenesulfonate]$\cdot 8H_2O$. Then, in 1993 a prediction of things to come appeared from the laboratories of Julius Rebek and coworkers[27] who limned the dimerization of a calix[4]arene tetraamide. A well defined solution dimer appeared in 1994 from the laboratories of Shinkai and coworkers[28] who demonstrated the *exo* rim-to-*exo* rim association of a pair of tetrapropyl ethers of calix[4]arene, *viz*. **6.15c** carrying carboxyl groups in the *p*-position and **6.15d** carrying pyridyl-containing arms in the *p*-position. In 1995 Shimizu and Rebek[29] provided persuasive proof for a dimer from the tetrabenzyl ether of a calix[4]arene carrying N-phenylurea moieties in the *p*-position (**6.15e**). Rebek revisited this system a year later, using the conformationally mobile tetramethyl ether which is driven to adopt the cone conformation upon dimerization.[30] In 1996 a set of similar compounds (**6.15f**) was described by Böhmer and coworkers,[31] and support for the dimer structures, initially based on ^1H NMR spectral interpretations and

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[25] J.-D. van Loon, R. G. Janssen, W. Verboom and D. N. Reinhoudt, *Tetrahedron Lett*. **1992**, 33, 5125.

[26] J. L. Atwood, G. W. Orr, F. Hamada, S. G. Bott and K. D. Robinson, *Supramol. Chem*. **1992**, 1, 15.

[27] C. Andreu, R. Beerli, N. Branda, M. Conn, J. de Mendoza, A. Galán, I. Huc, Y, Kato, M. Tymoschenko, C. Valdez, E. Wintner, R. Wyler and J. Rebek, Jr., *Pure & Appl. Chem*. **1993**, 65, 2313.

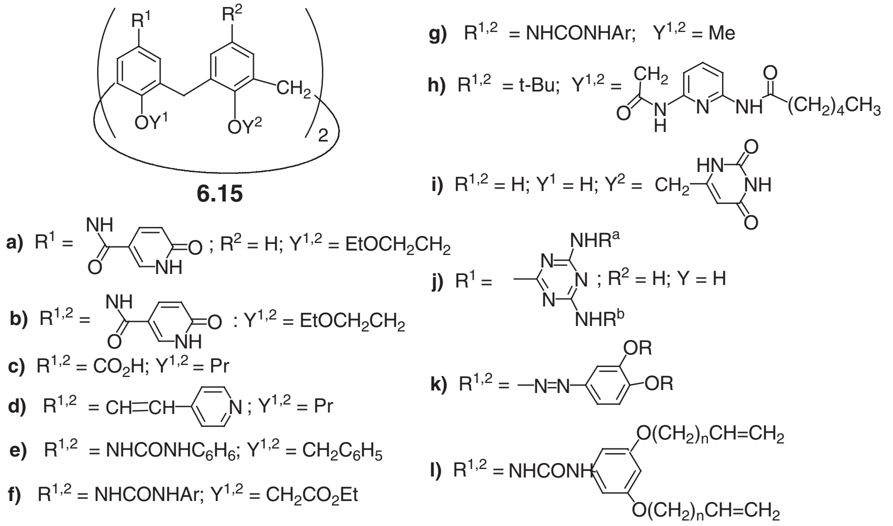
[28] K. Koh, K. Araki and S. Shinkai, *Tetrahedron Lett*. **1994**, 35, 8255.

[29] K. D. Shimizu and J. Rebek, Jr., *J. Proc. Natl. Acad. Sci. USA* **1995**, 92, 12403.

[30] R. K. Castellano, D. M. Rudkevich and J. Rebek, Jr., *J. Am. Chem. Soc*. **1996**, 118, 10002.

[31] O. Mogck, V. Böhmer and W. Vogt, *Tetrahedron* **1996**, 52, 8489; O. Mogck, M. Pons, V. Böhmer and W. Vogt, *J. Am. Chem. Soc*. **1997**, 119, 5706.

mass spectral observations,[32] was reinforced by an X-ray crystallographic determination.[33] Whether or not a dimer forms, however, is dependent on several factors, including the solvent and the particular groups attached to the exo rim.[34] Also, the stability of the dimer is influenced by the conformational characteristics of the monomeric unit.[35]



6.15

The dimers derived from *p*-ureidocalix[4]arenes, represented schematically by **6.16**, have several interesting features. Although comprising two monomers, each with C_4 symmetry, the two halves that are stitched together at the equator by sixteen hydrogen bonds and are turned by 45° (time average) to generate a system with S_8 symmetry (if the two halves are identical, *i.e.* a homo dimer) or C_4 symmetry (if the two halves are different, *i.e.* a hetero dimer). The dimers can act as complexing agents[36] and, indeed, generally do not form as dimers unless there is a non-polar molecule such as benzene or toluene (*e.g.* the solvent) available to perform a templating role and become ensconced in the resulting capsular cavity.[37] Competition experiments with the dimer from **6.15e**

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[32] C. A. Schalley, R. K. Castellano, M. S. Brody, D. M. Rudkevich, G. Siudzak and J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, 121, 4568.

[33] O. Mogck, E. F. Paulus, V. Böhmer, I. Thondorf and W. Vogt, *J. Chem. Soc. Chem. Commun.* **1996**, 2533; I. Thondorf, F. Broda, K. Rissenen, M. O. Vysotsky and V. Böhmer, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1796.

[34] A. Shivanyuk, M. Saadiovi, F. Broda, I. Thondorf, M. O. Vysotsky, K. Rissanen, E. Kolehmainen and V. Böhmer, *Chem. Eur. J.* **2004**, 10, 2138; M. O. Vysotsky, I. Thondorf and V. Böhmer, *Angew. Chem. Intl. Ed. Engl.* **2000**, 39, 1264; Y. Cao, M. O. Vysotsky and V. Böhmer, *J. Org. Chem.* **2006**, 71, 3429.

[35] M. O. Vysotsky, O. Mogck, Y. Rudzevich, A. Shivanyuk, V. Böhmer, M. S. Brody, Y. L. Cho, D. M. Rudkevich and J. Rebek, Jr., *J. Org. Chem.* **2004**, 69, 6115.

[36] F. Broda, M. O. Vysotsky, V. Böhmer and I. Thondorf, *J. Org. Biomol. Chem.* **2006**, 4, 2424.

[37] A pair of calix[4]arenes, one with ureido groups and the other with carboxyl groups, form a hetero dimer in aqueous solution (J. S. Sasine, R. E. Brewster, K. L. Caran, A. M. Bentley and S. B. Shuker, *Org. Lett.* **2006**, 8, 2913. Also, *cf.* F. Corbellini, R. Fiammengo, P. Timmerman, M. Crego-Calama, K. Versluis, A. J. R. Heck, I. Luyten and D. N. Reinhoudt, *J. Am. Chem. Soc.* **2002**, 124, 6569.

show that the tightness of complexation decreases in the order: benzene > chloroform > toluene > *o*-xylene > *p*-xylene > ethylbenzene. Similar experiments with the dimer from **6.15f** (Ar = *p*-fluorophenyl) show the order of decreasing affinity to be: *p*-diflurobenzene > pyrazine > fluorobenzene > pyridine > benzene > phenol > aniline > chlorobenzene.[38] The addition of strong hydrogen bond-forming molecules can "denature" the dimers to monomers as in the case of **6.15e,f** with N-phenyl-N′-phenylethylurea which is too large to occupy the cavity of the dimer (estimated to have a volume of *ca.* 210 Å^3). Still another interesting feature is observed with the dimethyl ether **6.15g**, which is conformationally mobile and, as a monomer, exists primarily in the partial cone conformation. Upon dimerization, however, the conformation changes to the cone as a result of the advantage gained from the intermolecular hydrogen bonding between its urea moieties.[39]

What might seem to be the most obvious way for creating a dimeric capsule, *viz*. by the interaction of a cationic calixarene with an anionic calixarene,[40] was not reported until 2002 when Reinhoudt and coworkers[41] mixed a *p*-sulfonatocalix[4]arene with a *p*-amidiniumcalix[4]arene to generate a water soluble capsule which showed complexing abilities for small charged guests such as acetylcholine. A similar capsule using **L**-alanyl moieties in place of sulfonato groups was subsequently prepared[42] which showed similar complexation characteristics, in contrast to the capsule prepared by Kraft and coworkers[43] from a *p*-dimethoxyphosphorylmethyl-calix[4]arene and a *p*-aminocalix[4]arene which failed to encapsulate guest molecules.

Interest in the ureidocalix[4]arenes continues unabated not only because of their potential complexing abilities but also because of the prospect of building topologically interesting structures. Pursuant to the latter are the experiments of Böhmer and coworkers who started with calixarenes such as **6.15l** carrying terminally functionalzed *p*-ureido moieties. Using a metathesis reaction with the Grubbs catalyst under high dilution conditions the alkenyl ends of **6.17** were joined to generate multiply bridged compounds including, *inter alia*, **6.18** (bridges only on the upper and lower hemispheres) and **6.19** (bridges spanning the upper and lower hemispheres).[44] Carrying this approach a step further, the Mainz group has made **6.20** which has eight bridges and is classed as an [8]catenane.[45]

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[38] B. C. Hamann, K. D. Shimizu and J. Rebek, Jr., *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1326.

[39] R. K. Castellano, D. M. Rudkevich and J. Rebek, Jr., *J. Am. Chem. Soc.* **1996**, 118, 10002.

[40] Shortly after the discovery of C_{60}, before the work of Atwood and Shinkai had appeared, this author attempted to sequester C_{60} by encapsulating it between the *p*-diallylamnomethylcalix[8]arene **6.29** and the *p*-carboxyethylcalix[8]arene **6.30**, but without success; *i.e.* an idea is a good one only if it can be brought to fruition.

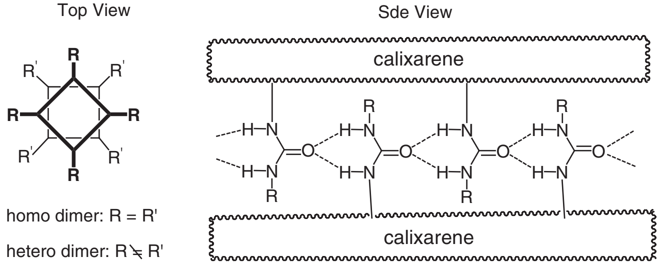
[41] F. Corbellini, R. Fiammengo, P. Timmerman, M. Crego-Calama, K. Versiuis, A. J. R. Heck, I. Luyten and D. N. Reinhoudt, *J. Am. Chem. Soc.* **2002**, 124, 6569.

[42] F. Corbellini, L. Di Costanzo, M. Crego-Calama, S. Geremia and D. N. Reinhoudt, *J. Am. Chem. Soc.* **2003**, 125, 9946.

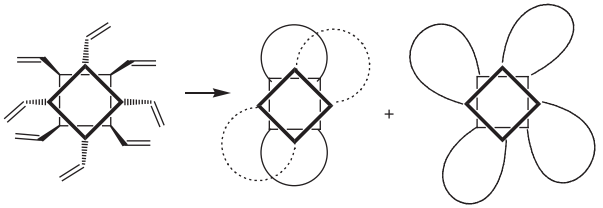
[43] R. Zadmard, T. Schrader, T. Grawe and A. Kraft, *Org. Lett.* **2002**, 4, 1687; R. Zadmard, M. Junkers, T. Schrader, T. Grawe and A. Kraft, *J. Org. Chem.* **2003**, 68, 6511.

[44] M. O. Vysotsky, M. Bolte, I. Thondorf and V. Böhmer, *Chem. Eur. J.* **2003**, 9, 3375.

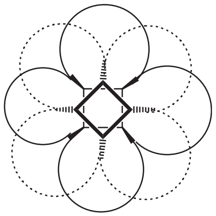
[45] L. Wang, M. O. Vysotsky, A. Bogdan, M. Bolte and V. Böhmer, *Science* **2004**, 304, 1312.



6.16



6.17 **6.18** **6.19**



6.20

6.2.2 Catenanes and Rotaxanes (*Apndx A-1, p. 47, 63*)

Catenanes and rotaxanes, of interest because of their topological appeal as well as their potential for practical application in molecular switches, motors, and machines, have not escaped the attention of calixarene chemists. In some rotaxanes the calixarene is simply used as a large "stopper" to prevent the axle to which it is attached from slipping out of the "wheel" through which it is threaded.[46] In the more interesting cases, however, the calixarene provides the wheel and, in some special cases such as the self-anchored rotaxane **6.21**[47] the axle as well. In the more traditional case the axle is a separate moiety, an illustrative example being 1,3,5-tris-N-phenylureidocalix[6]arene threaded with a dipyridinium moiety carrying long tails on the nitrogen atoms which are terminated with large groups to produce the rotaxane **6.22**.[48] A four-fold [2]rotaxane based on a ureidocalix[4]arene dimer has been reported.[49] In most of the examples of calixarene-contaning catenanes that have been published, however, the calixarene simply serves as one of the sides of the cavity of a calix[4]tube carrying a bridge on the *endo* rim that contains two di-pyridinium moieties.[50]

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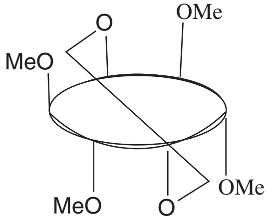
[46] C. Fischer, M. Nieger, O. Mogek, V. Böhmer, R. Ungaro and F. Vögtle, *Eur. J. Org. Chem.* **1998**, 155.

[47] S. Kanamathareddy and C. D. Gutsche, *J. Am. Chem. Soc.* **1993**, 115, 6572.

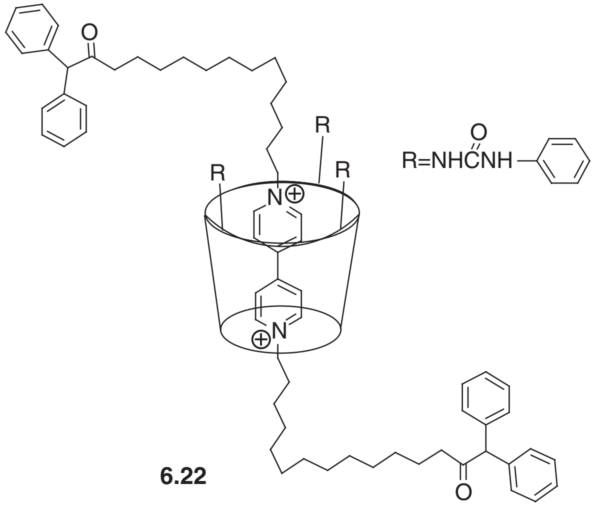
[48] A. Arduini, R. Ferdani, A. Pochini, A. Seechi and F. Ugozzoli, *Angew. Chem. Intl. Ed. Engl.* **2000**, 39, 3453; A. Credi, S. Dumas, S. Silvi, M. Venturi, A. Arduini, A. Pochini and A. Secchi, *J. Org. Chem.* **2004**, 69, 5881.

[49] C. Gaeta, M. O. Vysotsky, A. Bogdan and V. Böhmer, *J. Am. Chem. Soc.* **2005**, 127, 13136.

[50] Z.-T. Li, G.-Z. Ji, S.-D. Yuan, A.-L. Du, H. Ding and M. Wei, *Tetrahedron Lett.* **1998**, 39, 6517.



6.21



6.22

6.2.3 Oligomeric and Polymeric Assemblies of Calixarenes

The 1992 attempt to create a calixarene dimer from **6.15b** (*vide supra*) resulted primarily in the formation of a polymeric assembly in $CDCl_3$ solution which could be denatured by treatment with imidazolidone.[26] A subsequent approach,[51] designed specifically to create polymeric assemblies, made use of the calix[4]arene **6.15h** substitued with diaminopyridine moieties on the *endo* rim. In the presence of dioctylbarbituric acid and Na^+ cations the hydrogen bonding in **6.15h** changes from intra- to intermolecular to produce a polymeric assembly in which the calixarene and barbituric acid constitute 1:1 units with $K_{assoc} = 150\,M^{-1}$. A somewhat similar approach, based on establishing predictable directionality of hydrogen bonding, makes use of calixarenes **6.15i,j** carrying uracil or diaminotriazine moieties.[52] The uracil-containing **6.15i** forms an unusually strong dimer ($K_{assoc} = 3.4 \times 10^3\,M^{-1}$), whereas the triazene-containing **6.15j** ($R^{a,b} = COC_5H_{11}$) is strongly intramolecularly hydrogen bonded (pinched cone conformation) and does not aggregate. Similarly, a mixture of **6.15i** and **6.15j** ($R^{a,b} = COC_5H_{11}$) fails to interact, but a mixture of **6.15j** ($R^{a,b} = COC_5H_{11}$) and 5-ethyl-5-phenylbarbituric acid in $CHCl_3$ solution produces a gel in which the aggregate is described as hydrogen bonded ribbons that form a network of fibers with a diameter up to *ca*. 100 nm. The closely related calixarene **6.15j** ($R^a = C_4H_9$; $R^b = H$; $Y = C_{12}H_{25}$) interacts with diethylbarbituric acid to produce a "double rosette" aggregate[53] represented by **6.23**.

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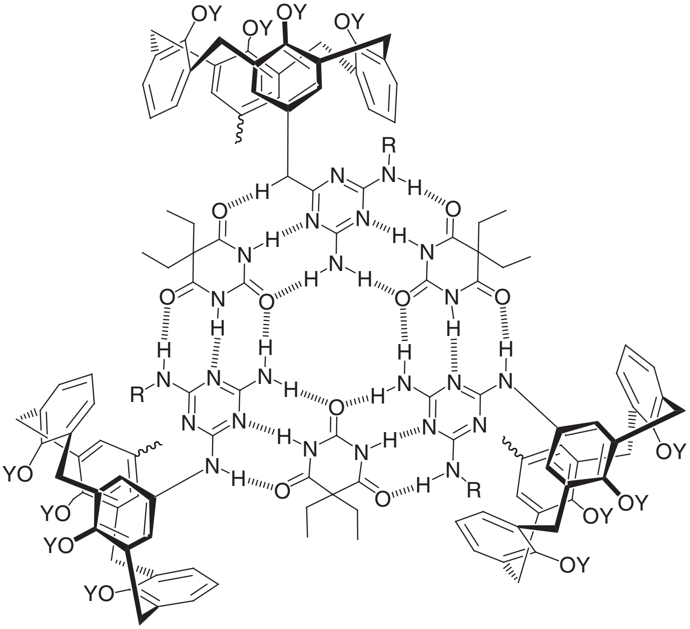
[51] P. Lhotak and S. Shinkai, *Tetrahedron Lett.* **1995**, 36, 4829.

[52] R. H. Vreekamp, W. Verboom and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* **1996**, 115, 363.

[53] R. H. Vreekamp, J. P. M. van Duynhoven, M. Hubert, W. Verboom and D. N. Reinhoudt, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1215.



6.23

Another approach to aggregate building employs guest molecules capable of complexing two separate calixarene units, leading either to dimers or oligomers depending on the structures of the host and guest. For example, the phenylazocalixarene **6.15k** (Ar = 3,4-bis(decyloxyphenyl)) reacts with $WOCl_4$ to form a complex[54] that aggregates in a columnar fashion, the W=O moiety of one calixarene unit inserting itself in the cavity of a neighboring molecule as depicted in **6.24**. In this case the tungsten moiety, although covalently bonded to a calixarene, can be considered to be the guest. An example in which the guest is completely non-covalently bonded is seen in the combination of calixarene **6.15k** with the diamide $HCONH(CH_2)_3NHCHO$ to yield a columnar array in which one end of the amide binds in the cavity of a calixarene and the other end forms hydrogen bonds with a neighboring calixarene.[55] In a similar vein a pair of calixarene units joined *endo* rim to *endo* rim *via* silicon bridges (a "koiland")[56] interacts with $CH_3C{\equiv}C\text{-}C{\equiv}CCH_3$ to form a columnar array represented by **6.25** (a "koilate"). The dipyridinium copper cation holds calix[4]arene sulfonates in like fashion to form aggregates for which X-ray

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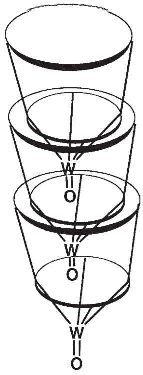
[54] B. Xu and T. M. Swager, *J. Am. Chem. Soc.* **1993**, 115, 1159.

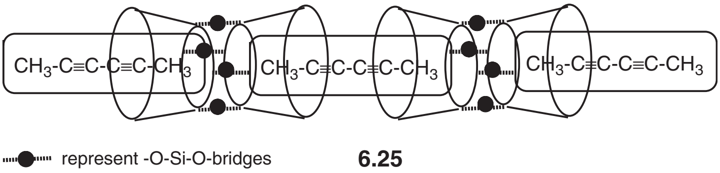
[55] B. Xu and T. M. Swager, *J. Am. Chem. Soc.* **1995**, 117, 5011.

[56] X. Delaigue, M. W. Hosseini, A. De Cian, J. Fischer, E. Leize, S. Kieffer, A. Van Dorsselaer, *Tetrahedron Lett.* **1993**, 34, 3285; X. Delaigue, M. W. Hosseini, R. Graff, J.-P. Kintzinger and J. Raya, *ibid.* **1994**, 35, 1711; F. Hajek, R. Graf, M. W. Hosseini, X. Delaigue, A. De Cian and J. Fischer, *ibid.* **1996**, 37, 1401; F. Hajek, E. Graf and M. W. Hosseini, *Tetrahedron Lett.* **1996**, 37, 1409.

crystallographic structures have been obtained.[57] A calix[8]arene carrying moieties on the *exo* rim that terminate in a multiplicity of decyl groups self organizes into nanorods.[58]



6.24



6.25

The influence of molecular shape on aggregation properties is nicely illustrated by the tetrapropyl ethers of calix[4]arenes carrying $CH_2NMe_3^+$ or $CH_2O(CH_2)_nNMe_3^+$ groups on the *exo* rim. The cone conformer aggregates in water to globular micelles, while the 1,3-alternate conformer forms stable vesicular arrays detectable by electron microscopy.[59] In a study of the simple aggregation properties in water, calixarenes carrying sulfonato or trimethylammonium groups have been categorized as being non-micellar, micelle-forming, or unimolecular micellar.[60]

6.2.4 Calixarenes in Monolayers and Interfaces

Regen (*cf.* Chapter 8) and Shinkai were among the first to experiment with calixarene-derived monolayers, the latter showing that monolayers of *p-tert*-butylcalixarenes respond selectively to the addition of cations.[61] For example, the hexakis-CH_2CO_2Et ether of *p-tert*-butylcalix[6]arene responds to butylammonium cations in the decreasing order *t*-Bu > *n*-Bu > *iso*-Bu > *sec*-Bu.[62] More recent detailed studies by Baglioni and coworkers[63] aimed at characterizing

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[57] J. L. Atwood, G.W. Orr, R. K. Juneja, S. G. Bott and R. Hamada, *Pure & Appl. Chem.* **1993**, 65, 1471.

[58] G. Podoprygorina, J. Zhang, V. Brusko, M. Bolte, A. Janshoff and V. Böhmer, *Org. Lett.* **2003**, 5, 5071.

[59] S. Arimori, T. Nagasaki and S. Shinkai, *J. Chem. Soc. Perkin Trans. 2* **1995**, 679.

[60] S. Shinkai, T. Arimura, K. Araki, H. Kawabata, H. Satoh, T. Tsubaki, O. Manabe and J. Sunamoto, *J. Chem. Soc. Perkin Trans. 1* **1989**, 2039; S. Arimori, T. Nagasaki and S. Shinkai, *J. Chem. Soc. Perkin Trans. 1* **1993**, 887.

[61] Y. Ishikawa, T. Kunitake, T. Matsuda, T. Otsuka and S. Shinkai, *J. Chem. Soc. Chem. Commun.* **1989**, 736.

[62] H. Kawabata and S. Shinkai, *Chem. Express* **1993**, 8, 765.

[63] (a) L. Dei, A. Casnati, P. Lo Nostro and P. Baglioni, *Langmuir* **1995**, 11, 1268; (b) L. Dei, A. Casnati, P. Lo Nostro, A. Pochini, R. Ungaro and P. Baglioni, *ibid.* **1996**, 12, 1589.

the monolayers of *p-tert*-butylcalix[6]arene and its N,N-diethylamidomethyl ether showed that with the parent compound the closely packed monomolecular films have only some of the phenolic groups immersed in the water (perpendicular orientation), whereas with the ether all six of the amide groups are in the water (parallel orientation). A study of calix[4]arenes carrying various numbers of $CO(CH_2)_{10}CH_3$ groups on the *exo* rim and OCH_2CO_2Et on the *endo* rim concluded that the most stable monolayers are formed from the calixarene containing one of each.[64]

The adsorption of calixarenes on metal surfaces has received recent study. The $CH_3(CH_2)_{12}S(CH_2)_{11}$ ethers of calix[4]arene and *p-tert*-butylcalix[4]arene, for example, form well-packed monolayers on a gold substrate, verified by IR spectroscopy and wetability experiments.[65] Calix[4]arenetetrathiol adsorbs on a rough Ag surface, the calixarene undergoing an inversion from the 1,3-alternate to the cone conformation in the process.[66] The latter system shows some ability to form complexes with aromatic hydrocarbons. An opposite situation exists in the system in which ferrocene-$CO(CH_2)_{10}SH$ adsorbed on a gold surface forms a complex with the dodecyl ether of *p*-sulfonatocalix[8]arene.[67] A somewhat more elaborate procedure for depositing a calixarene on a metal surface involves first treating a silver surface with $HS(CH_2)_{10}C{\equiv}CC{\equiv}C(CH_2)_{10}CO_2H$, then polymerizing the adsorbed acetylenic chains followed by exposure to $SOCl_2$ (to convert the CO_2H to COCl groups) and treatment with *p-tert*-butylcalix[4 or 6]arene.[68] The procedure has the advantage of employing readily available calixarenes without the necessity of altering their *endo* rim substituents. Evidence was adduced to indicate that the assemblies interact with volatile organic compounds by specific interaction with the calixarene cavities rather than by nonspecific adsorption. Silver nanoparticles immobilized on glass and covered by adsorbed self assembled calix[4]arenes have been used to detect trace concentrations of polycyclic aromatic hydrocarbons.[69] Scanning force microscopy of spin-coated samples of calix[8]arene **6.26** on graphite reveals a tabular nanorod structure.[70] With the same analytical technique a tri-partite assembly of *p*-guanidinocalix[4]arene, a functionalized porphyrin and an aminated silica particle was shows to have the structure **6.27**.[71]

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[64] G. Merhi, N. Munoz, A. W. Coleman and G. Barrat, *Supramol. Chem.* **1995**, 5, 173.

[65] B.-H. Huisman, E. U. Thoden van Delzen, F. C. J. M. van Veggel, J. F. J. Engbersen and D. N. Reinhoudt, *Tetrahedron Lett.* **1995**, 36, 3273.

[66] W. Hill, R. Wehling, C. G. Gibbs, C. D. Gutsche and D. Klockow, *Anal. Chem.* **1995**, 87, 1575.

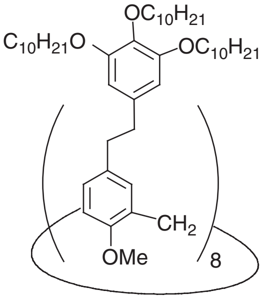
[67] L. Zhang, L. A. Godinez, T. Lu, G. W. Gokel and A. E. Kaifer, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 235.

[68] D. L. Dermody, R. M. Crooks and T. Kim, *J. Am. Chem. Soc.* **1996**, 118, 11912.

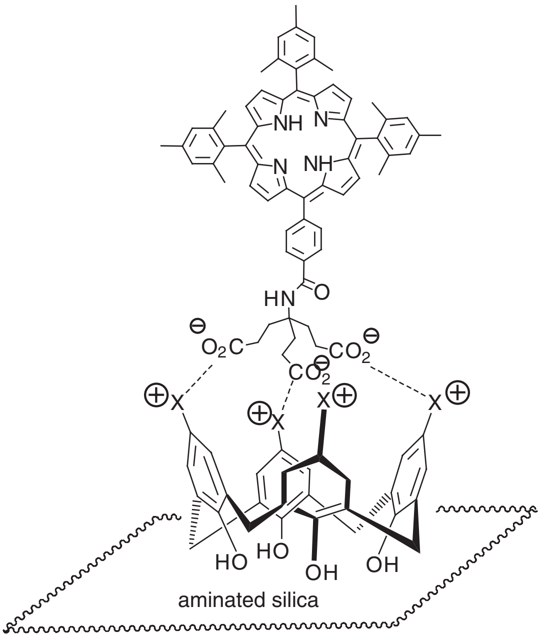
[69] P. Leyton, S. Sanchez-Cortes, J. V. Garcia-Ramos, C. Domingo, M. Campos-Vallette, C. Saitz and E. Clavijo, *J. Phys. Chem. B* **2004**, 108, 17484.

[70] G. Podopyrgorina, J. Zhang, V. Brusko, M. Bolte, A Janshoff and V. Böhmer, *Org. Lett.* **2003**, 5, 5071.

[71] M. Kopaczyñska, T. Wang, A. Schulz, M. Dudic, A. Casnati, F. Sansone, R. Ungaro and J.-H. Fuhrhop, *Langmuir* **2005**, 21, 8460.



6.26



6.27

X-Ray crystallography, although providing a detailed and definitive structure for a compound, is still an indirect procedure and not a direct photographic picture. With the advent of atomic force microscopy (AFM), however, direct imaging is now possible, and this technique has been applied to the calixarenes. A monolayer dispersion of *p-tert*-butylcalix[6]arene and octadecanol has been prepared and transferred to a treated mica surface and then studied by AFM.[72] Although the images are rather blurred, it is stated that their shape and size are in good accordance with dimensions estimated from inspection of CPK models.

6.3 Calixarene Polymers

Interest in calixarene-containing polymers emerged in the mid 1980s when a number of patents describing their preparation were issued.[73] A 1988 publication then appeared from the academic laboratory of Shinkai and coworkers who treated *p*-chlorosulfonylcalix[6]arene with poly(ethyleneimine) to produce a calixarene polymer.[74] Three years later McKervey and coworkers reported the azobisisobutyronitrile-induced polymerization of a *p-tert*-butylcalix[4]arene carrying an $OCH_2CO_2CH_2CH_2OCOC(Me){=}CH_2$ group on the *endo* rim.[75] Interest

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[72] M. Namba, M. Sugawara, P. Bühlmann and Y. Umezawa, *Langmuir* **1995**, 11, 635.

[73] S. J. Harris, J. G. Woods and J. M. Rooney, US Pat 4,699,966, 10th Feb, **1987**.

[74] S. Shinkai, H. Kawaguchi and O. Manabe, *J. Polymer Sci. Part C: Polymer Lett.* **1988**, 26, 391.

[75] S. J. Harris, G. Barrett and A. M. McKervey, *J. Chem. Soc. Chem. Commun.* **1991**, 1234.

continues to the present day, and a variety of approaches have been used for the construction of calixarene-containing polymers. Following the Shinkai method, one of these involves attachment of calixarene moieties to a preformed polymeric matrix by treating *p*-*tert*-butylcalix[8]arene with the acid chloride of a carboxyl-containing polymer derived from a styrene-divinylbenzene copolymer.[76] Similarly, treatment of polyethyleneimine with mono-*p*-3-bromopropylcalix[4]arene yields a water soluble polymer.[77] With *p*-chloromethylcalix[4]arene and polyethyleneimine, on the other hand, an insoluble cross linked polymer is obtained. A calix[4]arene crown-6 with ω-hydroxyundecyloxy groups on the *endo* rim can be affixed to a silica base to produce a cation-selective colloid.[78] Water soluble calix[4]arene-modified gold nanoparticles have been prepared by treating gold hydrosols with a calix[4]arene carrying two $O(CH_2)_{11}SH$ groups on the *endo* rim.[79] Attachment to a dextran of *p*-*tert*-butylcalix[4]arene carrying bi-pyridyl groups on the *endo* rim gives a water soluble polymer.[80] A calixarene polymer carrying a terminal epoxy group has been reported.[81] Following the Harris/McKervey approach, the attachment of a methacryl group to the *exo* rim of calixarenes[82] provides monomers that can be homo-polymerized or copolymerized, *e.g.* with 2-(6-sulfo-2-naphthoxy)ethyl methacryate.

Calixcrown telomers with $\bar{M}_n = 5000 - 7000$ have been prepared from calixcrown monomers in which the linkages are ether groups, ester groups, or Si-O-Si groups.[83] An analogous copolymer with $M_w = 15,000\text{-}24,000$ has been prepared[84] by treating a mixture of the A,C-dimethyl ether of calix[4]arene and bisphenol-A with NaH followed by CH_2Br_2. Star polymers with molecular weights as high as *ca.* 250,000 are produced from a calix[8]arene.[85]

6.4 Concluding Remarks

The discussions in Chapters 1–6 dealing with the methods for making, shaping, and embroidering the calixarene baskets have been prologue to the critical subject of testing their carrying capacities which is the essential focus of the following chapter.

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[79] T. R. Tshikhudo, D. Demuru, Z. Wang, M. Brust, A. Secchi, A. Arduini and A. Pochini, *Angew. Chem. Intl. Ed. Engl.* **2005**, 44, 2913.

[80] P. Engrand and J.-B. Regnouf-de-Vains, *Tetrahedron Lett.* **2002**, 43, 8863.

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[82] D. M. Gravett and J. E. Guillet, *Macromolecules* **1996**, 29, 617.

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[84] A. Dondoni, C. Ghiglione, A. Marra and M. Scoponi, *J. Chem. Soc. Chem. Commun.* **1997**, 673.

[85] S. Jacob, I. Majoros and J. P. Kennedy, *Macromolecules* **1996**, 29, 8631.

CHAPTER 7

Filling the Baskets: Complex Formation with Calixarenes

> *"Love, lay thy phobias to rest*
> *Inhibit thy taboos*
> *We twain shall share, forever blest,*
> *A complex built for two"*
>
> Keith Preston (1884–1927). Love Song, Freudian

The ability of calixarenes to act as baskets is one of their most intriguing properties, accounting for much of the interest that they have received since their reincarnation in the 1970s. The discussions of the methods for making, shaping and embroidering the calixarene baskets have been prologue to the critical subject of testing their carrying capacities. This chapter deals with the various facets of calixarene complexation by first considering solid state systems and then proceeding to solution state systems involving both aqueous and non-aqueous solvents.

7.1 Solid State Complexes (*Apndx B-6*)

Many calixarenes form solid state complexes, this property having been observed even before the structures of the compounds had been established. Among the phenol-derived calixarenes, for example, *p-tert*-butylcalix[4]arene forms complexes with chloroform,[1] benzene,[2] toluene,[3] xylene[2] and anisole;[2] *p-tert*-butylcalix[5]arene forms complexes with isopropyl alcohol[2,4] and

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[1] C. D. Gutsche, B. Dhawan, K. H. No and R. Muthukrishnan, *J. Am. Chem. Soc.* **1981**, 103, 3782.
[2] M. Coruzzi, G. D. Andreetti, V. Bocchi, A. Pochini and R. Ungaro, *J. Chem. Soc. Perkin Trans. 2* **1982**, 1133.
[3] G. D. Andreetti, R. Ungaro and A. Pochini, *J. Chem. Soc. Chem. Commun.* **1979**, 1005.
[4] A. Ninegawa and H. Matsuda, *Makromol. Chem. Rapid Commun.* **1982**, 3, 65.

acetone; *p*-*tert*-butylcalix[6]arene forms a complex containing chloroform and methanol;[1] *p*-*tert*-butylcalix[7]arene forms a complex containing methanol;[5] and *p*-*tert*-butylcalix[8]arene forms a complex with chloroform.[1] The tenacity with which the guest molecule is held by the calixarene, however, varies widely within the series. Whereas the cyclic tetramer and hexamer hold their guests very tightly, retaining residual amounts even after long heating at high temperatures under vacuum, the cyclic octamer loses its guest chloroform upon standing a few minutes at room temperature and atmospheric pressure. The cyclic octamer crystallizes from chloroform as beautiful glistening needles, which quickly change to a white powder while the disappointed chemist ruefully watches. Since the time of these early examples of solid state calixarene complexes, many more have been added. Occluded solvent from which the calixarene is crystallized is a very frequent occurrence and must be taken into account when bringing the experimental carbon and hydrogen analysis values into agreement with the calculated values.

The structures of solid state calixarene complexes are most effectively revealed by X-ray crystallography (*cf.* Section 3.2), the first example being the 1979 picture obtained by the Parma group showing a toluene molecule ensconced in the cavity of *p*-*tert*-butylcalix[4]arene[3] (*cf.* Figure 3.2). This complex has since been studied *via* inelastic neutron scattering,[6] by variable temperature solid state ^{13}C NMR spectroscopy, by differential scanning calorimetry[7] and at higher resolution.[8] Among the several other early examples are the demonstrations (a) by Atwood and coworkers[9] that the pentaammonium salt of *p*-sulfonatocalix[4]arene forms an *endo*-calix complex with methyl sulfate and (b) by McKervey and coworkers,[10] who found that the tetracarbonate of *p*-*tetra*-butylcalix[4]arene forms a complex with acetonitrile. In both of these cases the calixarene assumes the cone conformation. The complex of the tetraacetate of *p*-*tert*-butylcalix[4]arene, on the other hand, assumes a 1,3-alternate conformation upon complexation with acetic acid dimer,[11] and *p*-*tert*-octylcalix[4]arene forms an intercalato-clathrate in which toluene is captured between the molecules of calixarene rather than within the calix.[12] This is the result of the flexible *p*-alkyl groups bending inward to fill the cavity, *i.e.* self-complexation, as shown in Figure 7.1. *p*-*tert*-Butylcalix[4]arene forms a complex with acetone in which two host molecules enfold the two hemispheres of the guest.[13] Conversely, the octamethyl ether of *p*-*tert*-butylcalix[8]arene

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[5] Y. Nakamoto and S. Ishida, *Makromol. Chem. Rapid Commun.* **1982**, 3, 705.

[6] M. Prager, R. Caciuffo, G. Amoretti, C. J. Carlile, G. Coddens, F. Fillaux, O. Francescangeli and F. Ugozzoli, *Molecular Physics*, **1994**, 81, 609.

[7] G. A. Facey, R. H. Dubois, M. Zakrzewski, C. I. Ratcliffe, J. L. Atwood and J. A Ripmeester, *Supramol. Chem.* **1993**, 1, 199.

[8] E. B. Brouwer, G. D. Enright, C. I. Ratcliffe and J. A. Ripmeester, *Supramol. Chem.* **1996**, 7, 79.

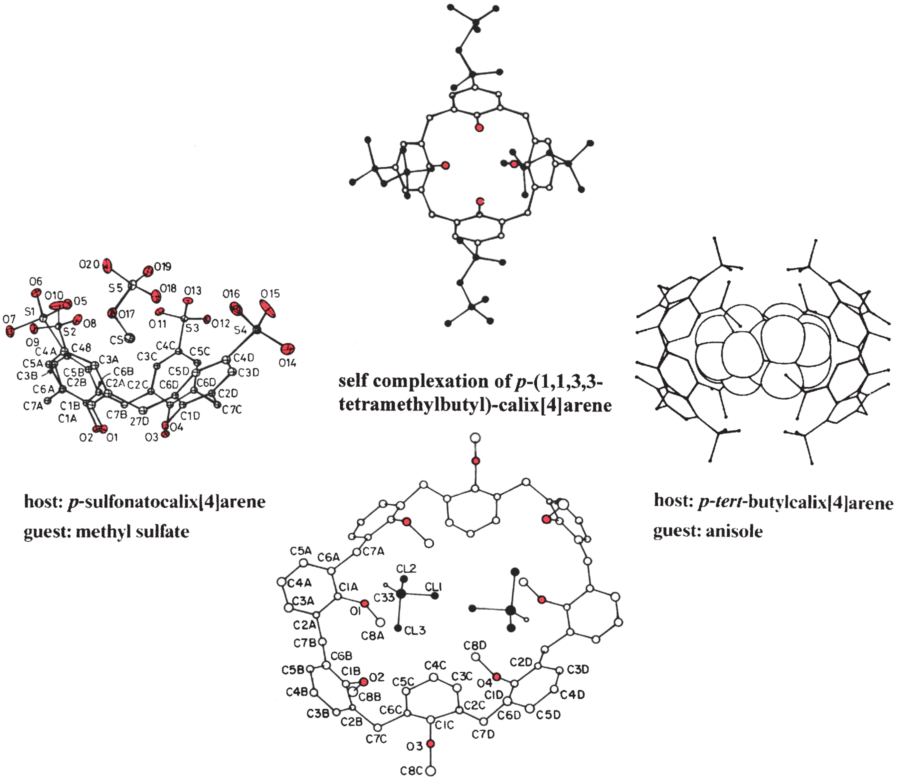
[9] S. G. Bott, A. W. Coleman and J. L. Atwood, *J. Am. Chem. Soc.* **1988**, 110, 610.

[10] M. A. McKervey, E. M. Seward, G. Ferguson and B. L. Ruhl, *J. Org. Chem.* **1986**, 51, 3581.

[11] C. Rizzoli, G. D. Andreetti, R. Ungaro and A. Pochini, *J. Mol. Struct.* **1982**, 82, 133.

[12] G. D. Andreetti, A. Pochini and R. Ungaro, *J. Chem. Soc. Perkin Trans. 2* **1983**, 1773.

[13] R. Ungaro, A. Pochini, G. D. Andreetti and P. Domiano, *J. Chem. Soc. Perkin Trans. 2* **1985**, 197.



host: *p*-sulfonatocalix[4]arene
guest: methyl sulfate

self complexation of *p*-(1,1,3,3-tetramethylbutyl)-calix[4]arene

host: *p-tert*-butylcalix[4]arene
guest: anisole

host: octamethyl ether of *p-tert*-butylcalix[8]arene
guest: chloroform

Figure 7.1 X-ray crystallographic structures of calixarene complexes.

forms a loose complex with chloroform in which one host molecule holds two guest molecules.

The work of the Parma group has provided insight into factors responsible for solid state complexation, or lack thereof, showing its dependence on the size of the calixarene,[2,14] the particular substituents in the *p*-positions and the conformational rigidity of the calixarene.[13] *tert*-Butyl groups prove to be particularly favorable for the formation of solid state *endo*-calix complexes, ostensibly (a) because they are not flexible enough to form intramolecular complexes (compare with *tert*-octyl) and (b) because they permit CH-π interactions.[15]

During the 1990s and on to the present day X-ray data for many hundreds of solid state calixarene complexes have been reported, so only an infinitesimal fraction of these are cited in this chapter as illustrative examples, *viz*. (a) the

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[14] R. Ungaro, A. Pochini, G. D. Andreetti and V. Sangermano, *J. Chem. Soc. Perkin Trans. 2* **1984**, 1979.

[15] G. D. Andreetti, O. Ori, F. Ugozzoli, C. Alfieri, A. Pochini and R. Ungaro, *J. Inclusion Phenom.* **1988**, 6, 523.

nitrobenzene complex of *p*-*tert*-butylcalix[4]arene showing guest-induced asymmetry;[16] (b) the *n*-pentane and cyclohexane complexes of *p*-*tert*-butylcalix[4]arene to probe the π-methyl theory of complexation;[16] (c) the H_2O complex of the sodium salt of *p*-sulfonatocalix[4]arene[17] to provide evidence for hydrogen bonding between H_2O and aromatic π electrons; (d) the pyridine complex of *p*-*tert*-butylcalix[7]arene;[18] (e) the $MeNO_2$ complexes of a calix bis-crown compound[19] and a pyridine-bridged calixarene;[20] and (f) the X-ray diffraction (and solid state NMR spectrum) of the xenon complex of *p*-*tert*-butylcalix[4]arene, which shows the Xe occupying two cavity sites defined by static disordered host *tert*-butyl groups.[21] Among other gases that can be entrapped in a solid state calixarene assembly[22] are CH_4, CF_6, C_2F_6 and CF_3Br. *p*-*tert*-Butylcalix[5]arene forms complexes with EtOAc[23] and tetralin,[24] and *p*-*tert*-octylcalix[5]arene forms a complex with toluene.[25] The calix[6]arene complexes include the dimethylformamide complex of *p*-cumylcalix[6]arene[26] and the Me_4N^+ and MeCN complexes[27,28] of *p* -*tert*-butylcalix[6]arene.

Many solid state calixarene complexes involve metals. In quite a few cases the metal is joined to the calixarene *via* a covalent/ionic bond, and one might quibble as to whether it should be called a true complex or a metallo-organic compound (*Apndx A-2, p. 561*). An early example showed a pair of *p*-*tert*-butylcalix[4]arene molecules joined at their *endo* rims by a pair of titanium or iron atoms.[29] Jack Harrowfield and coworkers obtained a complex comprising one molecule of *p*-*tert*-butylcalix[8]arene and two europium atoms embedded within the pinched cone conformer along with five DMF molecules (one in a bridging position and four singly coordinated to the europium atoms).[30] Atwood and coworkers have provided a number of interesting examples of metal-containing calixarenes such as the *p*-*tert*-butylcalix[4]arene tetramethyl

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[16] E. B. Brouwer, G. D. Enright and J. A. Ripmeester, *Supramol. Chem.* **1996**, 7, 7. A useful method is described for making complexes that involves vapor diffusion of the guest into a *m*-nitrotoluene solution of the calixarene.

[17] J. L. Atwood, F. Hamada, K. D. Robinson, G. W. Orr and R. L. Vincent, *Nature* **1991**, 349, 683.

[18] G. D. Andreetti, F. Ugozzoli, Y. Nakamoto and S.-I. Ishida, *J. Inclusion Phenom. Molec. Recognit. Chem.* **1991**, 10, 241.

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[27] J. M. Harrowfield, W. R. Richmond and A. N. Sobolev, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 257.

[28] P. Thuéry, N. Keller, M. Lance, J.-D. Vigner and M. Nierlich, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1995**, 20, 373.

[29] M. M. Olmstead, G. Sigel, H. Hope, X. Xu and P. P. Power, *J. Am. Chem. Soc.* **1985**, 107, 8087. Also *cf.* G. D. Andreetti, G. Calestani, F. Ugozzoli, A. Arduini, E. Ghidini, A. Pochini and R. Ungaro, *J. Inclusion Phenom.* **1987**, 5, 123.

[30] B. M. Furphy, J. M. Harrowfield, D. L. Kepert, B. W. Skelton, A. H. White and F. R. Wilner, *Inorg. Chem.* **1987**, 26, 4231.

ether-toluene-Na^+ complex in which the sodium atom is located at the *endo* rim and the toluene resides within the cavity.[31] X-Ray crystallography of the sodium salts of the *p*-sulfonatocalixarenes shows them to consist of alternating hydrophilic and hydrophobic layers, characterized as "organic clays",[32] with an interlayer separation of *ca.* 13.9 Å and layer thicknesses of *ca.* 8.7 Å and 5.2 Å, respectively. Complexes of *p*-sulfonatocalix[4]arene with $Ni(C_5H_5N)_3(NO_3)_2$[33] or protonated adenine[34] are stated to be bilayers of anionic calixarenes intercalated with bilayers of cations separated by a bed of water molecules. Still another crystal motif is achieved with a mixture of *p*-sulfonatocalix[4]arenecrown-6 ether and a metal cation such as Na^+, which produces an assembly referred to as a "Russian doll" in which the cation is inside the crown ether which is inside the dimeric capsular calixarene unit.[35]

In the years following these early examples the interactions of various calixarenes with a sizeable fraction of the elements in the periodic table have been investigated. Included among these are (a) silicon and titanium to give what have been called "koilands";[36] (b) aluminum and zinc to form similar bis-calixarenes;[37] (c) mercury to form complexes with one[38a] or two[37b] atoms of the metal; (d) lutetium, lanthanum, thulium[39] and tantalum(V) complexes;[40] (e) europium to give a complex in which the calixarene is viewed as a "third sphere ligand for the metal ion;[41] (f) molybdenum[42] and (g) uranium complexes.[43] A very recent example comes from the study carried out by Hanna and coworkers, which showed the effect of the metal (Li^+, Na^+, K^+, Rb^+, Cs^+) on the structure of the products from *p*-*tert*-butyl- and *p*-H calix[4,6 and 8] arenes.[44] A rare example involving a very large calixarene is the complex of

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[31] S. G. Bott, A. W. Coleman and J. L. Atwood, *J. Am. Chem. Soc.* **1986**, 108, 1709.

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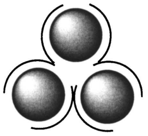
[42] J. A. Acho and S. Lippard, *J. Inorg. Chim. Acta* **1995**, 229, 5; L. Liu, L. N. Zakharov, J. A. Golen, A. L. Rheingold, W. H. Watson and T. A. Hanna, *Inorg. Chem.* **2006**, 45, 4247.

[43] L. Salmon, P. Thuéry and M. Ephritikhine, *Chem. Commun.* **2006**, 856.

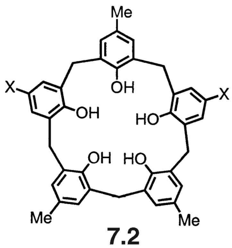
[44] T. A. Hanna, L. Liu, A. M. Angeles-Boza, X. Kou, C. D. Gutsche, K. Ejsmont, W. H. Watson, L. N. Zakharov, C. D. Incarvito and A. L. Rheingold, *J. Am. Chem. Soc.* **2003**, 125, 6228.

p-*tert*-butylcalix[12]arene with two uranyl cations, the calixarene serving as a double pentadentate ligand.[45]

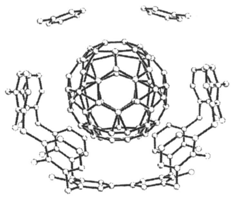
In 1992 Williams and Verhoeven[46] obtained evidence for the formation of a complex between C_{60} and the water-soluble sodium salt of the $(CH_2)_3SO_3H$ ether of calix[8]arene. Two years later a solid calixarene complex of C_{60} was isolated, almost simultaneously, by Williams and coworkers,[47] Atwood and coworkers[48] and Shinkai and coworkers,[49] who mixed toluene solutions of *p*-*tert*-butylcalix[8]arene and C_{60}-containing soot. Two recrystallizations of the precipitate (initial composition 89% C_{60} and 11% C_{70}) yielded material of $> 99.5\%$ purity from which C_{60} was obtained by treating the solid complex with $CHCl_3$. Calix[8]arenes with *p*-H, Me, Et, *n*-Pr, *i*-Pr, *t*-Amyl, *t*-Octyl and Ph groups are all less effective than the *t*-Bu compound.[50] An X-ray crystal structure of the complex has yet to be obtained, but ^1H NMR and CP-MAS ^{13}C NMR spectral measurements indicate that the calix[8]arene assumes a twisted double cone conformation with C_2 symmetry rather than that of a pleated loop. Molecular mechanics calculations suggest that the 1:1 complex of C_{60} and *p*-*tert*-butylcalix[8]arene is actually a micelle-like trimeric aggregate[51] schematically represented by **7.1**. A slightly different picture is presented by the calix[5]arene **7.2** ($X = I$), which forms a complex with C_{60} that is shown by X-ray analysis[52] to consist of two calixarene molecules acting as hemispherical caps around one C_{60}, an intramolecular example of which is illustrated by the complex with bis-calix[5]arene **7.3** obtained by crystallization from toluene.[53] A cautionary note has been voiced by Raston and coworkers, who used synchrotron X-ray diffraction to show that the 2:1 complex of *tert*-butylcalix[6]arene with C_{70} is *not* an *endo*-calix structure in which the guest resides in the cavities of the calixarenes.[54]



7.1



7.2



7.3

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[45] P. C. Leverd, I. Dumazet-Bonnamour, R. Lamartine and M. Nierlich, *Chem. Comm.* **2000**, 493.

[46] R. M. Williams and J. W. Verhoeven, *Rec. Trav. Chim. Pays Bas* **1992**, 111, 531.

[47] R. M. Williams, J. M. Zwier, J. W. Verhoeven, G. H. Nachtegaal and A. P. M. Kentgens, *J. Am. Chem. Soc.* **1994**, 116, 6965.

[48] J. L. Atwood, G. A. Koutsantonis and C. L. Raston, *Nature* **1994**, 368, 229.

[49] T. Suzuki, K. Nakashima and S. Shinkai, *Chem. Lett.* **1994**, 699.

[50] T. Suzuki, K. Nakashima and S. Shinkai, *Tetrahedron Lett.* **1995**, 36, 249.

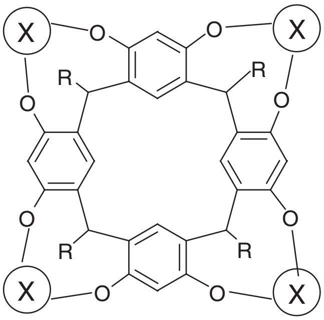
[51] C. L. Raston, J. L. Atwood, P. J. Nichols and I. B. N. Sudria, *J. Chem. Soc. Chem. Commun.* **1996**, 2615.

[52] Haino, M. Yanase and Y. Fukazawa, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 259; *idem*, *Tetrahedron Lett.* **1997**, 38, 3739.

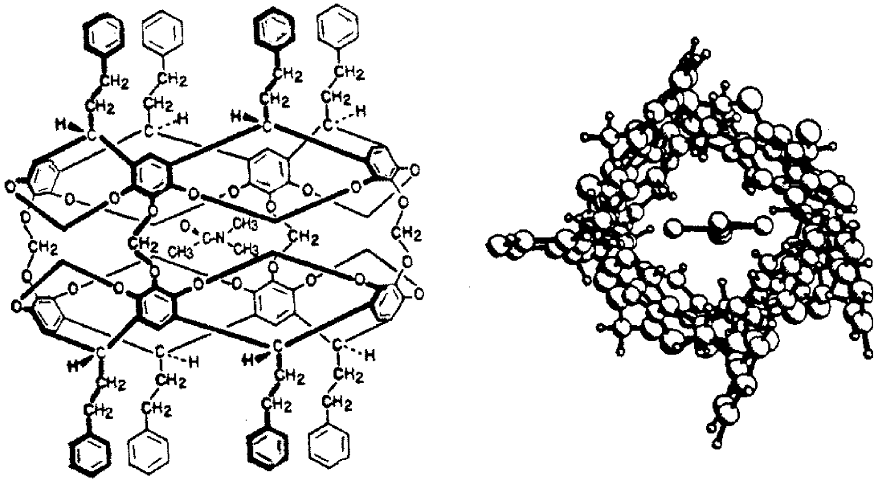
[53] J. Wang, S. G. Bodige, W. H. Watson and C. D. Gutsche, *J. Org. Chem.* **2000**, 65, 8260.

[54] M. Makha, C. L. Raston, A. N. Sobolev and P. Turner, *Crystal Growth & Design* **2006**, 6, 224.

As part of a comprehensive program dealing with host-guest chemistry for which he shared the 1987 Nobel Prize, Donald Cram studied the sold state complexation characteristics of the calix[4]resorcarene-derived cavitands and carcerands. A cavitand is produced from a calix[4]resorcarene by the insertion of bridges between the OH groups near the *exo* rim, as depicted in structure **7.4**. The joining together of a pair of cavitands at the *exo* rims then produces a carcerand. Both the cavitands and carcerands can capture other molecules within their cavities, the carcerands in many cases holding them with extraordinary tenacity. An illustrative example is the complex **7.5** of a carcerand with $(CH_3)_2NCOCH_3$ (called a "carcaplex").[55]



7.4



7.5

These systems have provided a fertile area for investigation, initially by Cram and coworkers and more recently by numerous other groups, especially that of John Sherman at the University of British Columbia in Canada. For surveys of this important facet of calixarene chemistry the reader is directed to several excellent reviews (*Apndx A-2, p.199; A-7; B-16*).

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[55] J. C. Sherman, C. B. Knobler and D. J. Cram, *J. Am. Chem. Soc.* **1991**, 113, 2194.

Going from large guests to the smallest possible guest, the question has been asked "Can a single molecule trap the electron?" Calculations by Shkrob and Schlueter[56] answer yes, predicting that a perhydrocalix[4]arene should form a "molecular capacitor" in which the electron is largely decoupled from valence electrons in the trap. Whether this proves true remains to be tested.

7.2 Solution State Complexes of Metal Cations with *Endo* Rim-substituted Calixarenes (*Apndx B-13*)

The determination of the structure of solid state calixarene complexes has provided the X-ray crystallographer with a rich field of research, and the results that have come from these studies have been interesting, instructive and useful. The major focus of calixarene complexation, however, has been on solution state complexes, usually with a demonstrated or putative application in mind.

The interaction between a host and a guest to form a complex can involve one or more of the following features: hydrophobic effects, hydrogen-bonding, electrostatic attraction, $\pi-\pi$ stacking, cation-π and CH-π interaction,[57] van der Waals attraction and charge-transfer interactions. The experimental measure of the collective magnitude of such interactions can be expressed in a variety of ways, including the rate of transport through a membrane (liquid or supported liquid), the stability constants as determined by spectroscopy or potentiometry or the percentage of extraction from water into an immiscible solvent in phase transfer processes. It should be realized, however, that there is not necessarily an exact parallelism between the values produced by these various measurements. For example, the rate of transport through a membrane is influenced by such things as the rate of complexation, the rate of transport within the membrane and the rate of decomplexation, features that are not involved in other types of measurements.

The actual acquisition of the data for determining complexation capabilities similarly employs a variety of experimental techniques. Among the most often used are NMR (complexation-induced shift) and/or UV-Vis spectrometry where picrate salts are frequently employed, taking advantage of the color of the picrate anion. Mass spectrometry[58] has also been found to be useful in measuring the complexation of calixarenes with metal cations and onium ions[59] (including ammonium, sulfonium and oxonium). Not surprisingly, the order of complex stability is different in the solution and gas phases. Induced circular dichroism is applicable to the measurement of the complexation behavior of chiral calixarenes.[60] The inclusion properties of calixarenes with neutral

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[56] I. A. Shkrob and J. A. Schlueter, *Chem. Phys. Lett.* **2006**, 431, 364.

[57] H. Takahashi, S. Tsuboyama, Y. Umezawa, K. Honda and M. Nisio, *Tetrahedron* **2000**, 56, 6185.

[58] K. Linnemayr, E. R. Schmidt and G. Ailmaier, *Rapid Commun. Mass Spectrom.* **1997**, 11, 427.

[59] F. Inokuchi, K. Araki and S. Shinkai, *Chem. Lett.* **1994**, 1383; F. Inokuchi, Y. Miyahara, T. Inazu and S. Shinkai, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1364.

[60] T. Arimura and S. Shinkai, *Bull. Chem. Soc. Jpn.* **1991**, 64, 1896.

molecules have been studied by means of capillary gas chromatography.[61] Conductivity measurements have been used to study the complexation behavior of calixcrowns with metal ions.[62] Capillary zone electrophoresis has been used for water soluble calixarenes.[63] And, using conductometric/potentiometric techniques Danil de Namor and coworkers have made careful studies of the complexation of calixarenes with metal cations and have calculated thermodynamic parameters for these processes.[64] A pair of recently introduced techniques includes (a) the use of epr measurements to ascertain the rate constants and activation parameters for the inclusion of the benzyl *tert*-butylnitroxide radical[65] and (b) the use of pulsed gradient spin echo (PGSE) NMR measurements.[66]

The precise structures of complexes are most directly obtained by X-ray crystallography, and the reasonable assumption is generally made that the solid state architecture reflects that of the solution state. Often, however, there are subtle differences between the two, and in some instances there are marked differences. In many cases the solution state structure can be inferred from ^{1}H NMR and ^{13}C NMR measurements, and modeling studies have also provided additional insights.[67] It should be noted that the significance and utility of the complexation effectiveness of a calixarene focuses not only on the absolute magnitude of its complexation constant but also on its ability as a host to discriminate among a group of guests.

7.2.1 Complexation with Parent Calixarenes

The parent calixarenes are almost totally insoluble in water and only sparingly soluble in most organic solvents, making it difficult to probe their complexing abilities. The first success was achieved by Reed Izatt and his coworkers at Brigham Young University in Provo, Utah. Izatt, who had carried out extensive investigations of crown ether complexation, perceived a structural resemblance with the calixarenes. Pursuing this idea he tested the calixarenes for their ability to transport cations across a liquid membrane.[68] His studies made use of

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[61] P. Mnuk and L. Feltl, *J. Chromatography A* **1995**, 696, 101; P. Mnuk, L. Feltl and V. Schurig, *J. Chromatography A* **1996**, 732, 63; R. Baudry, O. Kalchenko, I. Dumazet-Bonnamour, F. Vocanson and R. Lamartine, *J. Chromat. Science* **2003**, 41, 157.

[62] A. D'Aprano, J. Vicens, Z. Asfari, M. Salomon and M. Iammarino, *J. Soln. Chem.* **1996**, 25, 955.

[63] K. Oshita, T. Takayanagi, M. Oshima and S. Motomizu, *J. Chromatography A* **2001**, 934, 113.

[64] A. F. Danil de Namor, E. Gil, M. A. Llosa Tanco, D. A. Pacheco Tanaka, L. E. Pulcha Salazar, R. A. Schulz and J. Wang, *J. Phys. Chem.* **1995**, 99, 16781.

[65] P. Franchi, M. Lucarini, G. F. Pedulli and D. Sciotto, *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 263.

[66] O. Mayzel, O. Aleksiuk, F. Grynszpan, S. E. Biali and Y. Cohen, *J. Chem. Soc. Chem. Commun.* **1995**, 1183.

[67] P. Guilbaud, A. Warnek and G. Wipff, *J. Am. Chem. Soc.* **1993**, 115, 8298; A. Varnek and G. Wipff, *J. Phys. Chem.* **1993**, 97, 10840.

[68] R. M. Izatt, J. Lamb, R. T. Hawkins, P. R. Brown, S. R. Izatt and J. J. Christensen, *J. Am. Chem. Soc.* **1983**, 105, 1782; S. R. Izatt, R. T. Hawkins, J. J. Christensen and R. M. Izatt, *ibid.* **1985**, 107, 63.

an apparatus in which an aqueous source phase containing the host molecule (the carrier) plus the guest cation is separated from an aqueous receiving phase by an organic phase (*e.g.* chloroform). He discovered that although the calixarenes are ineffective cation carriers in neutral solutions, they possess significant transport ability for Group I cations in strongly basic solution. The cesium cation, in particular, showed a high transport value. These results are in sharp contrast to 18-crown-6 compounds, which are more effective in neutral solution. Control experiments showed that the monomeric unit, *p*-*tert*-butylphenol, has little or no transport ability, supporting the idea that the macrocyclic ring plays a critical role. On the basis of a comparison of the ion transport capacity of a series of *exo* rim-bridged calixarenes (*cf.* structure **2.21**, p 45), Böhmer and coworkers[69] suggested that at least in the case of cesium the transport is by an *endo*-calix complex. This has been substantiated by ^{133}Cs NMR studies[70] and by an X-ray structure of the cesium complex of *p*-*tert*-butylcalix[4]arene,[71] which shows the cesium to be inside the cavity (closer to the faces of the aromatic rings than to the oxygen atoms). *Endo*-complexation may be unique to cesium, however, and a study of the complexation of the monoanion of *p*-*tert*-butylcalix[4]arene with the alkali metals shows that the stability constants fall in the order $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$, which agrees with calculations which support *exo* complex structures.[72] *Endo* complexation, based on NOE measurements,[73] was proposed for the complex of *p*-allylcalix[4]arene with *tert*-butylamine in CH_3CN solution, but NOE measurements on a similar system along with molecular dynamics calculations[74] show that although the *endo* complex may be inherently more stable, solvation favors the *exo* complex.

7.2.2 Complexation with *Endo* Rim-substituted Calixarenes

7.2.2.1 Endo Rim Ethers (Apndx A-2, p. 385)

Most of the studies subsequent to those of Izatt's group have focused on a wide variety of derivatives rather than on the calixarenes themselves. The earliest examples of *endo* rim-substituted calixarenes investigated for their complexation properties were the ethyleneoxy compounds **7.6a**,[75] which showed only a

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[69] H. Goldman, W. Vogt, E. Paulus and V. Böhmer, *J. Am. Chem. Soc.* **1988**, 110, 6811.

[70] R. Assmus, V. Böhmer, J. M. Harrowfield, M. I. Ogden, W. R. Richmond, B. W. Skelton and A. H. White, *J. Chem. Soc. Dalton Trans* **1993**, 2427.

[71] J. M. Harrowfield, M. I. Ogden, W. R. Richmond and A. H. White, *J. Chem. Soc.* **1991**, 1159.

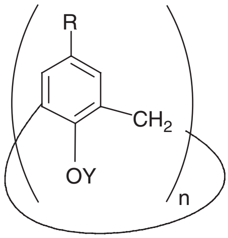
[72] R. Abidi, M. V. Baker, J. M. Harrowfield, D. S.-C. Ho, W. R. Richmond, B. W. Skelton, A. H. White, A. Varneck and G. Wipff, *Inorg. Chim. Acta.* **1996**, 246, 275.

[73] C. D. Gutsche, M. Iqbal and I. Alam, *J. Am. Chem. Soc.* **1987**, 109, 4314.

[74] F. Fraternali and G. Wipff, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1997**, 28, 63; R. Puchta, T. Clark and W. Bauer, *J. Molec. Modeling* **2006**, 12, 739.

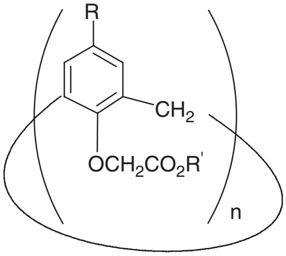
[75] V. Bocchi, D. Foina, A. Pochini, R. Ungaro and G. D. Andreetti, *Tetrahedron* **1982**, 38, 373; R. Ungaro, A. Pochini and P. Domiano, *J. Inclusion Phenom.* **1985**, 3, 35; R. Ungaro, A. Pochini, G. D. Andreetti and F. Ugozzoli, *ibid.* **1985**, 3, 409.

modest degree of cation binding capacity. Surprisingly, however, the simple *n*-propyl ether **7.6b** (R = H; *n* = 4) showed strong complexation with K^+ ($K_{assoc} = 50\,118\ M^{-1}$) and Ag^+ ($K_{assoc} = 19\,950\ M^{-1}$) if the calixarene is in the 1,3-alternate conformation.[76] The special ability of the 1,3-alternate conformer to form tight complexes is attributed to coordination of the cation with the ether oxygens combined with π-donor participation with the aryl rings of the calixarene. However, the solid state Na^+ complex of the conformationally flexible tetramethyl ether of *p*-*tert*-butylcalix[4]arene exists in a cone conformation in which the sodium ion is located outside the calix on the *endo* rim and a molecule of toluene is located within the calix.[31] A study[77] of the kinetics and mechanism of complexation of this calixarene with Cs^+ in acetonitrile/chloroform suggests that the initial complex is with the partial cone conformer, which then converts to the 1,3-alternate conformer to tightly bind the Cs^+.



7.6

a) Y = $(CH_2CH_2O)nR'$
b) Y = Pr
c) R = $CH_2N(CH_2C{=}CH_2)_2$
d) R - CH_2CO_2H



7.7

a) R = *t*-Bu; R' = H; n = 4
b) R = *t*-Bu; R' = Et; n = 4
c) R = H; R' = H; n = 4
d) R = H; R' = Et; n = 4
e) R = t-Bu; R' = H; n = 6
f) R = *t*-Bu; R' = Et; n = 6
g) R = H; R' = Et; n = 6

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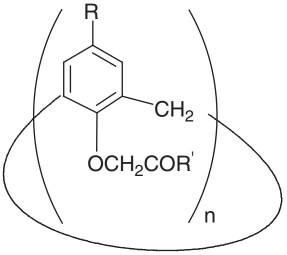
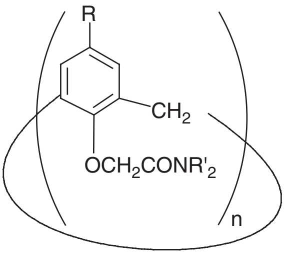
[76] A. Ikeda and S. Shinkai, *Tetrahedron Lett.* **1992**, 33, 7385*; idem*, *J. Am. Chem. Soc.* **1994**, 116, 3102. However, an X-ray structure of the Ag^+ complex of the tetramethyl ether of calix[4]arene shows it to be in the partial cone conformation (W. Xu, J. Puddephatt, K. Muir and A. A. Torabi, *Organometallics* **1994**, 13, 3054).

[77] U. C. Meier and C. Detellier, *J. Phys. Chem.* **1998**, 102, 1888.



7.8

a) R = *t*-Bu; R' = Me; n = 4
b) R = *t*-Bu; R' = Et; n = 4
c) R = *t*-Bu; R' = *t*-Bu; n = 5
d) R = *t*-Bu; R' = Et; n = 6



7.9

a) R = *t*-Bu; R' = Et; n = 4
b) R = *t*-Bu; R'R' = $(CH_2)_4$; n = 4
c) R = *t*-Bu; R' = $CH_2C{\equiv}CH$
d) R = *t*-Bu; R' =, Et; n = 6
e) R = H; R' = Et; n = 6

7.2.2.2 Endo Rim Esters (Apndx A-2, p. 385)

Much more effective than the simple ethers in most cases are the members of a family of compounds with the general structures **7.7–7.9**. These have been pursued with great zeal by a number of research groups, particularly that of Anthony McKervey and coworkers at the University of Cork, Ireland. Earliest to be studied among this family of compounds were the esters **7.7**[78] for which it was determined by means of phase transfer extraction measurements that the cyclic tetramers, pentamers and hexamers extract all of the alkali cations with the cyclic tetramer working best with Na^+, the cyclic pentamer working better with K^+, Rb^+ and Cs^+, and the cyclic hexamer working best with Rb^+ and Cs^+ but very poorly with Na^+. The cyclic heptamer and octamer are quite ineffective. The strength and/or discrimination of complexation with these esters can be adjusted not only by changing the ring size but also by changing the ester group R', the *p*-substituent R and the conformation. For example, the *tert*-butyl esters **7.7** ($R' = t$-Bu) are stronger complexers than the ethyl esters ($R' = Et$) for $n = 4$ and 5, illustrating the effect of the ester group. The de-*tert*-butyl ester **7.7g** shows a four-fold greater discrimination than **7.7f** between Cs^+ and Na^+, illustrating the influence that the *p*-substituent may sometimes exert.[79] The cone conformer of **7.7b** is more selective for Na^+ (X-ray crystal

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[78] (a) G. Barrett, M. A. McKervey, J. F. Malone, A. Walker, F. Arnaud-Neu, L. Guerra, M. Schwing-Weill, C. D. Gutsche and D. R. Stewart, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1475; (b) F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. L. Ruhl, M.-J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.* **1989**, 111, 8681; (c) F. Arnaud-Neu, G. Barrett, S. Cremin, M. Deasy, G. Ferguson, S. J. Harris, A. J. Lough, L. Guerra, M. A. McKervey, M. J. Schwing-Weill and P. Schwinte, *J. Chem. Soc. Perkin Trans 2* **1992**, 1119.

[79] F. Arnaud-Neu, S. Fanni, L. Guerra, W. McGregor, K. Ziat, M.-J. Schwing-Weill, G. Barrett, M. A. McKervey, D. Marrs and E. M. Seward, *J. Chem. Soc. Perkin Trans. 2* **1995**, 113: For a comparison of primary and tertiary amides *cf.* F. Arnaud-Neu, S. Barboso, F. Berny, A. Casnati, N. Muzet, A. Pinalli, R. Ungaro, M.-J. Schwing-Weill and G. Wipff, *J. Chem. Soc. Perkin Trans. 2* **1999**, 1727.

structure[80]) than the other three conformers which are more effective for K^+ complexation,[81] illustrating the importance of conformation. A more subtle conformation effect is operative with the *exo* rim-bridged calixarenes **2.21** (*cf.* Chapter 2, p 45) carrying CH_2CO_2Et moieties on all four of the *endo* rim oxygen atoms. When $n = 7$ and 9 selective complexation of Na^+ is observed, but when $n = 5$ or 6 complexation falls drastically by a factor of $> 10^5$ due to the inability of the system to assume the necessary four-fold symmetry.[82] Stability constants for esters determined in MeOH or CH_3CN generally mimic the results obtained from extraction experiments; the values for K_{assoc}, which range from 10^2 to $10^{6.5}\,M^{-1}$, are comparable to those for dibenzo-18-crown-6 but lower than those for the cryptands by factors of 10^3 to 10^5. Calorimetric measurements[83] have provided ΔG°, ΔH° and $T\Delta S^\circ$ values for the complexation of **7.7b**, and they show that with Li^+ the complexation is entropy driven, whereas with the other alkali cations it is enthalpy driven. The Na^+ complex of **7.7b** undergoes reversible decomposition upon irradiation with a low-pressure Hg lamp, the decomposition being both solvent dependent (occurs in toluene but not in MeOH) and anion dependent (iodide and thiocyanate most labile, perchlorate least labile).[84]

7.2.2.3 Endo Rim Ketones (Apndx A-2, p. 385)

Compounds of the general structure **7.8** have complexing features[78b,85] rather similar to those of the esters **7.7**. Stability constant measurements and extraction data indicate that the cyclic tetrameric ketones are better than their ester analogs for the extraction of Li^+ as well as Rb^+ and Cs^+. The ketone **7.8c** has a broader range of extraction capability than its cyclic tetramer and hexamer counterparts but shows little selectivity among the cations. A study of **7.7b** and **7.8a** for the complexation of bivalent cations shows the efficacy of CH_3CN as the solvent.[86]

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[80] A. Ikeda, H. Tsuzuki and S. Shinkai, *Tetrahedron Lett.* **1994**, 35, 8417.

[81] K. Iwamoto and S. Shinkai, *J. Org. Chem.* **1992**, 57, 7066.

[82] V. Böhmer, W. Vogt and H. Goldmann, *J. Org. Chem.* **1990**, 55, 2569; F. Arnaud-Neu, V. Böhmer, L. Guerra, M. A. McKervey, E. F. Paulus, A. Rodriquez, M.-J. Schwing-Weill, M. Tabatabai and W. Vogt, *J. Phys. Org. Chem.* **1992**, 5, 471.

[83] (a) A. F. Danil de Namor, N. de Apaza Sueros, M. A. McKervey, G. Barrett, F. A. Arnaud-Neu and M.-J. Schwing-Weill, *J. Chem. Soc. Chem. Commun.* **1991**, 1546; (b) F. Arnaud-Neu, G. Barrett, S. Fanni, D. Marrs, W. McGregor, M. A. McKervey, M.-J. Schwing-Weill, V. Vetrogon and S. Wechsler, *J. Chem. Soc. Perkin Trans. 2* **1995**, 453.

[84] G. Barrett, D. Corry, B. D. Creaven, B. Johnston, M. A. McKervey and A. Rooney, *J. Chem. Soc. Chem. Commun.* **1995**, 363.

[85] S. E. J. Bell, J. K. Browne, V. McKee, M. A. McKervey, J. F. Malone, M. O'Leary and A. Walker, *J. Org. Chem.* **1998**, 63, 489; G. Ferguson, B. Kaitner, M. A. McKervey and E. M. Seward, *J. Chem. Soc. Chem. Commun.* **1987**, 584.

[86] A. F. Danil de Namor, S. Chahine, D. Kowalska, E. E. Castellano and O. E. Piro, *J. Am. Chem. Soc.* **2002**, 124, 12824.

7.2.2.4 Endo Rim Amides

Amides of the general structure **7.9** were first prepared and studied by Ungaro and coworkers[87] and then in considerable detail by McKervey and coworkers[79,83b,88] and by Paul Beer and coworkers at the University of Oxford, England.[89] The cyclic tetrameric amides (**7.9**, $n = 4$) qualitatively resemble the esters and ketones with respect to the complexation of alkali cations in showing a preference for Na^+, but quantitatively they are considerably more effective. For example, the K_{assoc} for the complex of **7.9a** with Na^+ is almost 10^3 greater than that for **7.7b** or **7.8a**. Again, though, this increased strength of complexation does not necessarily mean increased selectivity, for **7.9a** is less selective for Na^+ relative to K^+ than is **7.7b**. On the other hand, the amides are particularly selective for Na^+ and K^+ relative to Rb^+, and **7.9e** (lacking *p*-*tert*-butyl groups) shows superior Cs^+/Na^+ selectivity to that of **7.9d**[90] (containing *p*-*tert*-butyl groups).

In contrast to the ethers **7.6a,b**, the esters **7.7a,b,d,f** and the ketones **7.8**, the amides very effectively complex the alkaline earth cations, first shown in the case of secondary amides[79,87,93] and later studied in considerable detail with the tertiary amides **7.9a,b** ($n = 4,5,6$).[79,87] *p*-*tert*-Butylcalix[4]arene **7.10c** carrying two OCH_2CONEt_2 and two OCH_2CO_2H groups on the *endo* rim is said to show "nearly perfect" Ca^{2+} selectivity relative to the other Group II cations.[91] The cations Ca^{2+}, Sr^{2+} and Ba^{2+} are much more tightly complexed than Mg^{2+}, the Ca^{2+}/Mg^{2+} selectivity with **7.9a,b** having a value approaching 10^8. A study of the complexation of Sr^{2+} as a function of ring size shows **7.9a,b** ($n = 6$) to be among the most effective members of the group. Amides **7.9a,b** ($n = 4$) are somewhat less effective, and amides **7.9a,b** ($n = 5$) are considerably less effective (*Apndx B-15, p. 573*). A molecular dynamics study predicts that **7.9a** should complex the alkaline earth cations in the diminishing order $Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+}$, in agreement with experiment.[94] Among other metal cations Ag^+ has been particularly well studied, and its stability constants for a broad range of hosts in MeOH have been determined. Chromium (VI) forms a complex with **7.11c**.[92] The amides[78b] prove to be superior to the esters and

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[87] A. Arduini, E. Ghidini, A. Pochini, R. Ungaro, G. D. Andreetti, G. Calestani and F. Ugozzoli, *J. Inclusion Phenom.* **1988**, 6, 119.

[88] F. Arnaud-Neu, M.-J. Schwing-Weill, K. Ziat, S. Cremin, S. J. Harris and M. A. McKervey, *New J. Chem.* **1991**, 15, 33.

[89] P. D. Beer, M. G. B. Drew, P. B. Leeson and M. L. Ogden, *J. Chem. Soc. Dalton Trans.* **1995**, 1273; P. D. Beer, M. G. B. Drew, M. Kan, P. B. Leeson, M. L. Ogden and G. Williams, *Inorg. Chem.* **1996**, 35, 2202; P. D. Beer, M. G. B. Drew, A. Grieve, M. Kan, P. B. Leeson, G. Nicholson, M. L. Ogden and G. Williams, *J. Chem. Soc. Chem. Commun.* **1996**, 1117; P. D. Beer, M. G. B. Drew, P. B. Leeson and M. I. Ogden, *Inorg. Chem. Acta* **1996**, 246, 133.

[90] S. Fanni, F. Arnaud-Neu, M. A. McKervey, M.-J. Schwing-Weill and K. Ziat, *Tetrahedron Lett.* **1996**, 37, 7975.

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[92] S. Bozkurt, A. Karakucuk, A. Sirit and M. Yilmaz, *Tetrahedron* **2005**, 61, 10443.

[93] S. K. Chang and I. Cho, *J. Chem. Soc. Perkin Trans. 2* **1986**, 211.

[94] N. Muzet, G. Wipff, A. Casnati, L. Domiano, R. Ungaro and F. Ugozzoli, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1065.

ketones,[87] and within the amides the cyclic pentamer **7.9a** ($n = 5$) is an especially strong complexing agent.

Trivalent cations are also effectively bound by the amides.[95] For example, **7.9a** ($n = 4$) forms 1:1 complexes with Pr^{3+} ($K_{assoc}\,3.16 \times 10^8\,M^{-1}$), Eu^{3+} ($K_{assoc}\,5.01 \times 10^8\,M^{-1}$) and Yb^{3+} ($K_{assoc}\,1.25 \times 10^8\,M^{-1}$). In extraction studies the cyclic tetramers are shown to prefer Eu^{3+} over Pr^{3+} and Yb^{3+}, and with Eu^{3+} the cyclic hexamers are better than the cyclic tetramers, with **7.9b** ($n = 6$) showing the highest extraction effectiveness (*Apndx B-15, p. 580*). An interesting study[96] of the effect of the *p*-substituents in the calix[6]arene series (*endo* rim substituents are $OCH_2CH_2OCH_2CONEt_2$) shows that removal of the *p-tert*-butyl groups favors the 1,2,3-alternate conformation which, in turn, favors the formation of a 2:1 complex with Eu^{3+}. X-Ray crystal structures of the Tm^{+3}, Ce^{3+} and Pr^{3+} complexes with the amides have been obtained.[97]

7.2.2.5 Endo Rim Carboxylic Acids

Carboxylic acids of the general structure **7.7a**'[98,99] differ from the esters, ketones and amides in having ionizable groups, the pK_a values in MeOH for the four carboxyl groups of **7.7a** being 8.3, 9.2, 10.9 and 13.4.

Although the calixarene carboxylic acids form complexes with some of the alkali metal cations, they have an even greater capacity for the more highly charged alkaline earth cations (first realized in the mid 1980s[100,101]). All are selective for Ca^{2+}, especially **7.7a** for which the Ca^{2+}/Mg^{2+} ratio is 2.7×10^{11} (10^4 higher than that of the amide **7.9b**). As noted already, the cone conformer of the mixed carboxylic acid amide **7.10c** has a particularly striking selectivity for Ca^{2+}, showing an almost infinitely greater attraction[91] for this ion than for Mg^{2+}, Sr^{2+} and Ba^{2+}. Included among other divalent cations that form complexes with the carboxylic acids such as **7.7a** (R = *tert*-octyl) is Cu^{2+}, which, interestingly, also requires the presence of Na^+. This unusual behavior[102] is attributed to the ability of Na^+ to preorganize the extractant to accept the Cu^{2+}.

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[95] N. Sabbatini, M. Guardigli, A. Mecati, V. Balzani, R. Ungaro, E. Ghidini, A. Casnati and A. Pochini, *J. Chem. Soc. Chem. Commun.* **1990**, 878; E. M. Georgiev and D. M. Roundhill, *Inorg. Chim. Acta.* **1997**, 258, 93; P. D. Beer, M. G. B. Drew and M. I. Ogden, *J. Chem. Soc. Dalton Trans.* **1997**, 1489; P. D. Beer, G. D. Brindley, O. D. Fox, A. Grieve, M. I. Ogden, E. Szemes and M. G. B. Drew, *J. Chem. Soc. Dalton Trans.* **2002**, 3101.

[96] F. de M. Ramirez, L. Charbonniére, G. Muller and J.-C. G. Bünzli, *Eur. J. Inorg. Chem.* **2004**, 2348.

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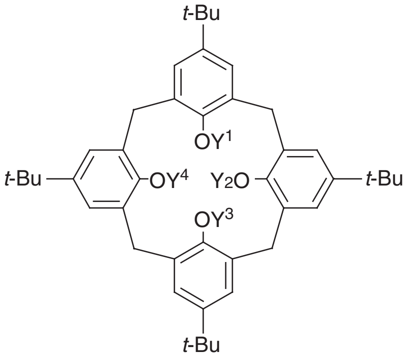


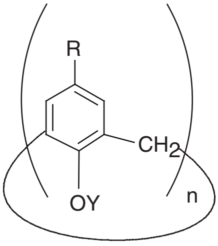
7.10

a) $Y^{1,3} = CH_2CO_2H$; $Y^{2,4} = H$

b) $Y^1 = CH_2CO_2H$; $Y^3 = CH_2CO_2Et$; $Y^{2,4} = H$

c) $Y^{1,3} = CH_2CO_2H$; $Y^{2,4} = CH_2CONEt_2$

d) $Y^{1\text{-}3} = CH_2CO_2H$; $Y^4 = CH_2CONHR$



7.11

a) $R = SO_3H$; $Y = CH_2CO_2H$

b) $R = SO_2.NHR'$, $Y = CH_2CH_2OCH_3$

c) R = t-Bu; $Y = CH_2CONHR$

d) $R = C(CH_3)_2CH_2C(CH_3)_3$; $Y = CH_2CO_2R'$

e) R = *t*-Bu; $Y = CH_2CONHOH$

f) R = *t*-Bu; $Y = R'_2P$

g) R = *t*-Bu; $Y = CH_2CSNR'_2$

h) R = *t*-Bu; $Y = CH_2CONH(CH_2)_mSEt$

i) $R = CH_2CH_2NH_2$; $Y = SO_2C_6H_4Br$

j) $R = CH_2PO_3H$; Y = Me

k) $R = (C_6H_5)_2P$; Y = Me

l) R = NHC(=NOH)CH=NOH; Y = Me

m) R = *t*-Bu; $Y = (CH_2)_4NHC(=X)NHC_6H_5$

n) R = *t*-Bu; $Y = CH_2CH_2P(O)(C_6H_5)2$

o) $R = NHCOCH_2P(O)(C_6H_5)_2$

p) R = *t*-Bu; $Y = CH_2P(O)R_2$

q) R = *t*-Bu; $Y = CH_2CH_2C(S)NMe_2$

The carboxylic acids form even stronger complexes with lanthanide cations than with alkali and alkaline earth cations, the log K_{assoc} values for **7.7a** (as a tetraanion) with Pr^{3+}, Eu^{3+}, Yb^{3+} being 20.7, 25.0 and 24.8 respectively (*cf*. ref. 80 in *Apndx B-15*). The complexing ability, however, is pH dependent, and only at high pH is **7.7a** more effective than the amide **7.9a**. Extraction experiments[103] indicate that the cyclic hexamer **7.7e** is better than the cyclic tetramer **7.7a**, with the order of extractability being

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[103] R. Ludvig, K. Inoue and T. Yamato, *Solv. Extr. Ion Exch.* **1993**, 11, 311.

$Nd^{3+} \approx Eu^{3+} > La^{3+} > Er^{3+} > Yb^{3+}$. The strength of complexation is also strongly influenced by the cation of the background electrolyte (*Apndx B-15, p. 82*). The tricarboxylic acid monoamide **7.10d** has been used to form a neutral complex[104] with Eu^{3+} and Tb^{3+}. The calix[4]arene dicarboxylic acid **7.10a** and the calix[6]arene ester **7.11** (R = *tert*-octyl; Y = CH_2CO_2R; $n = 6$) are useful extractants for the rare earth cations.[105]

Some of the carboxycalixarenes of the general structure **7.7a** and **7.11a** have proved to be highly effective complexation agents for the uranyl cation.[106] Not only are the high complexation constants of the water soluble *p*-sulfonato calixarenes **7.11a** ($n = 5$ and 6) noteworthy ($\log K_{assoc} = 18.4$ and $18.7\,M^{-1}$), but the large discrimination factors of 10^{12}–10^{17} relative to Cu^{2+}, Zn^{2+} and Ni^{2+} are quite remarkable. The analogous *p*-*tert*-butylcalix[5] and [6]arenes are somewhat less effective uranophiles, but the corresponding hydroxamic acid **7.11e** ($n = 6$) is even better than **7.11a** ($n = 6$) and competes efficiently with ${CO_3}^{2-}$ anions.[107] The special effectiveness of the "superuranophiles" has been interpreted in terms of preorganization, although this has been questioned.[108]

7.2.2.6. *Endo Rim Phosphorus- and Sulfur-containing Groups*

The calixarene **7.11f** ($n = 4$) containing four OPR_2 groups on the *endo* rim reacts with $[Cu(CO)Cl]_n$ to form a complex containing eight Cu atoms and two calixarene molecules.[109] It also reacts with $[Fe(CO)_3(n_2\text{-}C_8H_{14})_2]$ to form a complex containing two Fe atoms, one calixarene molecule and six molecules of CO.[110] The calixarene **7.11p** ($n = 4$) containing four $OCH_2P(O)Ph_2$ groups forms a palladium complex in which a Pd^{2+} is coordinated with each of the phosphorus centers.[111] The related diamide-diphosphine oxide calix[4]arenes exhibit the extraction order $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$.[112] The (carbamoylmethyl)-phosphine oxide (CMPO) moiety in **7.11o** is especially effective

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[104] D. M. Rudkevich, W. Verboom, E. van der Tol, C. J. van Staveren, F. M. Kaspersen, J. W. Verhoeven and D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans. 2* **1995**, 131.

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[111] C. Dielman, C. Loeber, D. Matt, A. De Cian and J. Fischer, *J. Chem. Soc. Dalton Trans.* **1995**, 3097.

[112] M. R. Yaftian, M. Burgard, D. Matt, C. Wieser and C. Dieleman, *J. Inclusion Phenom. Molec. Recognit.* **1997**, 27, 127.

for complexing trivalent metal ions,[113] including lanthanides[114] and actinides.[115]

A class of hosts that form only weak complexes with the alkali and alkaline earth cations but strong complexes with Ag^+, Pb^{2+} and Cd^{2+} are the thioamides **7.11g**.[116] The cyclic pentamer **7.11g** ($R' = Pr$, $n = 5$) is particularly effective for the extraction of Cd^{2+}, and the cyclic hexamer **7.11g** ($R' = Et$, $n = 6$) shows a high Ag^+/Cu^{2+} and Ag^+/Pb^{2+} selectivity. Calixarenes **7.11h** ($n = 4$), containing "hard" binding sites at the oxygen atoms and "soft" binding sites at the sulfur atoms, have the potential for forming ditopic bimetallic complexes. There is some evidence that this has been accomplished with Ag^+ and Na^+ using the compound in which $n = 6$, although the same compound with Cd^+ excludes the Na^+ cation.[117] Calixarenes **7.11n,l** ($n = 4$–8)[118] are highly efficient extractants for europium, thorium, neptunium, plutonium and americium. The N,N-dimethyldithiocarbamoylethyl ether **7.11q** ($n = 4$) is an effective extractant[119] for palladium and other heavy metals.

7.2.2.7 Nitrogen-containing Chelating Groups on the Endo Rim

The interaction of Cu^+ with *p*-*tert*-butylcalix[4]arenes carrying one, two, three or four O-bipyridylmethyl groups on the *endo* rim have been investigated.[120] The mono(bipyridylmethyl) ether forms a 2:1 intermolecular complex, and the A,B- and A,C-diethers both form 1:1 intramolecular complexes. With Cu^{2+} in MeOH solution a complex is obtained that rapidly transforms to the Cu^+ complex, the result of reduction by MeOH which is oxidized to HCHO. The interaction of Pb^{2+}, Hg^{2+} and Cd^{2+} with *p*-*tert*-butylcalix[4]arenes carrying O-alkylamino moieties on the *endo* rim have also been briefly explored.[121] The *p*-*tert*-butylcalix[4]arene **7.10d** carrying amide and carboxyl moieties on the

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[113] S. Barboso, A. G. Carrera, S. E. Matthews, J. Arnaud-Neu, V. Böhmer, J.-F. Dozol, H. Rouquette and M.-J. Schwing-Weill, *J. Chem. Soc. Perkin Trans. 2* **1999**, 719; A. Arduini, V. Böhmer, L. Delman, J. F. Desreux, J.-F. Dozol, M. A. G. Carrera, B. Lambert, C. Musigmann, A. Pochini, A. Schivanyuk and F. Ugozzoli, *Chem.-Eur. J.* **2000**, 6, 2135.

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[118] (a) J. F. Malone, D. J. Marrs, M. A. McKervey, P. O'Hagan, N. Thompson, A. Walker, F. Arnaud-Neu, O. Mauprivez, M.-J. Schwing-Weill, J.-F. Dozol, H. Rouquette and N. Simon, *J. Chem. Soc. Chem. Commun.* **1995**, 2151; (b) F. Arnaud-Neu, V. Böhmer, J.-F. Dozol, C. Grüttner, R. A. Jakobi, D. Kraft, O. Mauprivez, H. Rouquette, M.-J. Schwing-Weill, N. Simon and W. Vogt, *J. Chem. Soc.* **1996**, 1175.

[119] A. T. Yordanov, J. T. Mague and D. M. Roundhill, *Inorg. Chim. Acta.* **1995**, 240, 441; *idem*, *Inorg. Chem.* **1995**, 34, 5084; A. T. Yordanov, D. M. Roundhill, J. T. Mague, *Inorg. Chim. Acta* **1996**, 250, 295.

[120] J.-B. Regnouf de Vains and R. Lamartine, *Helv. Chim. Acta.* **1994**, 77, 1817.

[121] A. F. Danil de Namor, F. J. Sueros Velarde and M. C. Cabaleiro, *J. Chem. Soc. Faraday Trans.* **1996**, 92, 1731.

endo rim forms complexes with uranyl and lanthanide ions.[122] Attachment of a pair of 1,4,7-triazacyclononane moieties to the *endo* rim of a calix[4]arene produces a compound[123] that forms a ferromagnetic complex with Ni^{2+}. A calix[6]arene with a 1,10-phenanthroline bridge across the A,D positions[124] forms a complex with Yb^{3+}.

7.2.3 Calixcrowns (*Apndx A-2, p. 365*)

Calixcrowns carrying bridging polyethyleneoxy moieties on the *endo* rim were first prepared by Ungaro and coworkers[125] in 1983. Not surprisingly they have proved to be especially effective cation complexing agents. In contrast to the esters, ketones and amides discussed above, many of which are selective for Na^+, the calixcrowns generally show a preference for the larger cations. A number of calixcrown dialkyl ethers **7.12** (Y = alkyl) have been studied,[126] and an interesting effect of conformation has been noted in the case of **7.12b** for which the structures of the cone, partial cone and 1,3-alternate conformers have all been established by X-ray crystallography. As illustrated by the data in Table 7.1,[126c] the partial cone conformer forms the strongest complexes with the impressive K^+/Na^+ selectivity of 1.18×10^4. In transport through a supported membrane, however, the selectivity is less dramatic, and it has been shown that with **7.12b**, in contrast to **7.12a**, the transport rate is affected by the rate of cation release.[127] The de-*tert*-butyl analog of **7.12c** is an especially strong

Table 7.1 Association constants for the cone, partial cone and 1,3-alternate conformers of **7.12b** with alkali picrates in $CDCl_3$.

	K_{assoc}, M^{-1}			
Conformation	Na^+	K^+	Rb^+	Cs^+
Cone	1.3×10^5	1.2×10^7	4.0×10^5	9.8×10^4
Partial Cone	7.5×10^5	8.9×10^9	1.5×10^9	1.6×10^6
1,3-Alternate	2.9×10^5	1.4×10^8	5.4×10^7	9.3×10^5

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[122] P. D. Beer, G. D. Brindley, O. D. Fox, A. Grieve, M. I. Ogden, F. Szemes and M. G. B. Drew, *J. Chem. Soc. Dalton Trans.* **2002**, 3101.

[123] P. D. Beer, M. G. B. Drew, P. B. Leeson, K. Lyssenko and J. I. Ogden, *J. Chem. Soc. Chem. Commun.* **1995**, 929.

[124] J. P W. Eggert, J. M. Harrowfield, U. Lüning, B. W. Skelton and A. H. White, *Polyhedron* **2006**, 25, 910.

[125] C. Alfieri, E. Dradi, A. Pochini, R. Ungaro and G. D. Andreetti, *J. Chem. Soc. Chem. Commun.* **1983**, 1075.

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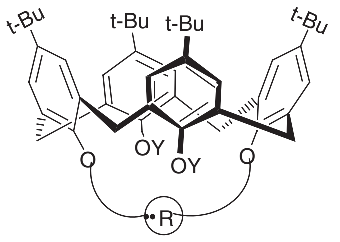
[127] E. G. Reichwein-Buitenhuis, H. C. Visser, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1995**, 117, 3913.

K^+ binder[128] and shows the very high K^+/Na^+ selectivity of *ca.* 3.4×10^5. *p*-*tert*-Butylcalix[6]arene bridged across the A,D positions with a crown moiety[129] forms a complex ($K_{assoc} = 750\,M^{-1}$) with Me_4N^+in $CDCl_3$. Calix[4]azacrowns have been shown to be effective in the complexation of lanthanides (Eu^{3+}, Tb^{3+}, Nd^{3+}, Er^{3+}, La^{3+}).[130] *p*-*tert*-Butylcalix[4]arene crown-4 compounds carrying a pair of di-ionizable groups on the *endo* rim[131] (*e.g.* CO_2H, $NHSO_2CF_3$) show a high selectivity for Ba^{2+}.



7.12

$R = CH_2(CH_2OCH_2)_nCH_2$

a) Y = Me; n = 3

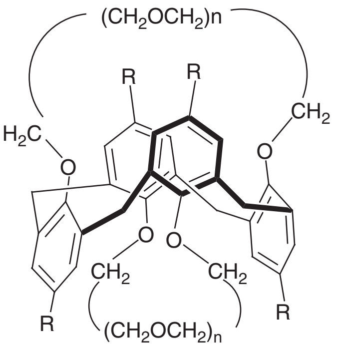
b) Y = Et; n = 3

c) Y = *i*-Pr; n = 3

d) Y = Me; n = 4

e) Y = *i* -Pr; n = 4

f) Y = H; n = 4



7.13

a) R= *t*-Bu; n = 4

b) R = H; n = 3

c) R = H; n = 4

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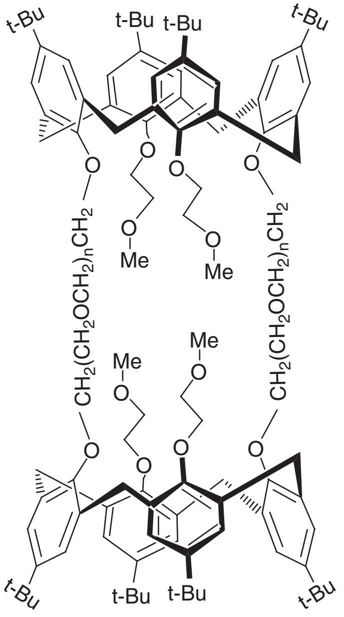
[128] A. Casnati, A. Pochini, R. Ungaro, C. Bocchi, F. Ugozzoli, R. J. M. Egberink, H. Struijk, R. Lugtenberg, F. de Jong and D. N. Reinhoudt, *Chem. Eur. J.* **1996**, 2, 436.

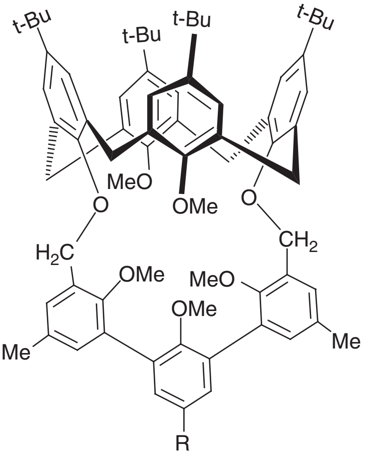
[129] A. Casnati, P. Jacopozzi, A. Pochini, F. Ugozzoli, R. Cacciapaglia, L. Mandolini and R. Ungaro, *Tetrahedron* **1995**, 51, 591.

[130] I. Quesiati, R. A. Sá Ferreira, L. D. Carlos, C. Beleizão, M. N. Berberan- Santos, B. de Castro, J. Vicens and U. Pischel, *Inorg. Chem.* **2006**, 45, 2652.

[131] C. Tu, K. Surowiec and R. A. Bartsch, *Tetrahedron Lett.* **2006**, 47, 3443.



7.14



7.15

The complexation of Cs^+ has commanded considerable attention from calixarene chemists because of its applicability to the removal of this metal from nuclear wastes. The calixcrowns in particular have been studied with this in mind.[132] The X-ray crystal structure of the Cs^+ complex of the conformationally mobile dimethyl ether of de-*tert*-butylated analogue of **7.12a** showed that the system adopts a 1,3-alternate conformation[133] which maximizes the cation-π interaction.[134] Supporting this lead was the finding that the di-isopropyl ether **7.12e**, fixed in the 1,3-alternate conformation, is highly selective for Cs^+. Its especially high Cs^+/Na^+ selectivity factor of *ca.* 4000 was attributed to the size of the crown ether (which is intermediate between an 18-crown-6 and a 21-crown-7) and to its inability to wrap around the smaller cations because of steric hindrance from the calixarene skeleton.[135] Another highly effective compound is a calix[4]arene bridged on the *endo* rim with a dibenzocrown-6

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[132] A. Casnati, A. Pochini, R. Ungaro, F. Ugozzoli, F. Arnaud, S. Fanni, M.-J. Schwing, R. J. M. Egberink, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1995**, 117, 2767.

[133] R. Ungaro, A. Casnati, F. Ugozzoli, A. Pochini, J.-F. Dozol, C. Hill and H. Rouquette, *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1506.

[134] R. A. Sachleben, J. C. Bryan, N. L. Engle, T. J. Haverlock, B. P. Hay, A. Urvoas and B. A. Moyer, *Eur. J. Org. Chem.* **2003**, 4862 have shown that calix[4]arene crowns lacking the OMe groups are even stronger Cs^+ complexers.

[135] A. Casnati, A. Pochini, R. Ungaro, F. Ugozzoli, F. Arnaud, S. Fanni, M.-J. Schwing, R. J. M. Egberink, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1995**, 117, 2767. For a molecular mechanics study for the design of a calixarene with a high Cs^+/K^+ selectivity *cf.* ref 134.

moiety[136] (*i.e.* **7.12e** with two benzene rings in place of two ethylene units).The complexing behavior of calix[4]arenes doubly bridged with polyoxyethylene chains (**7.13**)[137,138] has also been studied both in experimental[139] and theoretical detail.[140] The bis-calix[4]arenecrown-6 **7.13a**, for example, is yet another Cs^+ ionophore, although the Cs^+/Na^+ factor of 850 is lower than for the dibenzo analogue of **7.12e**. Compound **7.13b**, a calix[4]arene-bis-crown-6, forms a binuclear complex with CsI in which a Cs^+ cation resides in each of the crown ether moieties.[141] Enhanced Cs^+ complexation has been demonstrated for calix[4]arene-bis-crown-6 ethers carrying a proton-ionizable (*e.g.* CO_2H or $C(O)NHSO_2CF_3$) on the *exo* rim of one of the aryl moieties.[142]

The bis-calixarene **7.14** (an "ionophoric tube"[143]) contains binding sites at each of its calixarene units and forms both 1:1 and 2:1 complexes with Na^+. In the 1:1 complex the lone cation can oscillate between the two sites *via* an intermolecular pathway (concentration-dependent) and/or an intramolecular pathway (concentration-independent). Both pathways have been detected and have been measured by ^1H NMR spectroscopy, the first pathway occurring at room temperature (25 °C) and the latter at a lower temperature (−25 °C). The intramolecular exchange occurs more rapidly with **7.14** ($n = 2$) than with **7.14** ($n = 3,4$), and a similar phenomenon has been noted in other systems. For example, in the 1:1 Ag^+ complex of the 1,3-alternate conformer of **7.6b** ($R = H$; $n = 4$) it is postulated that the Ag^+ passes from one site to the other through the interior of the molecule,[144] *viz.* "tunneling across a π-basic tube". And, in the 1:1 complexes of **7.13c** the cations K^+, Rb^+, Cs^+ and $NH_4{}^+$ all are postulated to tunnel in the same fashion.[145] A calix[4]arene A,C-bridged with $(OCH_2CH_2OCH_2CH_2)_2NC_6H_{13}$ acts as a "molecular syringe", accepting

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[136] V. Lamare, J.-F. Dozol, F. Ugozzoli, A. Casnati and R. Ungaro, *Eur. J. Org. Chem.* **1998**, 1559; J. S. Kim, J. H. Pang, Y. Yu, W. K. Lee, I. H. Suh, K. Kim, M. H. Cho, E. T. Kim and D. Y. Ra, *J. Chem. Soc. Perkin Trans 2* **1999**, 837.

[137] Z. Asfari, S. Pappalardo and J. Vicens, *J. Inclusion Phenom. Molec. Recognit. Chem.* **1992**, 14, 189; Z. Asfari, J. Weiss, S. Pappalardo and J. Vicens, *Pure & Appl. Chem.* **1993**, 65, 585; S. Wenger, Z. Asfari and J. Vicens, *J. Inclusion Phenom. Molec. Recognit. Chem.* **1995**, 20, 293; Z. Asfari, C. Naumann, G. Kaufmann and J. Vicens, *Tetrahedron Lett.* **1996**, 37, 3325; B. Pulpoka, Z. Asfari and J. Vicens, *ibid.* **1996**, 37, 6315. For the X-ray crystal structure *cf.* R. Abidi, Z. Asfari, J. M. Harrowfield, A. N. Sobolev and J. Vicens, *Aust. J. Chem.* **1996**, 49, 183.

[138] H. Yamamoto, T. Sakaki and S. Shinkai, *Chem. Lett.* **1994**, 469.

[139] F. Arnaud-Neu, Z. Asfari, B. Souley and J. Vicens, *New J. Chem.* **1996**, 20, 453. For an experimental/theoretical study of thiacalixcrowns *cf.* V. Lamare, J.-F. Dozol, P. Thuéry, M. Nierlich, Z. Asfari and J. Vicens, *J. Chem. Soc. Perkin Trans 2* **2001**, 1920.

[140] A. Varnek and G. Wipff, *J. Computational Chem.* **1996**, 17, 1520; *idem*, *J. Molec. Structure (Theochem)* **1996**, 363, 67.

[141] P. Thuéry, M. Nierlich, V. Lamare, J.-F. Dozol, Z. Asfari and J. Vicens, *Acta Cryst.* **1996**, C52, 2729.

[142] V. S. Talanov, G. D. Talanova and R. A. Bartsch, *Tetrahedron Lett.* **2000**, 41, 8221;V. S. Talanov, G. G. Talanova, M. G. Gorbunova and R. A. Bartsch, *ibid.* **2002**, 43, 1629.

[143] F. Ohseto and S. Shinkai, *Chem. Lett.* **1993**, 2045; *idem*, *J. Chem. Soc. Perkin Trans.2* **1995**, 1103.

[144] A. Ikeda and S. Shinkai, *J. Am. Chem. Soc.* **1994**, 116, 3102; J. S. Kim, S. H. Yang, J. A. Rim, J. Y. Kim, J. Vicens and S. Shinkai, *Tetrahedron Lett.* **2001**, 42, 8047.

[145] K. N. Koh, K. Araki, S. Shinkai, Z. Asfari and J. Vicens, *Tetrahedron Lett.* **1995**, 36, 6095.

Ag^+ in the azacrown cavity in the neutral state but expelling it to the polyether cavity upon protonation.[146]

7.2.4 Calixspherands

A particularly good example of the power of preorganization combined with conformational adaptation is seen in the calix[4]spherands (**7.15**), compounds in which a hemispherand moiety is affixed to the *endo* rim of a calix[4]arene.[126b] Although the hemispherand part of the molecule is constrained in a rigid conformation that already is most appropriate for metal ion complexation, the calixarene part retains some conformational mobility. In the uncomplexed state the calixspherand exists in the cone conformation, both in solution (as shown by ^{1}H NMR/NOESY measurements) and in the solid state (as shown by X-ray crystallography[147]). Upon complexation with a cation, however, **7.15** (R = Me) transforms to a flattened partial cone conformer, forming very tight complexes with Na^+ ($K_{assoc} = 2.1 \times 10^{12}\,M^{-1}$), K^+ ($K_{assoc} = 2.2 \times 10^{13}\,M^{-1}$) and Rb^+ ($K_{assoc} = 3.6 \times 10^{9}\,M^{-1}$). The rate of decomplexation of Rb^+ ($k_d = 6.9 \times 10^{-5}\,s^{-1}$), measured by a radioactive metal ion exchange method,[148] is considerably greater than that of Na^+ ($k_d = 6.0 \times 10^{-9}\,s^{-1}$) and K^+ ($k_d = 1.0 \times 10^{-8}\,s^{-1}$). High kinetic stability of the Rb^+ complex is desirable for its intended medical use as an organ imaging reagent, and it was discovered that this can be achieved by introducing larger alkyl groups onto the middle oxygen of the hemispherand. Thus, **7.15** (R = Et) shows $K_{assoc} = 4.4 \times 10^{9}\,M^{-1}$ and $k_d = 1.4 \times 10^{-6}\,s^{-1}$; **7.15** (R = *i*-Pr) shows $K_{assoc} = 7.5 \times 10^{9}\,M^{-1}$ and $k_d = 4.4 \times 10^{-8}\,s^{-1}$, corresponding to an increase in the half-time for decomplexation of 2.8 hrs for **7.15** (R = Me) to 139 hrs for **7.15** (R = Et) and 180 days for **7.15** (R = *i*-Pr).[149] The corresponding Na^+ and K^+ complexes have decomplexation half-times of several years. The increased kinetic stability of the complexes with **7.15** (R = Et and *i*-Pr) is attributed to the greater ability of the larger alkyl groups to shield the cation embedded in the calixspherand from solvent molecules. A functionalized calixspherand has been attached to a low molecular weight protein.[150]

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[146] A. Ikeda, T. Tsudera and S. Shinkai, *J. Org. Chem.* **1997**, 62, 3568.

[147] L. C. Groenen, J. A. J. Brunink, W. I. Iwema-Bakker, S. Harkema, S. Wijmenga and D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans. 2* **1992**, 1899.

[148] W. I. Iwema-Bakker, M. Haas, H. J. den Hertog Jr., W. Verboom, D. de Zeeuw and D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans. 2* **1994**, 11.

[149] W. I. Iwema-Bakker, J. Haas, C. Khoo-Beattie, R. Ostaszewski, S. M. Franken, H. J. den Hertog, Jr., W. Verboom, D. de Zeeuw, S. Harkema and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1994**, 116, 123.

[150] W. I. Iwema Bakker, M. Haas, H. J. den Hertog, Jr., W. Verboom, D. de Zeeuw, A. P. Bruins and D. N. Reinhoudt, *J. Org. Chem.* **1994**, 59, 972.

7.3 Solution State Complexes of Metal Cations with *Exo* Rim-substituted Calixarenes

Many fewer papers have been published on metal cation complexation with *exo* rim-substituted calixarenes than with *endo* rim-substituted calixarenes. One early example of the former involves the interaction of Ni^{2+}, Cu^{2+}, Co^{2+}, Fe^{2+} and Pd^{2+} with the cone conformer of **7.11i** ($n = 4$) in which the four ethylamine appendages behave more or less independently of one another rather than as a single trialkylenetetramine-like moiety.[151] Calixarenes **7.11a**[106b,152] and **7.11j**[153] ($n = 5$ and 6) with SO_3H or $CH_2PO_3H_2$ groups in the *p*-positions have proved to be excellent uranophiles (*vide infra*), showing complexation constants of *ca.* 10^{19} and $10^{17.5}$ M^{-1}, respectively, and a high selectivity relative to Ni^{2+}, Zn^{2+} and Cu^{2+}. The diphenylphosphinocalixarene **7.11k** ($n = 4$) forms complexes with a variety of cations, as measured by extraction efficiency with the following descending order of extractability:[154] $Hg^{2+} > Cu^{2+} > Cd^{2+} > Zn^{2+} > Ni^{2+} > Al^{3+} > Na^{+} > K^{+}$. The calix[6]arene **7.11l** ($n = 6$) carrying *vic*-dioxime groups forms complexes with Cu^{2+}, Co^{2+} and Ni^{2+}containing three metal ions.[155] Calixarenes **7.17b,c** interact with Cu^{+} and Cu^{2+} to form complexes containing two metal ions which are useful in redox systems.[156] Calixarenes carrying *p*-phenylazo groups show highly selective binding for Ag^{+}, Hg^{+} and Hg^{2+} cations.[157] Attachment of two or four tetrazole groups to the *exo* rim produces a calyx[4]arene that forms a complex with Pd^{2+}.[158]

References to the work of Shinkai have appeared in numerous places throughout this book. Entering the field in 1984,[159] Sejii Shinkai has become one of the most prolific of the calixarene chemists and has made striking contributions that have taken calixarene chemistry in several new directions. He was born in Fukuoka, Japan, in 1944 and received his Ph.D. degree in 1972 from Kyushu University under the direction of Toyoki Kunatake. After a two-year postdoctoral stint in the laboratories of Thomas Bruice at the University of California at Santa Barbara, he returned to his native country where he has held faculty positions at several universities and currently heads the Center for Future Chemistry at Kyushu University, his *alma mater*.

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[151] C. D. Gutsche and K. C. Nam, *J. Am. Chem. Soc.* **1988**, 110, 6153.

[152] T. Nagasaki, K. Kawano, K. Araki and S. Shinkai, *J. Chem. Soc. Perkin Trans. 2* **1991**, 1325.

[153] T. Nagasaki, T. Arimura and S. Shinkai, *Bull. Chem. Soc. Jpn.* **1991**, 64, 2575.

[154] F. Hamada, T. Fukagaki, K. Murai, G. W. Orr and J. L. Atwood, *J. Inclusion Phenom. Molec. Recognit. Chem.* **1991**, 10, 57.

[155] M. Yilmaz and H. Deligoz, *Synth. React. Inorg. Met-Org. Chem.* **1993**, 23, 67; H. Deligoz and M. Yilmaz, *ibid.* **1996**, 26, 943.

[156] D. Xie and C. D. Gutsche, *J. Org. Chem.* **1998**, 63, 9270.

[157] E. Nomura, H. Taniguchi and Y. Otsuji, *Bull. Chem. Soc. Jpn.* **1993**, 66, 3797.

[158] V. Boyko, R. Rodik, O. Danylyuk, L. Tsymbal, Y. Lampeka, K. Suwinska, J. Lipkowski and V. Kalchenko, *Tetrahedron* **2005**, 61, 12282.

[159] S. Shinkai, S. Mori, T. Tsubaki, T. Sone and O. Manabe, *Tetrahedron Lett.* **1984**, 25, 5315.

Seiji Shinkai

Bringing to calixarene chemistry a viewpoint that reflects the influence of his training in physical organic chemistry, he embarked on an ambitious program that focused on the uses to which calixarenes can be put. A good example involves the attempt to fashion a compound capable of extracting uranium from sea water which contains about three billion tons of UO_2^{2+} (strongly complexed to CO_2) but in a concentration of only *ca.* 3 parts per billion. In the first edition of this book (*Apndx A-9, p. 190*) it was stated that "if the 'greenhouse' effect proves to be responsible for adverse global changes in climate it may force greater attention to nuclear energy". At the time of the writing of this second edition, that possibility has become a well-established reality. Addressing this problem in the mid 1980s, Shinkai and coworkers[106b] found that although *p*-sulfonato calix[4]arene shows little ability to form a complex with UO_2^{2+}, both the cyclic pentamer and cyclic hexamer show high K_{assoc} values and dramatic selectivities with factors of 10^{12-17} relative to Mg^{2+}, Ni^{2+}, Zn^{2+} and Cu^{2+}. Patents were issued[160] describing a polymer-bound hexakis(carbethoxymethyl) ether of *p*-sufonatocalix[6]arene as "partially nitrated, aminated, and fixed on cross-linked chloromethylated polystyrene". This resin was found to absorb 108 μg of uranium from sea water per 0.1 g. of resin in 7 days at a flow rate of 30 mL/min.

7.4 Anion Complexes with Calixarenes (*Apndx A-2, p. 421; A-4, p. 111*)

For every metal cation there is a counter anion, the latter generally considered to be merely a passive passenger in the complexation phenomena discussed above. This may not always be the case, however, and increasing attention is being focused on the anion. The goal of developing anion-specific receptors has frequently been stimulated by a desire to understand how biological systems utilize negatively charged entities. Selective complexation of anions, however,

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[160] S. Shinkai, O. Manabe, Y. Kondo and T. Yamamoto (Kanebo Ltd.), Jpn. Kokai Tokkyo Koho, JP 62,136,242, **1987** (*Chem. Abstr.* 108:6441q); Y. Kondo, T. Yamamoto, O. Manabe and S. Shinkai (Kanebo Ltd.), Jpn. Kokai Tokkyo Koho, JP 62,210,055, **1987** (*Chem. Abstr.* 108:116380b).

can be more difficult than that of cations, and a variety of considerations come into play, including (a) the charge, (b) the size, which is often larger than that of the metal cation, (c) the shape; whereas the metal cations are spherical, the anions frequently are not, (d) pH dependence, often more critical than in the case of metal cations and (e) solvation, which has a strong influence on the binding strength.

Among the earliest investigations of this facet of calixarene complexation are those of Beer and coworkers,[161] who attached cobaltocenium moieties to the *exo* rim of a calix[4]arene to obtain **7.16c**, which shows the following stability constants in DMSO solution: HSO_4^- ($40\,M^{-1}$), Cl^- ($70\,M^{-1}$), NO_3^- ($125\,M^{-1}$), $H_2PO_4^-$ ($6380\,M^{-1}$), $MeCO_2^-$ ($41,520\,M^{-1}$).[162] They also showed[163] that a pair of calix[4]arenes joined by two OCH_2COCH_2O moieties on the *endo* rims is selective for F^- relative to Cl^-, HSO_4^- and $H_2PO_4^-$, the anion stability constants being 1330, 172, 21 and $91\,M^{-1}$, respectively. Calixarene **7.16a**, substituted in a similar fashion on the *exo* rim, also forms complexes with anions,[162] including $H_2PO_4^-$. A calix[4]arene with an *exo* rim-bridge comprising two L-alanine units with a pyridine moiety in between is a strong complexer for carboxylate.[164] The potentiating effect of Na^+ is illustrated by **7.18**, which binds acetate in preference to diphenylphosphate in the absence of Na^+ but just the reverse in the presence of Na^+.[165] The X-ray structure of the BF_4^- complex of a calix[4]arene carrying Ar-Ru^{+2} groups attached to each of the four aromatic rings shows that one of the BF_4^- ions is firmly embedded in the cavity.[166]

Anion complexing agents are not restricted to calixarenes containing positively charged or electron deficient centers. Some neutral molecules also bind anions selectively *via* hydrogen bond interactions.[167] For example,[168] calixarene **7.11b** ($R' = Pr$; $n = 4$) complexes $H_2PO_4^-$, HSO_4^-, Cl^-, NO_3^- and ClO_4^- with association constants of 350, 970, 360, 240 and $<1\,M^{-1}$, respectively, and **7.11b** ($R' = COCH_3$, $n = 4$) shows an especially high complexation constant of 103, $400\,M^{-1}$ for HSO_4^-. A variety of urea- and thiourea-containing calixarenes have been prepared, including the *endo* rim-substituted tetramer **7.11m** ($n = 4$; $X = O$

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[161] P. D. Beer, M. G. B. Drew, C. Hazlewood, D. Hesek, J. Hodacova and J. E. Stokes. *J. Chem. Soc. Chem. Commun.* **1993**, 229. For the ferrocenium analogue *cf.* P. D. Beer, Z. Chang, M. J. Goulden, A. Graydon, S. E. Stokes and T. Wear, *J. Chem. Soc. Chem. Commun.* **1993**, 1834.

[162] P. D. Beer, M. G. B. Drew, D. Hesek and K. C. Nam, *J. Chem. Soc. Chem. Commun.* **1997**, 107.

[163] P. D. Beer, P. A. Gale and D. Hesek, *Tetrahedron Lett.* **1995**, 36, 767.

[164] F. Sansone, L. Baldini, A. Casnati, M. Lazzaretto, F. Ugozzoli and R. Ungaro, *Proc. Natl. Acad. Sci.* **2002**, 99, 4842.

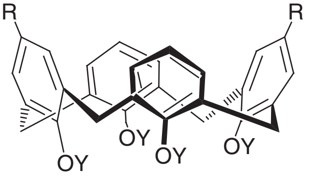
[165] G. Tumcharern, T. Tuntulani, S. J. Coles, M. B. Hursthouse and J. D. Kilburn, *Org. Lett.* **2003**, 5, 4971.

[166] J. W. Steed, R. K. Juneja and J. L. Atwood, *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 2456; M. Staffilani, K. S. B. Hancock, K. J. W. Steed, K. T. Holman, J. L. Atwood, R. K. Juneja and R. S. Burkhalter, *J. Am. Chem. Soc.* **1997**, 119, 6324.

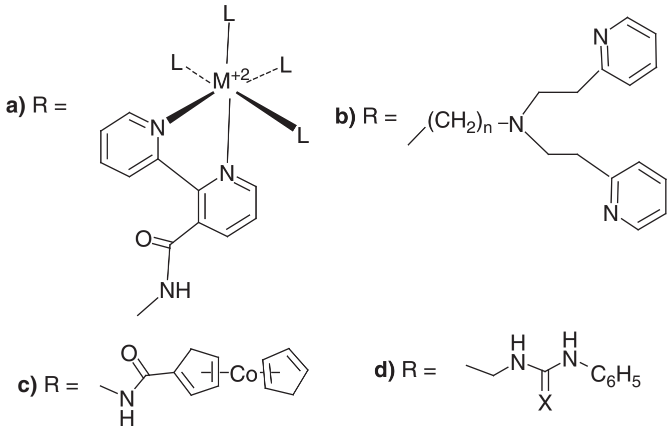
[167] For an example of a thiacalix[4]arene-based anion receptor *cf.* P. Zlatusková, M. Tkadlecová and P. Lhoták, *Tetrahedron* **2004**, 60, 11383.

[168] Y. Morzherin, D. M. Rudkevich, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.* **1993**, 58, 7602.

or S), the *endo* rim-substituted hexamer[169,170] **7.17a** and the *exo* rim-substituted **7.16d** (Y = Pr; X = O or S).[171] The first set of compounds binds anions in the order $Cl^- > Br^- > CN^-$ with only a small affinity for I^- and SCN^- and no affinity for F^- and $H_2PO_4{}^-$. The second set of compounds, possessing C_3 symmetry and containing three urea or thiourea groups, shows selectivity for Br^- over Cl^- and a high affinity for tricarboxylate anions such as benzene-1,3,5-tricarboxylate ($K_{assoc} = 87{,}000\,M^{-1}$ when X = O; $190{,}000\,M^{-1}$ when X = S), benzene-1,2,4-tricarboxylate ($K_{assoc} = 23{,}000\,M^{-1}$ when X = O; $2500\,M^{-1}$ when X = S) and cyclohexane-1,3,5-tricarboxylate ($K_{assoc} = 101{,}000\,M^{-1}$ when X = O and $29{,}000\,M^{-1}$ when X = S). The third set of compounds containing two urea or thiourea groups on the *exo* rim shows considerable selectivity for acetate ($K_{assoc} = 2200\ M^{-1}$) over butyrate, phthalates and halide anions when X = O. The analog of **7.17e** carrying a single urea or thiourea on the *exo* rim shows modest selectivity for butyrate over acetate when X = O or S.



7.16



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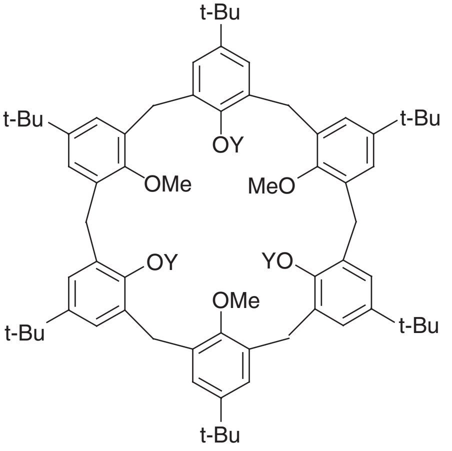
[169] J. Scheerder, M. Fochi, J. F. J. Engbersen and D. N. Reinhoudt, *J. Org. Chem.* **1994**, 59, 7815; J. Scheerder, J. F. J. Engbersen, A. Casnati, R. Ungaro and D. N. Reinhoudt, *J. Org. Chem.* **1995**, 60, 6448.

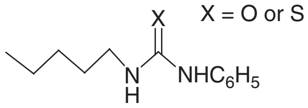
[170] For a diquinone analogue of **7.11m** *cf.* K. C. Nam, S. O. Kang, H. S. Jeong and S. Jeon, *Tetrahedron Lett.* **1999**, 40, 7343. For a Monte Carlo investigation *cf.* N. A. McDonald, E. M. Duffy and W. L. Jorgensen, *J. Am. Chem. Soc.* **1998**, 129, 5104.

[171] A. Casnati, M. Fochi, P. Minari, A. Pochini, M. Reggiani, R. Ungaro and D. N. Reinhoudt, *Gazz. Chim. Ital.* **1996**, 126, 99.

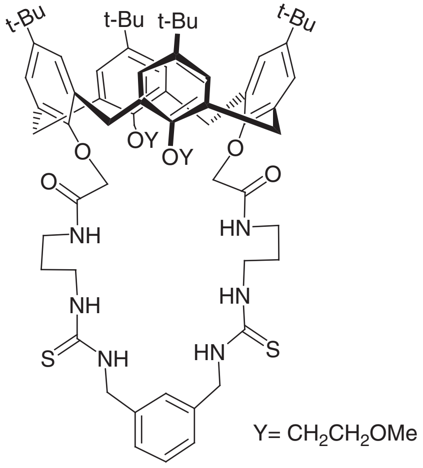


7.17

a) Y=



b) Y=CH$_2$CONEt$_2$



7.18

In 1996 Jonathan Sessler and his coworkers at the University of Texas at Austin published a short paper[172] describing the complexation of anions by the calixpyrrole **2.48** (R = Me; *cf.* Chapter 2, p 52), citing stability constants of 17,170 M^{-1} for F^-, 350 M^{-1} for Cl^-, 10 M^{-1} for I^-, 97 M^{-1} for $H_2PO_3^-$ and <10 M^{-1} for HSO_4^-. From this modest beginning has come a plethora of papers describing a number of variations on this theme that includes, *inter alia*, calixpyrroles with a variety or R groups, expanded calixpyrroles and calixpyrrole-porphyrin hybrids (calixphyrins). An interesting visual demonstration of the anion complexing ability of these compounds is described in a paper[173] entitled "Naked-Eye Detection of Anions in Dichloromethane: Colorimetric Anion Sensor Based on Calix[4]pyrrole". For reviews on what is now a quite extensive literature on the subject *cf. Apndx B-7 and Apndx D-8.*

7.5 Salt Complexes with Calixarenes

The experiments described above in Sections 7.1–7.4 focus on the cation or the anion of a salt as separate, essentially non-interacting, entities. The experiments described in this section focus on them collectively and involve "ditopic receptors" that contain two sites, one attracting the cation and the other attracting the anion. For example, calixarene **7.19**, containing an *exo* rim bridge, forms a complex with UO_2^{2+}, which, along with the amide moieties, provides an

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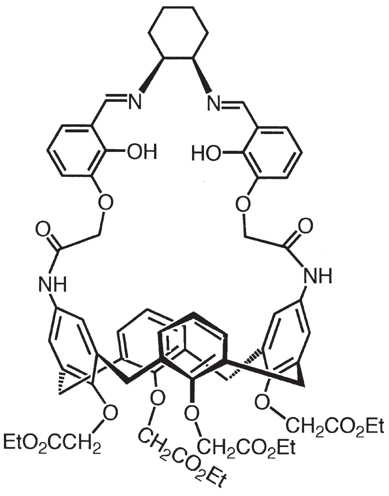
[172] P. A. Gale, J. L. Sessler, V. Král and V. Lynch, *J. Am. Chem. Soc.* **1996**, 118, 5140.

[173] H. Miyaji, W. Sato and J. L. Sessler, *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 1777.

anion-binding site;[174] it also contains four *endo* rim ester groups that provide a cation-binding site. As a consequence, it acts as a ditopic receptor and complexes NaH_2PO_4 with a K_{assoc} of $390\,M^{-1}$. In a similar vein **7.20** (shown as the complex) effectively transports CsCl through a supported liquid membrane,[175] while **7.21** solubilizes NaCl, NaBr, NaI, KBr and KI in $CHCl_3$ but not KCl or the Cs salts.[176] Another approach involves the calix[4]arene **7.22** (carrying two crown ether-amide moieties) which forms 1:1 stoichiometric complexes with potassium salts with association constants:[177] Cl^- ($3500\ M^{-1}$), NO_3^- ($1300\ M^{-1}$), HSO_4^- ($5600\ M^{-1}$), $H_2PO_4^-$ ($> 10^4\,M^{-1}$). A somewhat unexpected ditopic receptor is comprised of four ureido groups on the *endo* rim of calix[4]arene and one ureido or thioureido group on the *exo* rim.[178] A pair of *p*-*tert*-butylcalix[4]arenes joined at the *endo* rims by OCH_2CH_2O bridges (a "calix[4]semitube") and carrying two ureido moieties on one of the *exo* rims binds (a) K^+ very tightly ($K_{assoc} > 10^5\,M^{-1}$) and Na^+, Rb^+ and Cs^+ much less tightly (K_{assoc} 0–80 M^{-1}) in $CDCl_3/CD_3OD$ and (b) the anions Cl^-, Br^-, I^- and OAc^- (K_{assoc} 15–730 M^{-1}, depending on the presence or absence of Na^+ or K^+).[179]



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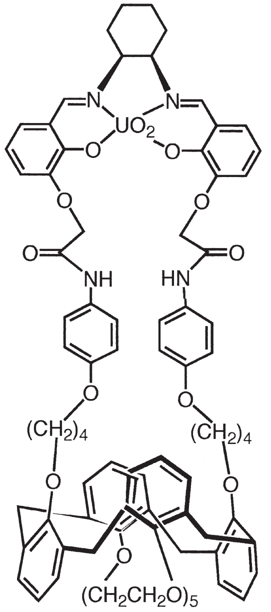

7.20

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[174] D. M. Rudkevich, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.* **1994**, 59, 3683.

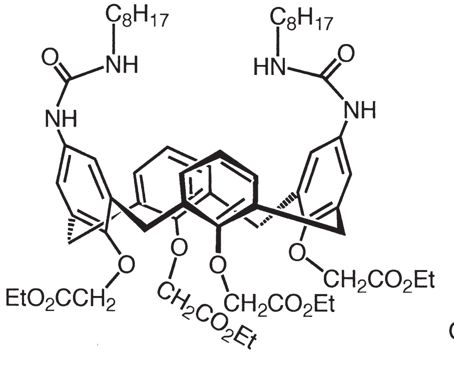
[175] D. M. Rudkevich, J. D. Mercer-Chalmers, W. Verboom, R. Ungaro, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1995**, 117, 6124.

[176] J. Scheerder, J. P. M. van Duynhoven, J. F. J. Engbersen and D. N. Reinhoudt, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1090.

[177] P. D. Beer, M. G. B. Drew, R. J. Knubley and M. I. Ogden, *J. Chem. Soc. Dalton Trans.* **1995**, 3117.

[178] N. Pelizzi, A. Casnati, A. Friggeri and R. Ungaro, *J. Chem. Soc. Perkin Trans. 2* **1998**, 1307.

[179] P. R. A. Weber and P. D. Beer, *J. Chem. Soc. Dalton Trans.* **2003**, 2249.



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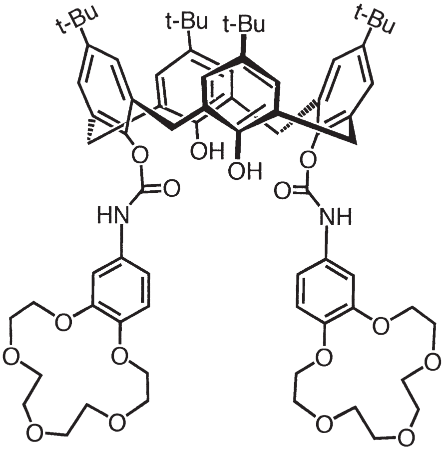

7.22

7.6 Solution State Complexes of Molecules with Calixarenes

7.6.1 Complexes with Molecular Cations (*Apndx A-4, p. 85*)

Among the earliest of the investigations of molecular cation complexation are those of Shinkai and coworkers[180] with *p*-sulfonatocalixarenes (**7.23**) as hosts and 4-(4′-dimethylaminophenylazobenzenediazonium tetrafluoroborate (**7.24**) as guests. Complexation reduces the rate of the decomposition of the benzenediazonium salts, so by measuring the rate of decomposition the following complexation constants were assigned: *ca.* $10^2\,M^{-1}$ for **7.23a** ($n = 6$), $4.2 \times 10^6\,M^{-1}$ for **7.23c** ($n = 6$) and $5.6 \times 10^4\,M^{-1}$ for **7.23d** ($n = 6$). To gain insight into the mode of binding of the arydiazonium salt in the calixarene cavity the interaction with **7.24** was explored. While **7.23a** ($n = 6$) fails to perturb the absorption of **7.24** at 612 nm in aqueous solution, **7.23b** ($n = 6$) shifts it to 609 nm and **7.23c** ($n = 6$) shifts it to 595 nm, indicating that the diazonium compounds are bound in the relatively hydrophobic site at the *endo* rim of the calixarene.

Another organic cation used effectively as the guest by the Shinkai group was trimethylanilinium.[181] By measuring the ^1H NMR shift values over a temperature range of 0–80 °C, they calculated ΔH°, ΔH° and ΔS° values and concluded that complexation with the cyclic tetramer (**7.23a**, $n = 4$) is driven by a favorable enthalpy change (stronger electrostatic interaction), whereas with the cyclic hexamer and octamer it is driven by an entropy increase (stronger hydrophobic interaction). It was emphasized that in studies with water soluble

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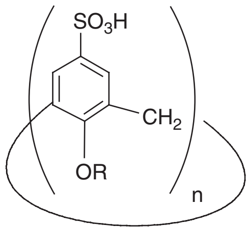
[180] S. Shinkai, S. Mori, K. Araki and O. Manabe, *Bull. Chem. Soc. Jpn.* **1987**, 60, 3679; S. Shinkai, S. Mori, T. Arimura and O. Manabe, *J. Chem. Soc. Chem. Commun.* **1987**, 238.

[181] S. Shinkai, K. Araki and O. Manabe, *J. Am. Chem. Soc.* **1988**, 110, 7214.

calixarenes an important feature that must be taken into consideration is their aggregation properties.[182] A calix[4]arene with anionic groups (SO_3^- and CO_2^-) on both *exo* and *endo* rims forms fairly strong complexes with cations such as $PhCH_2NMe_3^+$(K_{assoc} 2500 M^{-1}).[183]



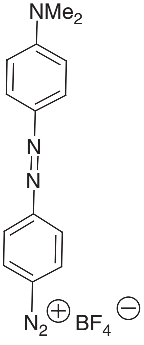
a) R = H

b) R = Me

c) R = n-hexyl

d) R = n-dodecyl

7.23



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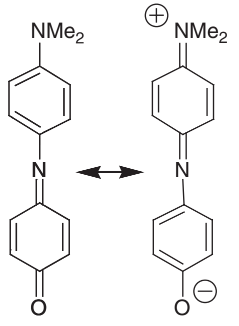

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The NH_4^+ cation acts, in many respects, like an inorganic cation and is often included in the complexation studies of the latter. Cations derived from amines, similarly, have considerable resemblance to inorganic cations, although the organic moiety introduces a significant steric factor. Thus, with the calix[4]crown-6 compound **7.12** ($n = 4$, Y = H) the binding strengths towards RNH_2 amines diminish in the order of increasing size of R in the amine,[184] *viz.* H > Me > Et ≈ Pr > Bu > Bu^i > Bu^s > Bu^t. With the larger guest molecule N-methylpyridinium the size of the calixarene cavity has a measurable effect, the K_{assoc} values with the methyl ethers of *p*-*tert*-butylcalix[4,6,8]arenes being 52, 190 and 132 M^{-1}, respectively.[185] Similarly, studies with **7.7** (R = *t*-Bu; R′ = alkyl; $n = 4$, 6 and 8) show that the cyclic hexamer is better than the cyclic tetramer or octamer for the complexation of butyl amine.[186] A calix[5]arene-crown-5 compound forms complexes with *n*-$BuNH_3^+$ in which the guest is shown to be inside the host (*endo* complexation).[187] A closely related study[188] involving a variety of ammonium guests, including acetylcholine and N-methylquinuclidinium, reached the same conclusion that the guest is in the cavity and that its ammonium portion is closely associated with the aromatic rings of the calixarene (π-cation interaction). Through the use of ^1H NMR shift and

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[182] S. Shinkai, A. Arimura, K. Araki, H. Kawabata, H. Satoh, T. Tsubaki, O. Manabe and J. Sunamoto, *J. Chem. Soc. Perkin Trans. 1* **1989**, 2039.

[183] G. Arena, A. Casnati, A. Contino, G. G. Lombardo, D. Sciotto and R. Ungaro, *Chem. Eur. J.* **1999**, 738.

[184] Y. E. Jung, B. M. Song and S.-K. Chang, *J. Chem. Soc. Perkin Trans. 2* **1995**, 2031; Also *cf.* S.-Y. Han, M.-H. Kang, Y. E. Jung and S.-K. Chang, *J. Chem. Soc. Perkin Trans. 2* **1994**, 835.

[185] K. Araki, H. Shimizu and S. Shinkai, *Chem. Lett.* **1993**, 205.

[186] S.-K. Chang, M. J. Jang, S. Y. Han, J. H. Lee, M. H. Kang and K. T. No, *Chem. Lett.* **1992**, 1937.

[187] S. Pappalardo and M. F. Parisi, *J. Org. Chem.* **1996**, 61, 8724.

[188] R. Arnecke, V. Böhmer, R. Cacciapaglia, A. Dalla Cort and L. Mandolini, *Tetrahedron* **1997**, 53, 4901.

relaxation time measurements of the complex formed from the calix[6]arene **7.7f** and $EtNH_3^+$, evidence was adduced for the Et group being embedded deep within the cavity.[189] A solvent effect has been observed[185] which shows that the strength of binding is greater in $CHCl_2CHCl_2$ than in $CHCl_3$, suggesting that only the smaller solvent is able to occupy the cavity of the host.

Amino acids and their methyl esters form complexes with a calix[4]arene rigidified by two crown ether moieties on the *endo* rim and four $CONHC(R)CO_2^-$ groups on the *exo* rim[190] (*e.g.* K_{assoc} for L-phenylalanine = 70 M^{-1}; K_{assoc} for the methyl ester of L-phenylalanine = 430 M^{-1}). Complexes of amino acids with a calix[6]arene carrying OCH_2CO_2R groups on the *endo* rim have been detected by MALDI spectroscopy.[191] Tropylium cation forms a complex with a calix[4]arene carrying four NHCONHR groups on the *exo* rim (**7.9a**).[192] Di-cationic alkylenediamines form complexes with ethers of *p*-*tert*-butylcalix[5]arene[193] and with a calix[5]arene-based heterotetratopic host.[194]

An interesting and surprising illustration of amine selectivity is shown by the pyridine-bridged calixarenes **7.26**, which form complexes not only with neutral molecules such as CH_3NO_2 but also with $CH_3NH_3^+ OTs^-$ (K_{assoc} 1970 M^{-1}) although not with its dimethyl-, trimethyl- or tetramethylammonium counterparts.[195] Selective transport of amino acid esters through a $CHCl_3$ liquid membrane can be effected with the calix[6]arene **7.8d** where tryptophane and phenylalanine esters travel 12–23 times faster than glycine and alanine esters.[196] An *exo* rim-capped calix[6]arene forms a complex with $PhNMe_3I$ in CD_2Cl_2 solution.[197] Double calix[4]arenes in which the two rings are directly connected[198] or are joined by a CH_2 group[199] or a $CH{=}CH$ group[200] all form complexes with N-methylpyridinium cation.

Guanidinium cation is very selectively complexed[201] by the triamide **7.27a** ($Y = CH_2CONEt_2$) with $K_{assoc} = 1.7 \times 10^7\ M^{-1}$, while the hexaamide **7.9a** ($n = 6$) binds it even more tightly ($K_{assoc} = 6 \times 10^8\ M^{-1}$) although less selectively. Guanidinium can also serve as a binding site in a calixarene. A striking example is the complex formed from the calixarene **7.27b** ($Y = Me$) and

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[189] S. Ahn, S.-K. Chang, T. Kim and J. W. Lee, *Chem. Lett.* **1995**, 297.

[190] F. Sansone, S. Barboso, A. Casnati, D. Sciotto and R. Ungaro, *Tetrahedron Lett.* **1999**, 40, 4741.

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[192] L. Frish, M. O. Vysotsky, S. E. Matthews, V. Böhmer and V. Cohen, *J. Chem. Soc. Perkin Trans. 2* **2002**, 88.

[193] D. Garozzo, G. Gattuso, F. H. Kohnke, P. Malvagna, A. Notti, S. Occhipinti, S. Pappalardo, M. F. Parisi and I. Pisagatti, *Tetrahedron Lett.* **2002**, 43, 7663.

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[198] P. Neri, A. Bottino, F. Cunsolo, M. Patelli and E. Gavuzzo, *Angew. Chem. Intl. Ed. Engl.* **1998**, 37, 166.

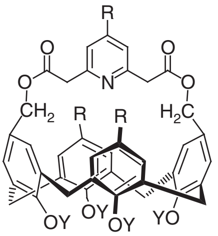
[199] K. Araki, K. Hisaichi, T. Kanai and S. Shinkai, *Chem. Lett.* **1995**, 569.

[200] P. Lhotak and S. Shinkai, *Tetrahedron Lett.* **1996**, 37, 645.

[201] A. Casnati, P. Minari, A. Pochini, R. Ungaro, W. F. Nijenhuis, F. de Jong and D. N. Reinhoudt, *Isr. J. Chem.* **1992**, 32, 79.

dioctanoyl-**L**-α-phosphatidylcholine (**7.28**). The guanidinium moiety provides a binding site for the phosphate group, and the calixarene cavity provides a binding site for the ammonium group[202] with a $K_{assoc} = 73{,}000\,M^{-1}$ in $CHCl_3$ solution.

An ammonium compound of biological importance is the cholinergic $2\text{-}O_2NC_6H_4CH(CH_3)OCH_2CH_2N(CH_3)_3{}^+$, which forms complexes with the *p*-sulfonatocalixarenes.[203] An interesting situation exists with a calix[5]arene carrying two *m*-carboxyphenyl moieties on the *exo* rim which binds two molecules of imidazole, the first with $K_{assoc} = 100\,M^{-1}$ and the second much more tightly with $K_{assoc} = 4000\,M^{-1}$. Molecular mechanics calculations suggest that one guest is bound between the two carboxylates solely by hydrogen bonding while the other is folded within the cavity and bound *via* the aromatic moieties of the calixarene both by hydrogen bonding and cation-π interaction. Alkyldiammonium ions form 2:1 (host to guest) complexes in $CHCl_3$/MeOH solution with a bis-calix[5]arene carrying $(CH_2)_3CH(CH_3)_2$ groups on eight of the *para* positions, the remaining two *para* positions being the points of attachment to a xylylene bridge (designated as an "exoditopic receptor").[204]



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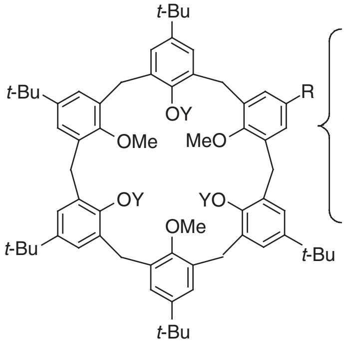

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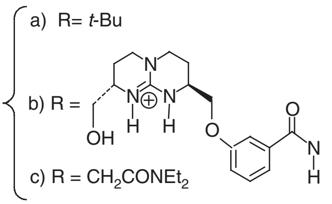

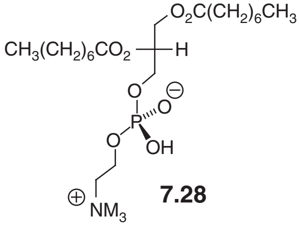

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The detailed structures of complexes in solution remain in many cases less certain than those in the solid state where X-ray crystallography usually reveals the orientation of the guest in the cavity of the host. In one study aimed at bridging this gap, the complex formed from the tetrasodium salt of *p*-sulfonatocalix[4]arene and trimethylanilinium chloride was studied in both the solution and the solid states.[205] In the solid state the X-ray crystal structure,

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[202] J. O. Magrans, A. R. Ortiz, M. A. Molins, P. H. P. Lobouille, J. Sánchez-Quesada, P. Prados, M. Pons, F. Gago and J. de Mendoza, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1712.

[203] A. Specht, J. Wirz, M. Goeldner, and L. Peng, *Synlett* **1999**, SI, 981; A. Specht, F. Ziaelli, P. Bernad, M. Goeldner and L. Peng. *Helv. Chim. Acta.* **2005**, 88, 2641.

[204] D. Garozzo, G. Gattusu, F. H. Kohnke, A. Notti, S. Pappalardo, M. F. Parisi, I. Pisagatti, A. J. P. White and D. J. Williams, *Org. Lett.* **2003**, 5, 4025.

[205] S. Shinkai, K. Araki, T. Matsuda, N. Nishiyhama, H. Ikeda, I. Takasu and M. Iwamoto, *J. Am. Chem. Soc.* **1990**, 112, 9053.

along with CP-MAS^{13}C NMR spectral data, show that the phenyl group resides within the cavity. In D_2O solution, however, the orientation of the guest is pD dependent, adopting the "phenyl-in-the cavity" orientation at pD = 0.4 but a mixture of this and the "trimethylammonium-in-the cavity" orientation at pD = 7.3. In another study involving the water soluble *p*-sulfonatocalix[5]arene the point was made that the large-scale self-assembly characteristic of the solid state can be an important influence, the dominance of crystal packing forces highlighting the problem of comparing solution and solid state data for complexes.[206]

7.6.2 Complexes with Neutral Molecules

7.6.2.1 Complexes in Aqueous Solution (Apndx A-2, p. 447)

An early study of the complexation of neutral molecules by water soluble calixarenes was carried out by the St Louis group[207] employing the *p*-diallylaminomethylcalix[*n*]arenes **7.6c** (*n* = 4–8) and the *p*-carboxyethylcalix[*n*]arenes **7.6d** (*n* = 4–8), the former soluble in dilute acid and the latter in dilute base. By means of a solid-liquid extraction technique[208] the K_{assoc} values were measured for a series of aromatic hydrocarbons of various dimensions, and a rough correlation between the dimensions of the calixarene basket and the aromatic guest was observed. For example, the calix[4]arenes (annulus dia. *ca.* 2Å) failed to show any complexation even with durene and naphthalene, which were the smaller of the guests tested; the calix[5]arenes (annulus 3×6.2 Å) and calix[6]arenes (annulus 3×7.6 Å) preferentially complexed naphthalene, anthracene and phenanthrene (K_{assoc} *ca.* $10^3\,M^{-1}$), which were the mid-sized guests; and the calix[7]arenes (annulus 3×8.6 Å) and calix[8]arenes (annulus 3×11.7 Å) formed the strongest complexes with the larger pyrene and perylene (K_{assoc} 10^3–$10^4\,M^{-1}$) but not with the even larger coronene and decacyclene.

The complexation properties of the *p*-sulfonatocalixarenes with neutral molecules have been investigated by Shinkai and coworkers.[209] Among the several guest molecules chosen for study was Phenol Blue (**7.25**), introduced many years ago as an indicator for solvent polarity.[210] It has an absorption at *ca.* 660 nm in water, shifting to shorter wavelengths in non-polar solvents (*e.g.* 552 nm in cyclohexane), this blue shift attributed to destabilization of the charge-separated excited state. Shinkai's group[159] discovered the surprising fact that Phenol Blue in the presence of **7.23a** (*n* = 6) shifts its absorption maximum to *longer* wavelength (685 nm), suggesting that the calixarene provides an

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[206] J. W. Steed, C. P. Johnson, C. L. Barnes, R. K. Juneja, J. L. Atwood, S. Reilly, R. L. Hollis, P. H. Smith and D. L. Clark, *J. Am. Chem. Soc.* **1995**, 117, 11426.

[207] C. D. Gutsche and I. Alam, *Tetrahedron* **1988**, 44, 4689.

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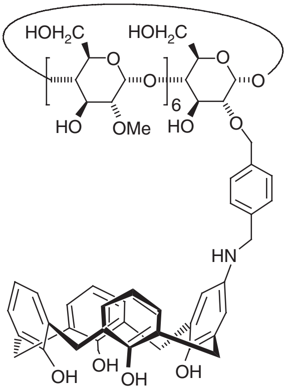
[209] S. Shinkai, S. Mori, H. Koreishi, T. Tsubaki and O. Manabe, *J. Am. Chem. Soc.* **1986**, 108, 2409; S. Shinkai, K. Araki and O. Manabe, *J. Chem. Soc. Chem. Commun.* **1988**, 187; S. Shinkai, H. Kawabata, T. Matsuda, H. Kasaguchi and O. Manabe, *Bull Chem. Soc. Jpn.* **1990**, 63, 1272; S. Shinkai, H. Kawabata, T. Arimura, T. Matsuda, H. Saroh and O. Manabe, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1073.

[210] L. G. S. Brooker and R. H. Sprague, *J. Am. Chem. Soc.* **1941**, 63, 3214.

environment even more polar than that of water. To rationalize this they postulated that the calixarene stabilizes the charge-separated excited state of Phenol Blue by forming an *endo*-calix complex (K_{assoc} 560 M^{-1}) in which electrostatic interactions with the sulfonate groups play a dominant role. The complexation of *p*-sulfonatocalix[4]arenes with smaller molecules has been studied more recently by Ungaro and coworkers,[211] who measured complexation constants for acetonitrile (15.8 M^{-1}), acetone (50 M^{-1}), methyl ethyl ketone (63 M^{-1}), ethanol (31.6 M^{-1}) and propanol (31.6 M^{-1}) with **7.23** ($n = 4$). The Parma group[212] also found that amino acids, including valine, leucine, phenylalanine, histidine and tryptophan, are complexed by this same host with K_{assoc} values ranging from 16 M^{-1} to 63 M^{-1}. A complex of *p*-sulfonatocalix[6]arene and the aromatic-like hydroxymethylferrocene in aqueous solution[213] has a $K_{assoc} = 3.7 \times 10^3\ M^{-1}$.

The water soluble β-cyclodextrin-calix[4]arene[214] **7.29** forms a complex[215] with 2-*p*-toluidino-6-naphthalenesulfonate with $K_{assoc} = 1.53 \times 10^5\ M^{-1}$. The cysteine-substituted calixarenes **7.30** ($n = 4$ and 6)[216] form complexes with 8-anilino-1-naphthalenesulfonate (ANS) ($K_{assoc} = 2.46 \times 10^3\ M^{-1}$ for $n = 4$; $1.82 \times 10^4\ M^{-1}$ for $n = 6$) and pyrene ($K_{assoc} = 8.5 \times 10^5\ M^{-1}$ for $n = 4$ and $4.12 \times 10^5\ M^{-1}$ for $n = 6$). Similarly, oxyethylated *p*-*tert*-butylcalix[4]arene (average chain length is 9 ethyleneoxy units; conformation is a mixture of cone and partial cone) forms a complex[217] with ANS ($K_{assoc} = 2 \times 10^4\ M^{-1}$) and pyrene ($K_{assoc} = 2.2 \times 10^4\ M^{-1}$).



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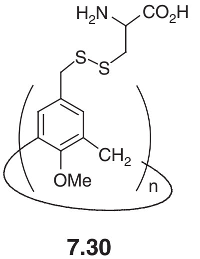

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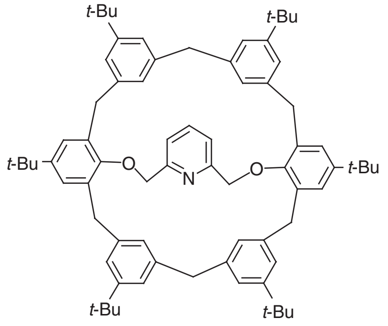

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[211] G. Arena, A. Contino, F. G. Gulino, A. M. D. Sciotto and R. Ungaro, *Tetrahedron Lett*. **2000**, 41, 9327.

[212] G. Arena, A. Contino, F. G. Gulino, A. Magri, F. Sansone, D. Sciotto and R. Ungaro, *Tetrahedron Lett*. **1999**, 40, 1597.

[213] L. Zhang, A. Macias, T. Lu, J. I. Gordon, G. W. Gokel and A. E. J. Kaifer, *J. Chem. Soc. Chem. Commun*. **1993**, 1017; L. Zhang, A. Macias, R. Isnin, T. Lu, G. W. Gokel and A. E. Kaifer, *J. Inclusion Phenom. Molec. Recognit. Chem*. **1994**, 19, 361.

[214] F. D'Alessandro, F. G. Gulino, G. Impellizzeri, G. Pappalardo, E. Rizzarelli, D. Sciotto and G. Vecchio, *Tetrahedron Lett*. **1994**, 35, 629.

[215] E. van Dienst, B. H. M. Snellink, L. von Piekartz, J. F. J. Engbersen and D. N. Reinhoudt, *J. Chem. Soc. Chem. Commun*. **1995**, 1151.

[216] T. Nagasaki, Y. Tajiri and S. Shinkai, *Recl. Trav. Chim. Pays Bas* **1993**, 112, 407.

[217] Y. Shi and Z. Yang, *J. Inclusion Phenom. Mol. Recognit. Chem*. **1994**, 18, 137.

7.6.2.2 Complexes in Non-aqueous Solution

The K_{assoc} values for complexes of calixarenes and neutral molecules in organic solvents are often very small. For example, the results of an early study of complexation between calixarenes and toluene in $CHCl_3$ solution,[218] using aromatic solvent induced shift (ASIS) measurements, indicated a K_{assoc} of *ca.* $1.1\,M^{-1}$. This has since been confirmed by a pulsed gradient spin echo (PGSE) NMR measurement.[66] The implications of an acidic C-H in the guest molecule are seen in a study of the interactions of a variety of $X\text{-}CH_2\text{-}Y$ molecules with the monomethyl ether of monodeoxy *p-tert*-butylcalix[4]arene.[219] The solvent CCl_4 was chosen on the premise that its size and lack of a C-H bond should prevent it from forming an *endo*-calix complex. The observed K_{assoc} constants for the guests ranged from $4.9\ M^{-1}$ for CH_2Cl_2 to $46\,M^{-1}$ for $ClCH_2CN$, the C-H acidity of the guest correlating well with the enthalpy of complexation. In a similar study a calix bi*s*-crown[19] showed a $K_{assoc} = 230\,M^{-1}$ with $MeNO_2$ in CCl_4 but only $27\,M^{-1}$ in $CDCl_3$. The pyridine-bridged calix[6]arene **7.31** forms a complex[220] with 4-nitrophenol in $CHCl_3$ with $K_{assoc} = 12\,M^{-1}$ but not with 1,6-dimethyl-4-nitrophenol or 1,3-dinitrophenol.

Complexation of urea, of special interest because of its medical implications, has been studied by Reinhoudt and coworkers.[221] By using the UO_2^{++} complex of the calix-salophen-crown ether **7.32** as the host where the electrophilic uranyl cation serves as a binding site for polar neutral compounds, they demonstrated that urea transport through a supported liquid membrane occurs with a flux of $18 \times 10^{-8}\,mol\,cm^{-2}\,h^{-1}$. When blood plasma containing urea was used as the source phase an even slightly higher flux of $20 \times 10^{-8}\,mol\,cm^{-2}\,h^{-1}$ was observed. Urea derivatives and DMSO are both complexed by a calix[4]arene carrying two ether groups and two OH groups on the *endo* rim along with a $PhNHCONHCH_2$ moiety on the *exo* rim.[222]

The complexation of C_{60} (*Apndx A-1, p. 173; A-2, p. 476;*), discussed above for the solid state, has also been extensively investigated in solution. First observed in aqueous solution with a water soluble calix[8]arene,[47,223] two years later a complex with C_{60} in toluene with $K_{assoc} = 110$ was demonstrated using a triply bridged calix[6]arene as the host molecule.[224] Then, the next year it was shown that an even tighter complex is formed with calix[5]arenes.[52] A survey of 28 calixarenes of various ring sizes corroborated the observation that the

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[218] C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.* **1985**, 107, 6059.

[219] K. Yoshimura and Y. Fukazawa, *Tetrahedron Lett.* **1996**, 37, 1435.

[220] H. Roos and U. Lüning, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2555.

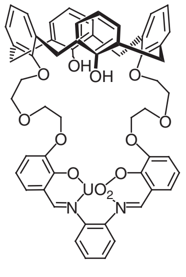
[221] W. F. Nijenhuis, A. R. van Doorn, A. M. Reichwein, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1991**, 113, 3607; W. F. van Straaten-Nijenhuis, A. R. van Doorn, A. M. Reichwein, F. de Jong and D. N. Reinhoudt, *J. Org. Chem.* **1993**, 58, 2265; A. M. Reichwein, W. Verboom, S. Harkema, A. L. Spek and D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans 2* **1994**, 1167.

[222] A. Arduini, E. Brindani, G. Giorgi, A. Pochini and A. Secchi, *Tetrahedron* **2003**, 59, 7587.

[223] For a determination of the K_{assoc} values for *p*-sulfonatocalix[5]arene and *p*-sulfonatothiacalix[4]arene *cf.* S. Kunsági-Máté, K. Szabó, I. Bitter, G. Nagy and L. Kollár, *Tetrahedron Lett.* **2003**, 45, 1387.

[224] K. Araki, K. Akao, A. Ikeda, T. Suzuki and S. Shinkai, *Tetrahedron Lett.* **1996**, 37, 73.

calix[5]arene system is particularly well suited for C_{60} complexation,[225] thus focusing much of the subsequent work on the cyclic pentamers. For example, Atwood and coworkers[226] found that *p*-benzylcalix[5]arene has a K_{assoc} of $2800\,M^{-1}$; Fukazawa and coworkers[52,227] showed that the presence of iodine atoms in some of the *p*-positions of calix[5]arene improves the complexation ability (*e.g.* the K_{assoc} in toluene is $2120\,M^{-1}$ for **7.2** (X = I) but only 588 for **7.2** (X = H). Perhaps surprisingly,[228] the octamethyl ether of *p*-*tert*-butylcalix[8]arene has a K_{assoc} of $2800\,M^{-1}$ for C_{60} and $4700\,M^{-1}$ for C_{70}, while the hexamethyl ether of *p*-*tert*-butylcalix[6]arene has a value of only $100\,M^{-1}$ for C_{60} yet a value of 2100 for C_{70}. Other simple calixarene systems have also been investigated, including the 2-naphthol-derived calix[4]arenes of Georghiou and coworkers,[229] homooxacalix[3]arenes[230] and azacalixarenes.[231] However, since the calix[5–8]arenes can surround only one hemisphere of a fullerene, it is to be expected that appropriately constructed bis-calixarenes capable of surrounding both hemispheres should probably be more effective. Although compound **7.33**, synthesized *via* a tandem Claisen rearrangement, shows only modest complexing ability ($K_{assoc} = 1300\,M^{-1}$),[232] some compounds with longer spanners[233] are far more impressive. Examples include **7.34** ($K_{assoc} = 76{,}000\,M^{-1}$ for C_{60} and $163{,}000\,M^{-1}$ for C_{70}) and its related compound with two C=C-C=C bridges[234] (K_{assoc} values increasing from $9700\,M^{-1}$ for C_{60} to $110{,}000\,M^{-1}$ for C_{78}).



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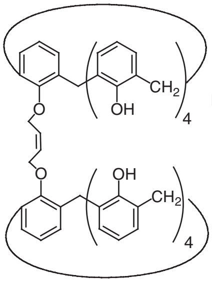

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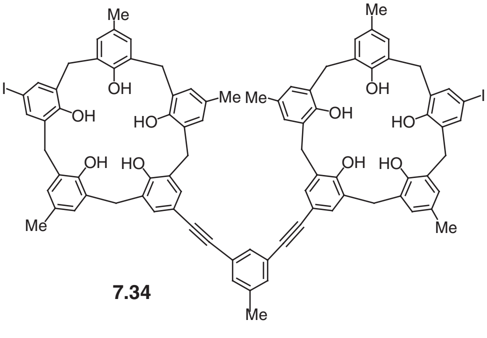

7.34

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[225] A. Ikeda, M. Yoshimura and S. Shinkai, *Tetrahedron Lett.* **1997**, 38, 2107.

[226] J. L. Atwood, L. J. Barbour, P. J. Nichols, C. L. Raston and A. Sandoval, *Chem. Eur J.* **1999**, 5, 990.

[227] T. Haino, M. Yanase and Y. Fukazawa, *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 997.

[228] For a recent determination of K_{assoc} values for several calix[4,5,6 and 8]arenes *cf.* S. Bhattacharya, S. K. Nayak, S. Chattopadhyay, M. Banerjee and A. K. Mukherjee, *J. Phys. Chem. B* **2003**, 107, 11830.

[229] P. E. Georghiou, S. Miyed and S. Chowdhury, *Tetrahedron Lett.* **1999**, 40, 611; P. E. Georghiou, A. H. Tran, S. S. Stroud and D. W. Thompson, *Tetrahedron* **2000**, 62, 2036 (containing a useful and cautionary study of the analytical techniques employed).

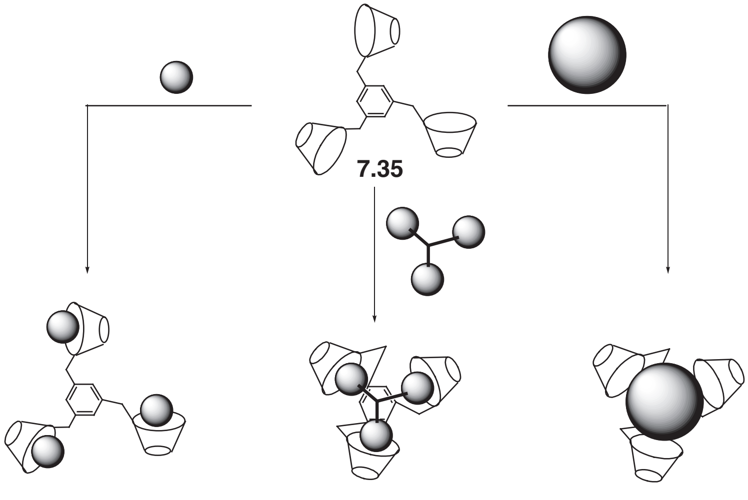
[230] K. Tsubaki, K. Tanaka, K. Fuji, K. Tanaka and T. Kinoshita, *Chem. Commun.* **1998**, 895; A. Ikeda, T. Haino, S. Shinkai, T. Akiyama and S. Yamada, *J. Am. Chem. Soc.* **2001**, 123, 4855.

[231] M.-X. Wang, X.-H. Zhang and Z.-Y. Zheng, *Angew. Chem. Int. Ed. Engl.* **2004**, 43, 838.

[232] J. Wang and C. D. Gutsche, *J. Am. Chem. Soc.* **1998**, 120, 12226.

[233] T. Haino, M. Yanase, C. Fukunaga and Y. Fukazawa, *Tetrahedron* **2006**, 62, 2025.

[234] T. Haino, C. Fukunaga and Y. Fukazawa, *Org. Lett.* **2006**, 8, 3545.



7.35

7.36 **7.37** **7.38**

Figure 7.2 Schematic representation of complexation of a tris-calix[5]arene with three types of guest molecules.

What might be called "pseudo bis-calixarenes" have been prepared from calixarenes carrying hydrogen bonding moieties (NHCONHR)[235] or metal-complexing (*e.g.* 1,10-phenanthroline)[236] moieties on the *exo* rim, which provide sites for bringing a pair of such molecules together to surround the fullerene. A host that can form a complex with fullerenes as well as with smaller molecules has been prepared by trimerization of a calix[5]arene carrying a HC≡CCO- group on the *exo* rim.[237] The resulting tris-calixarene **7.35** forms a 1:1 complex **7.38** with fullerene in which it is proposed that all three of the calixarenes surround the guest. With tris(aminomethyl)amine it similarly forms a 1:1 complex **7.37** with an amino moiety in each of the three cavities, but with N,N-dimethylethylenediamine it forms a 1:3 complex **7.36**, as illustrated in Figure 7.2. In a reversal of the usual order of things, a fullerene immobilized on a high-surface silica serves as the stationary phase in an HPLC column for the analysis of calixarene mixtures, with *p-tert*-butylcalix[8]arene showing a higher retention value than *p-tert*-butylcalix[6]arene.[238]

Joining the quest to find artificial receptors for large guests, Reinhoudt and coworkers[239] have shown that the calix[4]resorcarene-substituted calix[4]arene **7.39** forms complexes with steroids with $K_{assoc} = 90–950\,M^{-1}$ in $CDCl_3$. The

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[235] M. Yanase, T. Haino and Y. Fukazawa, *Tetrahedron Lett.* **1999**, 40, 2781.

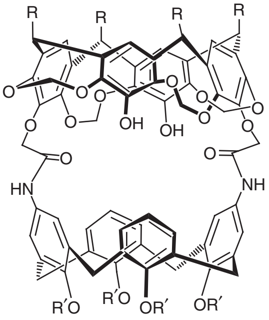
[236] T. Haino, H. Araki, Y. Yamanaka and Y. Fukazawa, *Tetrahedron Lett.* **2001**, 42, 3203.

[237] J. Wang and C. D. Gutsche, *J. Org. Chem.* **2002**, 67, 4423.

[238] F. Gasparrini, D. Misiti, F. Della Negra, M. Maggini, G. Scorrano and C. Villani, *Tetrahedron* **2001**, 57, 6997.

[239] I. Higler, P. Timmerman, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.* **1996**, 61, 5920.

complexation of sugars has been studied in some detail with the calix[4]resorcarenes but less so with the phenol-derived calixarenes. With the bis-boronic acid calixcrown **7.40** Shinkai and coworkers[240] detected 1:1 complexes with **D**-glucose, **D**-talose and **D**-allose but not with **D**-mannose, **D**-galactose, **D**-fructose or **D**-fucose. The conformationally semi-mobile calixarene was postulated to assume a cone conformation when complexed. Addition of Li^+, Na^+, Mg^{+2} and Ca^{+2} weakens the complexation, while addition of K^+, Rb^+ or Cs^+ strengthens it (cited as examples of negative and positive allosterism, respectively). A more elaborate host for carbohydrates is **7.41**, which contains an *exo* bridge comprising a pair of chiral dipeptide moieties with a phosphate group in between.[241] An interesting host for diketopiperazines is **7.42** in which four intermolecular hydrogen bonds hold the guest in the cavity of the host[242] ($K_{assoc} = 2400–19,000\ M^{-1}$).



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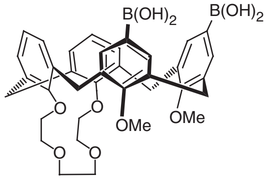

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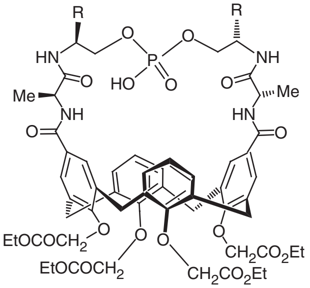

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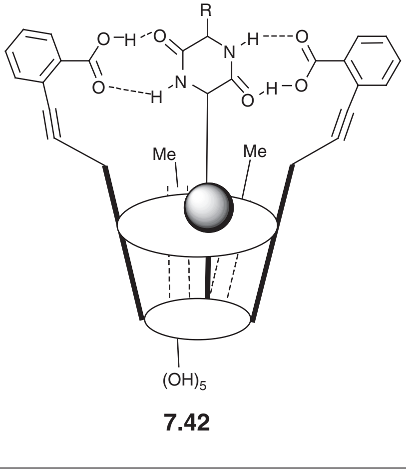

7.42

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[240] F. Ohseto, H. Yamamoto, H. Matsumoto and S. Shinkai, *Tetrahedron Lett*. **1995**, 36, 6911.

[241] M. Segura, B. Bricoli, A. Casnati, E. M. Muñoz, F. Sansone, R. Ungaro and C. Vicent, *J. Org. Chem*. **2003**, 68, 6296.

[242] T. Haino, K. Nitta and Y. Fukazawa, *Tetrahedron Lett*. **2000**, 41, 4139.

A useful feature of the calixarenes, discovered early in the present decade, is their ability to form complexes with nitrogen oxides (*Apndx A-1, p. 151*). In 2000 Kochi and coworkers reported[243] that nitric oxide (as NO^+) forms a strong complex in CD_2Cl_2 with the cation radical that is produced by the oxidation of the methyl ether of *p*-*tert*-butylcalix[4]arene (*e.g.* electrochemically or with F_3CCO_2H and dichlorodicyanobenzoquinone). An X-ray structure showed that the nitric oxide is sandwiched between a pair of parallel aromatic rings of the calixarene in the 1,3-alternate conformation, referred to as a "Venus flytrap". Two years later Rudkevich and coworkers[244] reported that the reaction of NO_2/N_2O_4 with the *n*-hexyl ether of *p*-*tert*-butylcalix[4]arene in chloroform in the presence of $SnCl_4$ produces an intense coloration resulting from the encapsulation of the nitrosonium cation NO^+, *e.g.* a complex analogous to the one made by Kochi but produced by the disproportionation of N_2O_4 to NO^+ and NO_3^-. In subsequent work[245] they fashioned a NO_2 sensor (made by attaching a functionalized calix[4]arene to silica gel) that distinguishes NO_2 from other gases such as H_2O, O_2, HCl, SO_x and NH_3. The ability of the complex to selectively nitrosate secondary amides[246] was demonstrated, and they showed that a bis-calix[4]arene with each ring in the 1,3-alternate conformation is also an effective host molecule.[247]

7.7 Gas Phase Complexes (*Apndx A-1, p. 151; C-1*)

Only a few studies involving host-guest interactions of calixarenes in the gas phase have been carried out. Such studies are of interest because, in the absence of solvent effects, only the intrinsic interactions between the host and guest are operative. Acid/base character can be radically different in the solution and gas phases as, for example, the reversal in the acidities that occurs with toluene *vs.* water, the former becoming the more acidic in the gas phase. Although initial attempts to observe gas phase complexes using fluorine-containing compounds as putative guests were unsuccessful,[248] such complexation has been demonstrated more recently with the triamide **7.27c**[201] and the calixarene esters **7.7**,[249] which form complexes with Na^+ and K^+; with the calixfurans (**2.48**), which complex ammonium ions;[250] with *p*-*tert*-butylcalix[4]arene, which complexes alkali and alkaline earth cations;[251] and with several *exo* rim-bridged

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[243] R. Rathore, S. V. Lindeman, K. S. S. P. Rao, D. Sun and J. K. Kochi, *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 2123; S. V. Rosokha and J. K. Kochi, *J. Am. Chem. Soc.* **2002**, 124, 5620; S. V. Rosokha, S. V. Lindeman, R. Rathore and J. K. Kochi, *J. Org. Chem.* **2003**, 68, 3947.

[244] G. V. Zyryanov, Y. Kang, S. P. Stampp and D. M. Rudkevich, *Chem. Commun.* **2002**, 2792.

[245] G. V. Zyryanov, Y. Kang and D. M. Rudkevich, *J. Am. Chem. Soc.* **2003**, 125, 2997.

[246] G. V. Zyryanov and D. M. Rudkevich, *Org. Lett.* **203**, 5, 1253.

[247] G. V. Zyryanov and D. M. Rudkevich, *J. Am. Chem. Soc.* **2004**, 126, 4264.

[248] T.-M. Liang, K. K. Laali, M. Cordero and C. Wesdemiotis, *J. Chem. Res. (S)* **1991**, 354.

[249] F. Inokuchi, Y. Shiomi, H. Kawabata, T. Sakaki and S. Shinkai, *Chem. Lett.* **1993**, 1595.

[250] R. M. Musau and A. Whiting, *J. Chem. Soc. Perkin Trans.1* **1994**, 2881.

[251] P. S. H. Wong, S. J. Yu and D. V. Dearden, *Inorg. Chim. Acta.* **1996**, 246, 259.

calix[4]arenes, which complex $MeCO_2R$, ROH, MeCOEt, MeCN and benzene.[252] The esters, ketones and nitriles guests are more tightly bound than are the alcohols or benzene, attributed to interactions between the acidic Me hydrogens of the guests and the π electrons of the calixarene cavity.

7.8 Theoretical Calculations (*Apndx A-2, p. 296, 334, 346; A-4, p. 11, 144; B-10*)

For discussions of (a) dynamic structures of host-guest systems *cf. Apndx A-2, p. 296*; (b) molecular dynamics of cation complexation and extraction *cf. Apndx A-2, p. 312; B-10, 11, 15*; (c) quantum mechanical calculations on alkali metal complexes *cf. Apndx A-2, p. 334*; (d) thermodynamics of calixarene-ion interactions *cf. Apndx A-2, p. 346*).

7.9 Templation

7.9.1 Templation in Calixarene Synthesis

The synthesis of calixarenes from *p-tert*-butylphenol was discussed in Chapter 2 in terms of kinetic control (cyclic octamer), thermodynamic control (cyclic tetramer) and template control (cyclic hexamer), the postulate in the last case being that appropriately sized cations (K^+ and Rb^+) provide a "nucleus" around which the cyclic array of aryl and methylene groups assemble. Although details are lacking, it seems likely that some sort of templation process must also be operative in the formation of the cyclic octamer in which eight *p-tert*-butylphenols and eight formaldehydes form a cyclic oligomer in such high yield.

7.9.2 Calixarenes as Templates

The $MeCOCH_2$ ether of *p-tert*-butylcalix[5]arene (**7.43**) has been cleverly employed by Sessler and coworkers[253] as a template for the synthesis of a calix[5]pyrrole (**7.44**) by treatment of **7.43** with pyrrole under acid-catalyzed conditions. Calixresorcarenes have been used as templates for the synthesis of large crown ethers by tethering the reactive moieties to a calix[4]resorcarene, effecting the cyclization of these moieties and then severing the cyclized product from its template.[254] The intramolecular joining of reactive moieties on the *exo* rim of a calix[4]arene is facilitated by the complexation of the calixarene with a second calixarene to form a heterodimer (*cf.* structure **6.16** in Chapter 6, p. 157).[255] The calixarene undergoing the joining reaction, in turn, serves as a

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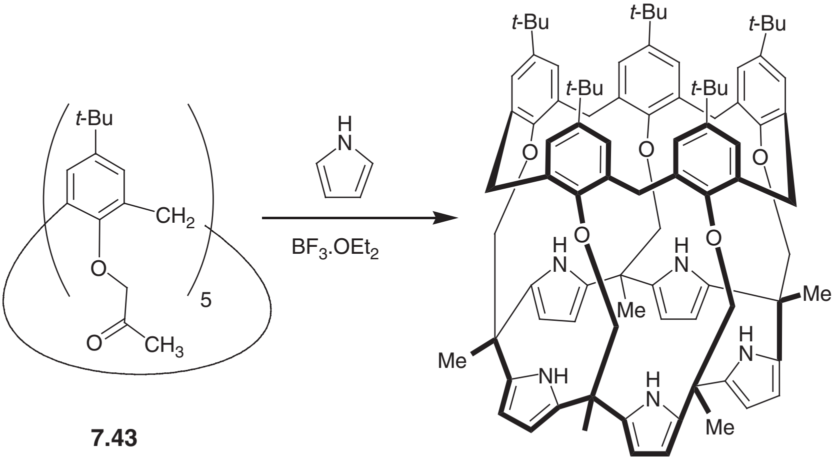
[252] A. Arduini, M. Cantoni, E. Graviani, A. Pochini, A. R. Secchi, R. Sicuri, R. Ungaro and M. Vicenti, *Tetrahedron* **1995**, 51, 599; R. Ungaro, A. Arduini, A. Casnati, A. Pochini and F. Ugozzoli, *Pure & Appl. Chem*. **1996**, 68, 1213.

[253] P. A. Gale, J. W. Genge, V. Král, M. A. McKervey, J. L. Sessler and A. Walker, *Tetrahedron Lett*. **1997**, 49, 8443.

[254] B. C. Gibb, *Chem. Eur. J.* **2003**, 9, 5180.

[255] M. O. Vysotsky, A. Bogdan, L. Wang and V. Böhmer, *Chem. Comm.* **2004**, 1268.

template for the construction of “huge macrocycles” by being severed from the newly formed ring.[256]



7.43

7.44

7.9.3 Templation in Conformational Phenomena

Numerous examples of the effect of guest cations, anions and molecules on the conformational behavior of calixarenes have been reported. One of the earliest studies was carried out by Shinkai and coworkers who showed that the rate of conformational inversion of *p*-sulfonatocalix[4]arene is strongly curtailed by the guest molecules phenyltrimethylammonium cation and adamantyltrimethylammonium cation.[257] The *tert*-butoxycarbonylmethyl ether of *p*-*tert*-butylcalix[6]arene adopts a 1,2,3-alternate conformation in the absence of metal cations[258] but changes to a cone conformer upon complexation with K^+. In more subtle fashion, complexation of Ag^+ by the 2-methylbutyl ether of calix[4]arene decreases the rate of C_{2v}-C_{2v} pinched cone conformational exchange.[259] The conformational outcome of derivatization of calix[4]arenes on the *endo* rim is often dependent on the particular base that is used, leading to the conclusion that a cone conformer is formed when the cation is Na^+, Ba^{2+} or Ca^{2+} which can act as templates, whereas the 1,3-alternate conformer is formed when the cation is Cs^+ which cannot act as a template (*Apndx B-21, p. 8949*). With *p*-*tert*-butylcalix[8]arene, on the other hand, complexation with Cs^+ has been shown to advantageously preorganize the system and facilitate the addition of a transannular bridge on the *endo* rim,[260] while K^+ and Rb^+

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[256] Y. Cao, L. Wang, M. Bolte, M. O. Vysotsky and V. Böhmer, *Chem. Comm.* **2005**, 3132.

[257] S. Shinkai, K. Araki, T. Matsuda and O. Manabe, *Bull. Chem. Soc. Jpn.* **1989**, 62, 3856.

[258] H. Otsuka, K. Araki and S. Shinkai, *Tetrahedron Lett.* **1993**, 34, 7275; *idem*, *Chem. Exp.* **1993**, 8, 479.

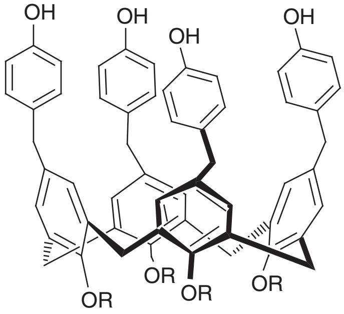
[259] A. Ikeda, H. J. Tsuzuki and S. Shinkai, *J. Chem. Soc. Perkin Trans. 2* **1994**, 2073.

[260] G. M. L. Consoli, F. Cunsolo, C. Geraci, E. Gavuzzo and P. Neri, *Tetrahedron Lett.* **2002**, 43, 1209.

serve this purpose better for *p*-*tert*-butylcalix[7]arene.[261] A good example of templation by a neutral molecule is the transformation of a bis-calixarene in which the calixarene moieties are *anti* to one another in the absence of a guest but change to a conformation in which they are *syn* to one another when complexed with C_{60} (*cf.* **7.3**, p. 169).[262]

7.9.4 Allosteric Effects

Allosterism might be defined as templation at a distance, a phenomenon well known with the enzymes. A simple calixarene example is seen in **7.45** where the strength with which the guest tetramethylammonium cation is held within the cavity is dependent on the particular anion that is complexed with the OH groups at the *exo* rim.[263] A more dramatic example is the bis-calixarene **7.46**, which forms the C_{60} complex **7.47** only in the presence of Cu^+, which organizes the system through chelation with the bipyridyl moieties.[264]



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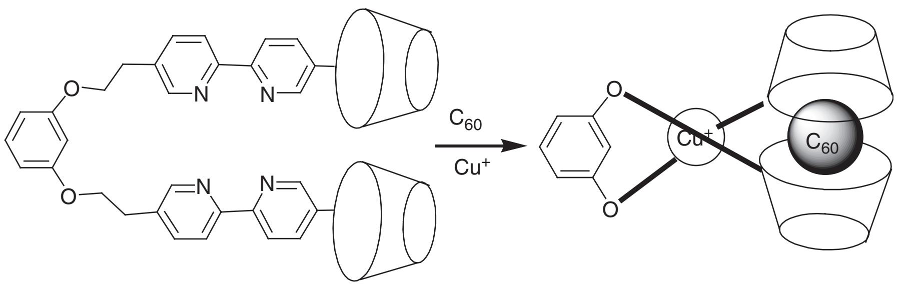

7.46 **7.47**

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[261] C. Gaeta, M. Martino and P. Neri, *Org. Lett*. **2006**, 8, 4409.

[262] J. Wang, S. G. Bodige, W. H. Watson and C. D. Gutsche, *J. Org. Chem*. **2000**, 65, 8260.

[263] A. Arduini, G. Giorgi, A. Pochini, A. Secchi and F. Ugozzoli, *J. Org. Chem*. **2001**, 66, 8302.

[264] T. Haino, Y. Yamanaka, H. Araki and Y. Fukazawa, *Chem. Comm*. **2002**, 402.

7.10 Concluding Remarks

Complexation phenomena, which have played an important role throughout the history of chemistry, came into particular prominence for organic chemists about 40 years ago with the advent of the cyclodextrins and the crown ethers. Complexation studies with the cyclodextrins have been directed primarily to non-ionic molecular guests, while those of the crown ethers have been mostly concerned with ionic guests. Calixarenes have added to the growing list of complex-forming macrocyclics, and they combine the features of both of these other two major players. As increasingly sophisticated calixarenes are becoming available through the efforts of the synthetic chemists, the list of new and interesting complexation agents continues to expand.

CHAPTER 8

Using the Baskets: Calixarenes in Action

"It is not enough that you should understand about applied science in order that your work may increase man's blessings. Concern for the man himself and his fate must always form the chief interest of all technical endeavors; concern for the great unsolved problems of the organization of labor and the distribution of goods in order that the creations of our mind shall be a blessing and not a curse to mankind. Never forget this in the midst of your diagrams and equations."

Albert Einstein, speech at the California Institute of Technology, February 16, 1931

Chemical research is sometimes more an art form than a rational science, particularly as practiced in academic environments. In contrast to the mission-orientation that motivates most industrial research, the chemist in the college or university laboratory enjoys the freedom to wander and wonder. Calixarene chemistry provides a curious and interesting blend of these two worlds of scientific research. Although the birth of calixarene chemistry occurred in an academic setting, it was the outcome of an investigation whose goal was to gain insight into the manufacture of Bakelite, one of the world's most profitable chemical commodities. Incorporated some years later, albeit unwittingly, into a different kind of industrial process by the Petrolite Corporation, it subsequently traversed the academic/industrial interface in St Louis to re-emerge as an integral part of a bioorganic chemistry research program. Elsewhere in the world calixarenes were simultaneously re-emerging as part of a polymer-oriented research program in Mainz and a crown ether-oriented research program in Parma. During the decade that followed, calixarene chemistry progressed steadily, if haltingly, in these academic laboratories, ultimately becoming visible to a wider community of researchers that included not only academics but also individuals and institutions with entrepreneurial aspirations. Chapters 2–7 of this book deal primarily, though not exclusively, with the art form aspects of calixarene chemistry, focusing on the methods that have been devised for synthesizing, contouring, functionalizing and filling these molecular baskets. In this last chapter attention is now turned to some of the ways in which the baskets have been, or might be, put to use. The ability of the calixarenes to spring into action and do something, whether it be truly useful in the utilitarian sense or just intriguing in an intellectual sense, provides the central focus.[1]

8.1 Calixarenes for Separations

8.1.1 Separations of Ions

The first patent explicitly describing a calixarene for a practical application was issued in 1984 and described the use of *p-tert*-butylcalix[8]arene for the recovery of cesium from nuclear wastes. Numerous papers relating to the complexation of cesium by modified calixarenes have since appeared (*cf*. Chapter 7), and significant research support has been provided for these studies by both the European and United States governments. Two of the hottest of the radioactive elements in nuclear wastes are ^{132}Cs and ^{90}Sr with half lives of 30 and 27.7 years, respectively. Efforts to find ways to remove them for disposal separately from the main body of the waste are being vigorously pursued. There are several excellent accounts of these efforts in which calixarenes are the complexing agents (*Apndx A-2, p. 642; A-3, p. 12, 26; C-2*). One of the many interesting approaches entails the use of a calix[4]arene-crown compound affixed to silica gel to provide a column capable of separating Cs^+ and K^+ from alkali metal ions.[2] Several other calixarenes for complexation of nuclides have also garnered attention, including (a) *p-tert*-butylcalix[4,6]arenes with OCH_2CO_2H groups on the *endo* rim for selective removal of actinium-125;[3] (b) CMPO-substituted *p-tert*-butylcalix[6,8]arenes (*Apndx A-3, p. 135*) for separation of actinides from lanthanides in radioactive wastes;[4] (c) *p-tert*-butylthiacalix[4]arene-derived hosts for Ra^{2+} extraction;[5] (d) a water soluble calix[4]arene-bis-benzocrown-6 for selective Cs^+ complexation in moderately salted media.[6]

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[1] A visionary review of supramolecular chemistry (J.-M. Lehn, *Chem. Soc. Rev.* **2007**, 36, 151), although not dealing with calixarenes *per se*, is recommended reading.

[2] G. Arena, A. Casnati, A. Contino, L. Mirone, D. Sciotto and R. Ungaro, *J. Chem. Soc. Chem. Commun.* **1996**, 2277.

[3] X. Chen, M. J. Darrell, R. Fisher and C. M. Wai, *Chem. Commun.* **1998**, 377.

[4] F. Sansone, M. Fontanella, A. Casnati, R. Ungaro, V. Böhmer, M. Saadioui, K. Liger and J.-F. Dozol, *Tetrahedron* **2006**, 62, 6749; for a review *cf.* H. H. Dam, D. N. Reinhoudt and W. Verboom, *Chem. Soc. Rev.* **2007**, 36, 367.

[5] F. W. B. van Leeuwen, H. Beijleveld, A. H. Velders, J. Huskens, W. Verboom and D. N. Reinhoudt, *Org. Biomol. Chem.* **2005**, 1993.

[6] S. Pellet-Rostaing, F. Chitry, J.-A. Spitz, A. Sorin, A. Favre-Réguillon and M. Lemaire, *Tetrahedron* **2003**, 59, 10313.

Another essential facet of the nuclear energy program concerns the procurement of uranium which currently is obtained exclusively from land-based sources. The intriguing prospect of recovering it from sea water was discussed in the previous chapter (*cf.* Section 7.3), and this continues to command attention, for example, through the use of flotation techniques with a C-undecylcalix[4]resorcarene.[7]

A hazard of considerable importance to life on earth is mercury, and calixarenes have entered this arena of environmental concern as well. Hosseini and coworkers[8] have shown that the mercaptocalix[4]arenes (for structures *cf.* **5.16f–g**, p 128) form strong complexes with Hg^{2+} and have a marked selectivity for this cation over Cd^{2+} and Pb^{2+}.

8.1.2 Separations of Molecules

The gases are among the smallest of molecules, and their complexation by calixarenes has been the focus of several studies. One of the most extensive has been carried out by Regen and coworkers, starting in 1988 with the concept of "perforated monolayers", which were defined as thin-film membranes bearing uniformly oriented and adjustable micropores; the calix[6]arenes were considered to be putative candidates.[9] This first paper was followed by a series of papers in which, perhaps serendipitously, poly[1-trimethylsilyl]-1-propyne was chosen as the porous membrane on which the calixarene was deposited. Among the calixarenes investigated were **8.1a**,[10] **8.1b**,[11] **8.1c**,[12] **8.1d**[13] and **8.1e**.[14] The monolayers prepared from these calixarenes showed varying degrees of permeation selectivity toward gas pairs such as He/N_2 and He/SbF_6, the film from **8.1d**, for example, having an He/SbF_6 value of 12.0. Although the original premise assumed that the "holes" through which the gasses pass are the calixarene annuli, it became uncertain as to whether this is actually the case or whether the holes are *between* the calixarene moieties in the monolayer assembly. Therefore, compounds **8.1c** and **8.1e** were chosen to maximize the probability of passage *through* the calixarene by blocking the interstitial spaces by intermolecular hydrogen bonding between the hydroxamic acid groups or by oxidation of the SH groups to covalently link the calixarenes and create a polymeric network.

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[7] Y. Koide, H. Terasaki, H. Sato, H. Shosenji and K. Yamada, *Bull. Chem. Soc. Jpn.* **1996**, 69, 785.

[8] P. Rao, O. Enger, E. Graf, M. W. Hosseini, A. De Cian and J. Fischer, *Eur. J. Chem.* **2000**, 1503.

[9] M. A. Markowitz, R. Bielski and S. L. Regen, *J. Am. Chem. Soc.* **1988**, 110, 7545.

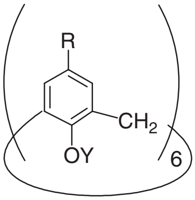
[10] M. A. Markowitz, V. Janout, D. G. Castner and S. L. Regen, *J. Am. Chem. Soc.* **1989**, 111, 8192.

[11] M. Conner, V. Janout and S. L. Regen, *J. Am. Chem. Soc.* **1993**, 115, 1178; P. Dedek, A. S. Webber, V. Janout, R. A. Handel and S. L. Regen, *Langmuir* **1995**, 10, 3943; R. A. Hendel, E. Nomura, V. Janout and S. L. Regen, *J. Am. Chem. Soc.* **1997**, 119, 6909.

[12] W. Lee, R. A. Handel, P. Dedek, V. Janout and S. L. Regen, *J. Am. Chem. Soc.* **1995**, 117, 6793, 10599.

[13] R. A. Hendel, V. Janout, W. Lee and S. L. Regen, *Langmuir* **1996**, 12, 5745.

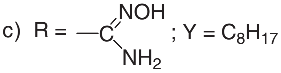
[14] X. Yan, V. Janout, J. T. Hsu and S. L. Regen, *J. Am. Chem. Soc.* **2002**, 124, 10962.



8.1

a) $R = HgO_2CCF_3$; $Y = C_4H_9$ to $C_{16}H_{33}$

b) $R = CONHCH_2CH_2SSCH_3$; $Y = C_8H_{17}$



c) $R = \text{—}C(=NOH)NH_2$; $Y = C_8H_{17}$

d) $R = CH_2CH_2CH_2B(OH)_2$; $Y = C_{16}H_{33}$

e) $R = CH_2SH$; $Y = C_{16}H_{33}$

In a somewhat different approach to the complexation of gases, the interstitial voids in crystals are a *desirable* feature. Crystal engineering has become an increasingly vigorous endeavor and has not escaped the attention of calixarene crystallographers like Atwood.[15] A simple, but representative, example is calix[4]arene, which forms 1:1 and 3:1 crystalline solvates with acetone. When the latter is heated it loses one molecule of acetone at 70 °C and the other two molecules at 222 °C to produce a crystal capable of incorporating guests such as CH_4 and Freons into its lattice.[16] *p-tert*-Butylcalix[4]arene crystals engineered in rather comparable fashion afford a material capable of absorbing N_2, O_2 and CO_2 but not H_2, and it was shown that when the crystal is exposed to a H_2/CO_2 mixture most of the CO_2 is removed to yield a hydrogen-rich gas. It is the *absorption* of H_2, however, that is of the greater interest, given its putative role as an energy source in the future, and this remains one of the major goals of crystal engineering.

8.2 Calixarenes as Sensors (*ref. 17; Apndx A-2, p. 627*)

The design of sensors to monitor the activity of chemical and biochemical species in various environments is an important and growing field of science that requires the interaction of a variety of disciplines – from solution chemistry to solid state electronics. For constructing a chemically based sensor the task is first to design a system that is sensitive specifically to the species being monitored and then to devise a way for transducing the chemical response, which is at the molecular level, to an electrical or optical signal at the macroscopically observable and measurable level. Calixarenes have been employed in such devices in a variety of interesting ways.

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[15] For a review *cf.* S. J. Dalgarno, P. K. Thallapally, L. J. Barbour and J. L. Atwood, *Chem. Soc. Rev.* **2007**, 36, 236. For additional information on the crystal engineering of calixarenes *cf. Apndx A-1, p. 335.*

[16] J. L. Atwood, L. J. Barbour and A. Jerga, *Science* **2002**, 296, 2367.

[17] D. Diamond and M. A. McKervey, *Chem. Soc. Rev.* **1996**, 25, 15.

8.2.1 Ion- and Molecule-selective Electrodes

Electrodes selective for H^+ (*i.e.* pH meters) have been known for many years. Electrodes selective for other ions, however, are a more recent arrival, their entrance due in large part to the work of Wilhelm Simon and coworkers.[18] Because of the biological importance of such sensors, particularly for blood sampling, the alkali and alkaline earth cations have been given major attention in developing these electrodes, the first calixarene-based ion selective electrode[19] being designed for Na^+. McKervey and Diamond and their coworkers have been especially active in this field and have devised ion selective electrodes for Na^+ using compounds such as the tetraesters **8.2a**.[20,21] Particularly effective are the CH_2CO_2Me ether **8.2a** ($R = t$-Bu, R'=Me)[22] and the partial cone conformer of the calix[4]crown compound **8.3**, which shows a Na^+/K^+ selectivity[23] of 10^5. An ion selective electrode based on *p-tert*-butylcalix[4]arene-crown-5[24] is selective for K^+. Electrodes based on the CH_2CO_2Et ether of *p-tert*-butylcalix[6]arene[25] and the diisopropyl ether of calix[4]arene-crown-6 in the 1,3-alternate conformation[26] are selective for Cs^+. Electrodes based on the diphenylphosphorylethyl ether of *p-tert*-butylcalix[4]arene[27] are selective for Ca^{2+}.

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[18] For a review *cf.* H. M. Widner, in *Analytical Methods and Instrumentation* **1993**, 1, 3.

[19] D. Diamond, *Anal. Chem. Symp. Ser.* **1986**, 25, 155; D. Diamond and G. Svehla, *Trends Anal. Chem.* **1987**, 6, 46.

[20] D. Diamond, G, Svehla, E. M. Seward and M. A. McKervey, *Anal. Chim. Acta* **1988**, 204, 223; A. Cadogan, Z. Gao, A. Lewenstam and A. Ivaska, *Anal. Chem.* **1992**, 64, 2496; K. M. O'Conner, M. Cherry, G. Svehla, S. J. Harris and M. A. McKervey, *Talanta* **1994**, 41, 1207. Similar esters have also been studied by K. Kimura, T. Matsuo and T. Shono, *Chem. Lett.* **1988**, 615; Y. Shibutani, H. Yoshinaga, K. Yakabe, T. Shono and M. J. Tanaka, *Inclusion Phenom. Molec. Recognit. Chem.* **1994**, 19, 333. The particular efficacy of the esters has been affirmed by a study by T. Sakaki, H. Takaaki, G. Deng, H. Kawabata, Y. Kawahara and S. Shinkai, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, 14, 285.

[21] T. Grady, A. Cadogan, T. McKittrick, S. J. Harris, D. Diamond and M. A. McKervey, *Analyt. Chim. Acta* **1996**, 336, 1.

[22] A. Cadogan, D. Diamond, M. R. Smyth, M. Deasy, M. A. McKervey, E. M. Seward and S. J. Harris, *Analyst* **1989**, 114, 1551; D. Diamond, G. Svehla, E. M. Seward and M. A. McKervey, *Anal. Chim. Acta.* **1988**, 204, 223; K. Cunningham, G. Svehla, S. J. Harris and M. A. McKervey, *Anal. Proceedings* **1991**, 28, 294.

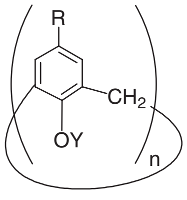
[23] H. Yamamoto and S. Shinkai, *Chem. Lett.* **1994**, 1115.

[24] Z. Brzózka, B. Lammerink, D. N. Reinhoudt, E. Ghidini and R. Ungaro, *J. Chem. Soc. Perkin Trans 2* **1993**, 1037.

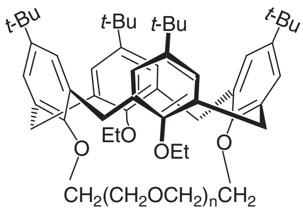
[25] A. Cadogan, D. Diamond, M. R. Smyth, G. Svehla, M. A. McKervey, E. M. Seward and S. J. Harris, *Analyst* **1990**, 115, 1207.

[26] C. Bocchi, M. Careri, A. Casnati and G. Mori, *Analyt. Chem.* **1995**, 67, 4234.

[27] T. McKittrick, D. Diamond, D. J. Marrs, P. O'Hagan and M. A. McKervey, *Talanta* **1996**, 43, 1145.



8.2



8.3

a) R = H or tert-Bu; Y = CH_2CO_2R'; n = 4)

b) R = tert-Bu; Y = CH_2CO_2-Et; n = 6

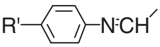
c) R = H; Y = $CH_2CO_2C_{19}H_{21}$; n = 6

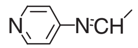
d) R = t-Bu, Y = $CH_2Ch_2S\overset{\overset{S}{\|}}{C}NEt_2$; n = 4

e) R = t-Bu; Y = $CH_2CH_2OCH_2\overset{\overset{S}{\|}}{C}NMe_2$; n = 4

f) R = t-Bu; Y = $CH_2\overset{\overset{S}{\|}}{C}NMe_2$; n = 4

g) R = $NMe_3{}^+Cl^-$; Y = Me

h) R =  ;Y = Me; n = 4

i) R =  ;Y = Me; n = 4

Ion selective electrodes for a variety of cations other than the alkali metal cations have also been designed. Calix[4]arenes carrying four $OCH_2CO_2CHN(CH_2)_3C{=}O$, $CH_2C(S)NEt_2$ or $CH_2CO_2CH_2CH_2SMe$ groups on the *endo* rim are useful for sensing Ag^+, Cu^{2+} and Pb^{2+} cations,[28,29] the last of these three compounds showing a modest 14.5 selectivity in favor of Ag^+ over Na^+. A number of $OP(S)(OEt)_2$ substituted *p*-*tert*-butylcalix[6]arenes show selectivity for Pb^{2+} over Cd^{2+}, the best being the A,C-disubstituted compound.[30] By the use of $C_5H_5N^+CH_2CONHNH_2$ (Girard's reagent) as the cationic species, a formaldehyde-selective electrode has been designed.[31] Carbon paste electrodes have been prepared from a calixarene polymer and shown to be applicable to voltammetric methods of analysis.[32]

Anion selective electrodes are less well developed than their cation counterparts, the first calixarene-based entry into this field being the calix[4]arene with two cobalticinium groups on the *exo* rim, which shows some ability to recognize

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[28] K. M. O'Conner, G. Svehla, S. J. Harris and M. A. McKervey, *Talanta* **1992**, 39, 1549; *idem*, *Anal. Proceedings* **1993**, 30, 137.

[29] E. Malinowska, Z. Brzózka, K. Kasiura, R. J. M. Egberink and D. N. Reinhoudt, *Analytica Chim. Acta* **1994**, 298, 245.

[30] W. Wroblewski, Z. Brzózka, R. G. Janssen, W. Verboom and D. N. Reinhoudt, *New J. Chem.* **1996**, 20, 419.

[31] W. H. Chan and R. Yuan, *Analyst* **1995**, 120, 1055.

[32] D. W. M. Arrigan, G. Svehla, S. J. Harris and M. A. McKervey, *Anal. Proceedings* **1992**, 29, 27; *idem*, *Electroanalysis* **1994**, 6, 97.

adipate anions.[33] The tetrapropyl ether of calix[4]arene carrying four ferrocenylureido moieties on the *exo* rim shows potential as an electrochemical sensor for anions, especially dihydrogen phosphate.[34] *p-tert*-Butylcalix[4]arenes with N-substituted ureidobutyl moieties on the *endo* rim have been used as anion-binding receptors in polyether electrolytes in connection with ionic transport in lithium cells.[35] A calix[4]arene bridged on the *endo* rim with a bipyridyl residue forms a complex with Ru^{2+} accompanied by two external bipyridyl molecules that selectively (electrochemically) senses $H_2PO_4^-$ in the presence of a 10-fold excess of HSO_4^- and Cl^- (the cation is tetrabutylammonium).[36]

Electrodes selective for a variety of molecules have been devised, such as the esters **8.1a,b**, which act as the host for the hydrazone generated *in situ* from heptanal and Girard's reagent-P. It is claimed that as little as 3.4 mg of heptanal can be detected.[37] In comparable fashion glucose can be determined with a calix[6]arene-containing ion sensitive electrode by *in situ* derivatization with lipophilic Girard's-P reagent.[38] Other examples include the use of various calix[8]arenes for sensing ammonium and pyridinium surfactants[39] as well as the calix[6]arene **8.1c** for discriminating among primary amines carrying R groups of various shapes and sizes.[40] Carboxylic acids have been determined by *in situ* conversion to amines *via* the Schmidt reaction followed by detection with a calix[6]arene chromophore.[41]

8.2.2 Field Effect Transistors[42]

Field effect transistors (FETS) combine the ion selective electrode with solid state technology and are referred to as CHEMFETs (chemically modified field effect transistors) and MEMFETs (membrane modified field effect transistors) or, more specifically, ISFETs (ion selective field effect transistors). They consist of a source region and a drain region embedded on a p-type silicon substrate and separated by a gate region, the conductance through which is sensitive to the surrounding environment.[43] Thus, the deposition on the gate region of a film containing an ion

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[33] P. D. Beer, M. G. B. Drew, C. Hazlewood, D. Hesek, J. Hodacova and S E. Stokes, *J. Chem. Soc. Chem. Commun*. **1993**, 229.

[34] A. J. Evans, S. E. Matthews, A. R. Cowley and P. D. Beer, *Dalton Trans*. **2003**, 4644.

[35] A. Blazejezyk, M. Szczupak, W. Wieczorek, P. Cmoch, B. G. Appetecchi, B. Scrosati, R. Kovarsky, D. Golodnitsky and E. Peled, *Chem. Mater*. **2005**, 17, 1535.

[36] F. Szemes, D. Hesek, Z. Chen, S. W. Dent, M. G. B. Drew, A. J. Goulden, A. R. Grieve, R. J. Mortimer, T. Wear, J. S. Weightman and P. D. Beer, *Inorg. Chem*. **1996**, 35, 5868; P. D. Beer, Z. Chen, A. J. Goulden, A. Graydon, S. E. Stokes and T. Tear, *J. Chem. Soc. Chem. Commun*. **1993**, 1834; P. D. Beer, Z. Chen, A. Goulden, A. Grieve, D. Hesek, F. Szemes and T. Wear, *ibid*. **1994**, 1269.

[37] W. H. Chan, P. X. Cai and X. H. Gu, *Analyst (Cambridge, UK)* **1994**, 119, 1853.

[38] W. H. Chan, Y. L. Wong-Leung, T. F. Lai and R. Yuan, *Analyt. Lett*. **1997**, 30, 45.

[39] N. V. Shvedene, T. V. Shishkanova, I. V. Pietnev, N. V. Belchenko, V. V. Kovalev, A. K. Rozov and E. A. Shokova, *Analyt. Lett*. **1996**, 29, 843; N. V. Shvedene, M. Y. Nemilova, V. V. Kovalev, E. A. Shokova, A. K. Rozov and I. V. Pletnev, *Sensors and Actuators B* **1995**, 26–27, 372.

[40] K. Odashima, K. Yagi, K. Tohda and Y. Umezawa, *Anal. Chem*. **1993**, 65, 1074.

[41] A. W. M. Lee, W. H. Chan and Y. S. Lam, *Analyst* **1995**, 120, 2841.

[42] For a review *cf*. D. N. Reinhoudt, *Sens. Actuators B6* **1992**, 179; *idem*, *Recl. Trav. Chim. Pays Bas* **1996**, *115*, 109.

[43] For a good picture *cf*. R. B. Chaabane, M. Gamoudi, G. Guillaud, C. Jouve, R. Lamartine, A. Bouazizi and H. Maaref, *Sensors and Actuators* **1996**, B31, 41.

selective compound renders the conductance between the source and drain regions ion selective, allowing this chemical response to be transduced into an electrical response. The various types of calixarenes that are effective for ion selective electrodes (*vide supra*) act in a comparable fashion in ISFETS, as first shown by Reinhoudt and coworkers,[44] who used the conformationally flexible dimethyl ether of calix[4]arene-crown-5 and its conformationally fixed diethyl ether analog in the partial cone conformation[24] for K^+ determination. This is but one of the many contributions David Reinhoudt has made to calixarene chemistry, and previous chapters have included numerous references to his work. He is a native of the Netherlands, where he was born in 1942 and schooled through to the Doctorate in 1969 from the Delft University of Technology, studying under the direction of Professor H. C. Beijerman. After a 5-year association with the Shell Co., where he started a crown ether research program, he joined the University of Twente, reaching the level of full professor in 1978. He is the scientific director of the MESA+ Research Institute and the chairman of the Board of NanoNed, the Dutch Network for Nanotechnology.

David Reinhoudt

The dipropyl ether of calix[4]arene-crown-6 in the 1,3-alternate conformation is useful for Cs^+ determination by CHEMFETS.[45] Ion selective CHEMFETs for various other ions including Cu^{2+} with **8.2d**, Cd^{2+} with **8.2e** and Pb^{2+} with **8.2f** have been reported,[46] but the Reinhoudt workers found that better results are obtained if the ionophore is covalently bound to the polysiloxane membrane that covers the gate region.[47] A similar approach is reported by

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[44] E. J. R. Sudhölter, P. D. van der Waal, M. Skowronska-Ptasinska, A. van den Berg, P. Bergveld and D. N. Reinhoudt, *Recl. Trav. Chim. Pays-Bas* **1990**, 109, 222.

[45] R. J. W. Lugtenberg, Z. Brzózka, A. Casnati, R. Ungaro, J. F. J. Engbersen and D. N. Reinhoudt, *Analytica Chimica Acta* **1995**, 310, 263.

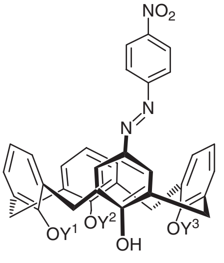
[46] P. L. H. M. Cobben, R. J. M. Egberink, J. G. Bomer, P. Bergveld, W. Verboom and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1992**, 114, 10573.

[47] J. A. J. Brunink, R. J. W. Lugtenberg, Z. Brzózka, J. F. J. Engbersen and D. N. Reinhoudt, *J. Electroanal. Chem.* **1994**, 378, 185; R. F. Cacciapaglia, A. R. van Doorn, L. Mandolini and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1992**, 114, 2611.

Kimura and coworkers[48] using calix[4]arenes carrying oligosiloxane moieties in silicone rubber membranes. A guanidinium-selective CHEMFET employs a calix[6]arene carrying three OCH_2CONEt_2 groups on the *endo* rim as the ionophore embedded in a PVC membrane containing potassium tetrakis(4-chlorophenyl)borate, which acts as a cation exchanger to preferentially extract the more liphophilic guanidinium cation into the membrane.[49]

8.2.3 Chromogenic and Fluorescent Sensors (*Apndx A-1, p. 311; A-2, p. 583, 598*)

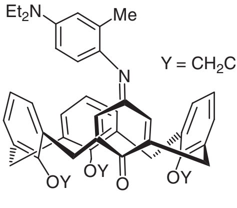
Substances that change color or change fluorescence in response to a change in their environment are an integral part of nature and have been put to human use since antiquity, a modern example of long standing being the application of indicator compounds to measure acidity and basicity. In recent years increasing attention has been paid to such chromogenic molecules, and a number of calixarene-based systems have been studied. One of the simplest is *p*-sulfonatocalix[4]arene, which forms a colored complex with Ce^{3+} and, thus, is specific for this ion among the rare earths.[50] Another early example employs the calix[4]arene **8.4a** carrying a *p*-nitrophenylazo chromophore, which changes its absorption when the Li^+ complex forms.[51] A related example, **8.4b** carrying a crown-4 moiety, shows a Na^+/K^+ selectivity of >1260, making it useful for optical sensing systems.[52] In fact, solutions of **8.4b** in soda-glass flasks rapidly turn deep green, which is the color of the Na^+ complex. Indoaniline-derived calixarenes **8.5** carrying OCH_2CO_2Et ether groups[53] show a bathochromic shift upon complexation with Ca^{2+}. The tri-*n*-propyl and *n*-hexyl ethers of *p*-*tert*-butylcalix[4]arene anchored *via* the fourth oxygen to a polymer support reversibly trap NO_2/N_2O_4 with a change in color to deep purple.[54]



8.4

a) $Y^{1\text{-}3} = CH_2CO_2Et$

b) $Y^{1,3} = CH_2(CH_2OCH_2)_2CH_2O$; $Y^2 = Et$



$Y = CH_2CO_2Et$

8.5

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[48] K. Kimura, T. Matsuba, Y. Tsujimura and M. Yokoyama, *Anal. Chem.* **1992**, 64, 2508; Y. Tsujimura, M. Yokoyama and K. Kimura, *Electroanalysis* **1993**, 5, 893; K. Kimura, Y. Tsujimura and M. Yodoyama, *Pure & Appl. Chem.* **1995**, 67, 1085.

[49] F. J. B. Kremer, G. Chiosis, J. F. J. Engbersen and D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans 2* **1994**, 677.

[50] I. Yoshida, N. Yamamoto, F. Sagara, K. Ueno, D. Ishii and S. Shinkai, *Chem. Lett.* **1991**, 2105.

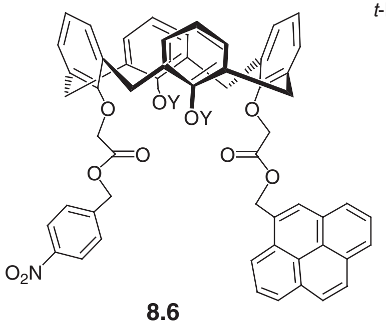
[51] H. Shimizu, K. Iwamoto, K. Fujimoto and S. Shinkai, *Chem. Lett.* **1991**, 2147.

[52] H. Yamamoto, K. Ueda, K. R. A. Samankumara Sandanayake and S. Shinkai, *Chem. Lett.* **1995**, 497.

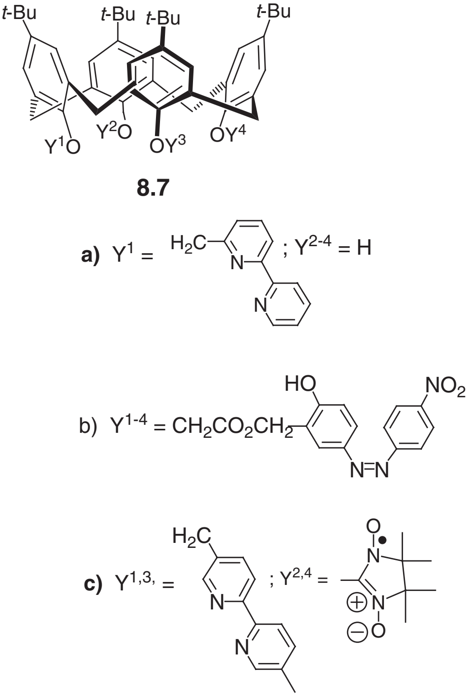
[53] Y. Kubo, S. Tokita, Y. Kojima, Y. T. Osano and T. Matsuzaki, *J. Org. Chem.* **1996**, 61, 3758.

[54] V. Kang and D. M. Rudkevich, *Tetrahedron* **2004**, 60, 11219.

Ion sensitive detectors that take advantage of the great sensitivity of fluorescence have been made by affixing moieties such as anthracene,[55] pyrene[56] and bisthiazolyl[57] to the *endo* rim of calix[4]arenes. In **8.6** the pyrene fluorescence is quenched in the absence of a metal ion but active in its presence. Employing the fluorescence properties of Ru^{2+}, a pH sensor has been devised from **8.7a** that forms a complex with Ru^{2+} in which the fluorescence depends on whether the calixarene is in the phenol or phenolate form.[58] Calixarene **8.31e**, characterized as an on/off molecular switch[59] controlled by pH, exhibits different fluorescent behaviors with Cu^{2+} and Zn^{2+}. The fluorescent intensity of a calix[4] crown-5 carrying pyrenyl groups on the *endo* rim is selectively quenched[60] by Pb^{2+}. In a further elaboration of this receptor two *p*-nitrophenylazo groups were added to the *exo* rim to create a system in which complexation causes a hypsochromic shift in the UV spectrum.[61]



8.6



8.7

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[55] C. Pérez-Jiménez, S. J. Harris and D. Diamond, *J. Chem. Soc. Chem. Commun.* **1993**, 480; *idem*, *J. Mater. Chem.* **1994**, 4, 145.

[56] I. Aoki, T. Sakaki, S. Tsutsui and S. Shinkai, *Tetrahedron Lett.* **1992**, 33, 89; I. Aoki, T. Sakaki and S. Shinkai, *J. Chem. Soc. Chem. Commun.* **1992**, 730; T. Jin, K. Ichikawa and T. Koyama, *J. Chem. Soc. Chem. Commun.* **1992**, 499.

[57] S. Pellet-Rostaing, J.-B. Regnouf-de-Vains and R. Lamartine, *Tetrahedron Lett.* **1996**, 37, 5889.

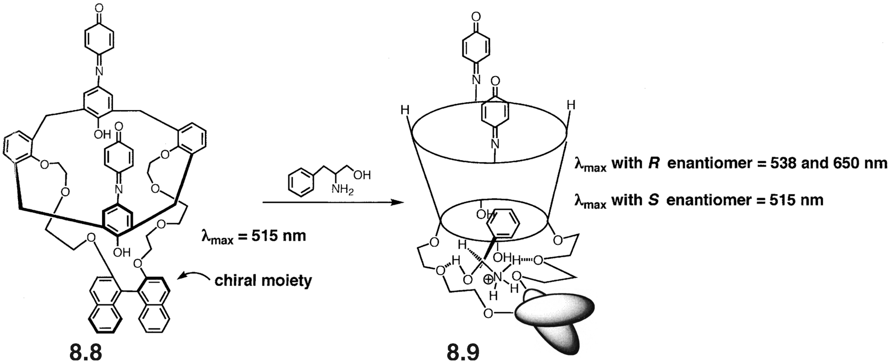
[58] R. Grigg, J. M. Holmes, S. K. Jones and W. D. J. Amilaprasadh Norbert, *J. Chem. Soc. Chem. Commun.* **1994**, 185.

[59] Y.-D. Cao, Q.-Y. Zheng, C.-F. Chen and Z.-T. Huang, *Tetrahedron Lett.* **2003**, 44, 4751.

[60] S. H. Lee, J. Y. Kim, S. K. Kim, J. H. Lee and J. S. Kim, *Tetrahedron* **2004**, 60, 5171.

[61] S. H. Lee, S. K. Kim, J. H. Bok, S. H. Lee, J. Yoon, K. Lee and J. S. Kim, *Tetrahedron Lett.* **2005**, 46, 8163.

In addition to ions, molecules have also been the target of calixarene-based chromogenic and fluorescent sensors. A particularly intriguing example is the chiral calixarene **8.8**, which experiences a148 Å bathochromic shift upon complexation with butyl amines (*t*-Bu $\gg$ *sec*-Bu > *i*-Bu > *n*-Bu) and which produces different colored complexes **8.9** with the **R** and **S** enantiomers of 1-phenylethylamine.[62]



8.8 **8.9**

Another compound capable of discriminating between the enantiomers of 1-phenylethylamine and norephedrine on the basis of fluorescence quenching is a chiral calix[4]arene carrying (S)-di-2-naphthylprolinol moieties on the lower rim.[63] A sensor for acetylcholine (**8.10**) is based on the ability of this molecule to displace **8.11** from its complex with *p*-sulfonato-calix[6]arene, **8.11** being non-fluorescent in the complex but fluorescent in the free state.[64] Test strips containing **8.7b** change from yellow to red in the presence of trimethylamine, providing a means for detecting this material in concentrations as low as 20 parts/billion.[65]

8.2.4 Nonlinear Optical Compounds

Molecules exhibiting nonlinear optical (NLO) behavior are of interest for a variety of applications, including frequency doubling of laser light, electro-optical switching devices and optical communication. Calixarene-derived compounds with this property[66] were introduced by Reinhoudt and coworkers with a variety of calix[4]arenes **8.12a,b,c** carrying nitro-containing moieties on the

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[62] Y. Kubo, S. Maeda, S. Tokita and M. Kubo, *Nature* **1996**, 382, 522.

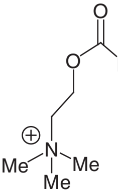
[63] T. Grady, S. J. Harris, M. R. Smyth and D. Diamond, *Anal. Chem.* **1996**, 68, 3775.

[64] K. N. Koh, K. Araki, A. Ikeda, H. Otsuka and S. Shinkai, *J. Am. Chem. Soc.* **1996**, 118, 755; A similar example using a calix[4]resorcarene is reported by M. Inouye, K. Hashimoto and K. Isagawa, *J. Am. Chem. Soc.* **1994**, 116, 5517. The binding of acetylcholine to *p*-sulfonatocalix[4 and 6]arenes has also been reported, with X-ray structures, by J.-M. Lehn, R. Meric, J.-P. Vigneron, M. Cesario, J. Guilhem, C. Pascard, Z. Asfari and J. Vicens, *Supramol. Chem.* **1995**, 5, 97.

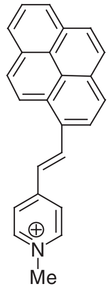
[65] M. McCarrick, S. J. Harris and D. Diamond, *J. Mater. Chem.* **1994**, 4, 217.

[66] For an evaluation of optical nonlinearities in calixarenes *cf.* J. O. Morley and M. Naji, *J. Phys. Chem. A* **1997**, 101, 2681.

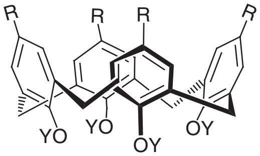
exo rim.[67] To study the macroscopic NLO properties of these materials, oriented thin films were prepared by spin-casting followed by poling by a strong DC electric field. For example, **8.12a** (Y = Pr), whose cone conformation possesses four non-conjugated D-p-A dipoles oriented in the same direction, forms a polymethacrylate film with good optical properties and high stability. The closely related compounds **8.12a** (Y = $C_{10}H_{21}$ to $C_{18}H_{35}$) have been studied in Langmuir–Blodgett monolayers,[68] and **8.12a** (Y = Pr) deposited on Si_3N_4 or SiON has been tested as a waveguide.[69] An even more tightly bound NLO monolayer is produced by the reaction of **8.12d** (Y = CH_2CH_2OEt) with a silica disc treated with $ClCH_2C_6H_4SiCl_3$ to produce **8.13**.[70]



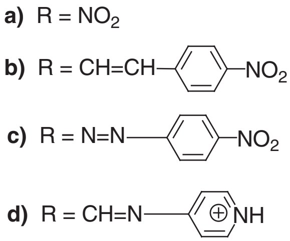
8.10

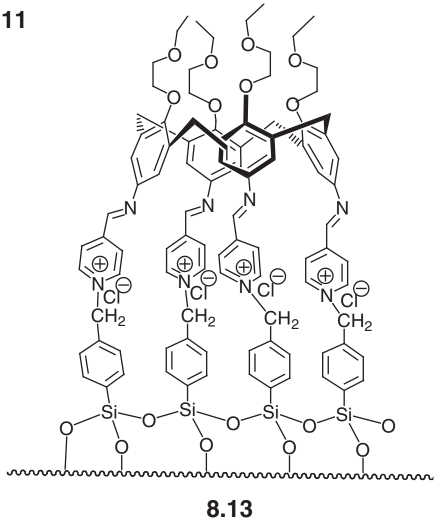


8.11



8.12





8.13

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[67] E. Kelderman, L. Derhaeg, G. J. R. T. Heesink, W. Verboom, J. F. J. Engbersen, N. F. van Hulst, A. Persoons and D. N. Reinhoudt, *Angew. Chem. Intl. Ed. Engl.* **1992**, 31, 1075; G. J. T. Heesink, N. F. van Hulst, B. Bölger, E. Kelderman, J. F. J. Engbersen, W. Verboom and D. N. Reinhoudt, *Appl. Phys. Lett.* **1993**, 62, 2015; E. Kelderman, G. J. T. Heesink, L. Derhaeg, T. Verbiest, P. T. A. Klaase, W. Verboom, J. F. J. Engbersen, N. F. van Hulst, K. Clays, A. Persoons and D. N. Reinhoudt, *Adv. Mater.* **1993**, 5, 925; E. Kelderman, E. Derhaeg, W. Verboom, J. F. J. Engbersen, S. Harkema, A. Persoons and D. N. Reinhoudt, *Supramol. Chem.* **1993**, 2, 183.

[68] M. Brake, V. Böhmer, P. Krämer, W. Vogt and R. Wortmann, *Supramol. Chem.* **1993**, 2, 65.

[69] K. Wörhoff, O. F. J. Noordman, H. Albers, P. V. Lambeck and N. F. van Hulst, *Optics Communications* **1996**, 124, 493.

[70] X. Yang, D. McBranch, B. Swanson and DeQ. Li, *Angew. Chem. Intl. Ed. Engl.* **1996**, 35, 538.

8.2.5 Other Sensors

Chemical sensors have been reported that are based on quartz micro balances or surface acoustic wave oscillators coated with the trimethylsilyl ethers *of* *p-tert*-butylcalix[4,6]arenes that are claimed to detect various solvent vapors in ppm amounts.[71] A bis(calix[4]diquinone) in which a pair of calix[4]diquinone moieties are intermolecularly joined *via* a pair of alkylene or 2,6-di(methylene)pyridyl bridges[72] is a good representative of a redox calixarene,[73] showing three redox waves in the voltammogram which change character upon the addition of cations (especially Cs^+ and Rb^+). Porous silicon coated with a *p*-carboxycalixarene exhibits electrochemiluminescence upon anodic oxidation.[74]

8.3 Calixarenes as Catalysts

8.3.1 Biomimetic Catalysts (*Apndx A-4, p. 241*)

As discussed in Chapter 1, it was the search in the 1970s for molecular baskets suitable for designing enzyme mimics that led to the reinvestigation of the chemistry that Zinke had reported in the 1940s. Although a good mimic for aldolase, the target of that early work, has yet to be achieved, several nice examples of calixarene-based enzyme mimics have been published. The earliest is the hydration of 1-benzyl-1,4-dihydronicotinamide (**8.14** → **8.15**) catalyzed by *p*-sulfanotocalix[6]arene,[75] mimicking the action of the enzyme glyceraldehyde phosphate dehydrogenase. The reaction was carried out at pH 6.30 and was conveniently followed by the shift in the absorption band from 340 to 360 nm. Plots of the rate of the reaction *vs.* the concentration of the calixarene showed saturation kinetics (Michaelis–Menten kinetics), indicating the presence of an intermediate. A similar study two years later[76] showed that *p*-carboxycalix[*n*]arenes are also catalysts, although considerably less effective, and that the cyclic hexamer ($K_{assoc} = 880\,M^{-1}$) is better than the cyclic tetramer (completely ineffective), pentamer ($K_{assoc} = 3800\,M^{-1}$), heptamer ($K_{assoc} = 5000\,M^{-1}$) or octamer ($K_{assoc} = 3700\,M^{-1}$). The inverse relationship between k_{cat} and K_{assoc} is illustrative of the fact that tight binding is not the *sine qua non* for catalysis, an observation that has been made in many other systems as well.

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[71] F. L. Dickert and O. Schuster, *Mikrochim. Acta* **1995**, 119, 55.

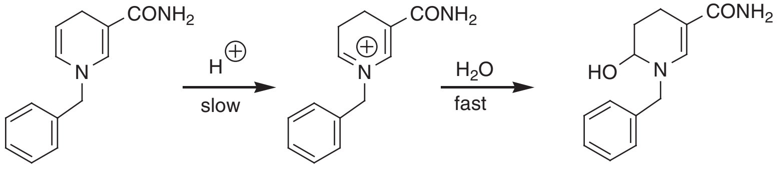
[72] P. R. A. Webber, P. D. Beer, G. Z. Chen, V. Felix and M. G. B. Drew, *J. Am. Chem. Soc.* **2003**, 125, 5774.

[73] P. D. Beer, P. A. Gale and G. Z. Chen, *Adv. Phys. Org. Chem.* **1998**, 31, 1; A. Casnati, E. Comelli, M. Fabbi, V. Bocchi, G. Mori, F. Ugozzoli, A. M. M. Lanfredi, A. Pochini and R. Ungaro, *Recl. Trav. Chim. Pays-Bas* **1993**, 112, 384.

[74] L. Zhang and J. L. Coffer, *J. Phys. Chem. B* **1997**, 101, 6874.

[75] S. Shinkai, S. Mori, H. Koreishi, T. Tsubaki and O. Manabe, *J. Am. Chem. Soc.* **1986**, 108, 2409.

[76] C. D. Gutsche and I. Alam, *Tetrahedron* **1988**, 44, 4689.



8.14 **8.15**

Most of the other examples of calixarene-catalyzed processes are "olysis" reactions such as (a) the hydrolysis of 2,4,-dinitrophenyl phosphate, which is catalyzed to a modest degree by calixarenes carrying *p*-trimethylammonium groups;[77a] and (b) the base-induced hydrolysis of *p*-nitrophenyl dodecanoate[77b] which is dramatically catalyzed *ca.* 10^5-fold more effectively by **8.2g** ($n = 6$) than by **8.2g** ($n = 4$).

Because of its biological relevance, the hydrolysis of phosphate diesters is of particular interest. An early example is seen in the work of the Shinkai group in 1991 involving regioselectivity in the ring-opening hydrolysis of cytidine-2′,3′-cyclic phosphate induced by *p*-sulfonatocalix[*n*]arenes. The largest value was a 3′/2′ cleavage ratio of 3.5 with *p*-sulfonatocalix[4]arene (as compared with a 1.5 ratio in the absence of the calixarene).[78] More recent and much more dramatic results come from the research of the European Consortium of calixarene chemists (including, *inter alia*, Reinhoudt and Ungaro and their groups of coworkers). In 1997 the Reinhoudt group published their results on the catalytic activity of the calix[4]arene **8.16a** carrying a pair of metal-chelating moieties on the *exo* rim[79] (*Apndx C-8*). In the presence of this complex ($M = Zn^{2+}$) the rate at which the substrate **8.17** (RNA model) undergoes transesterification to a cyclic phosphate with extrusion of *p*-nitrophenol in neutral solution at 25 °C is increased by a factor of 2.3×10^4. The proposed pathway for the catalysis is illustrated by **8.21**.

Expanding on this initial work, several more papers followed which showed that (a) the Cu^{2+}complex of **8.16e** ($M = Cu^{2+}$) is an efficient catalyst for the substrates **8.17** (RNA model) and **8.18** (DNA model);[80] (b) calixarene **8.16b**, with a single chelating moiety on the upper rim, is considerably less effective than the doubly substituted counterpart **8.16a,** and the addition of dimethylaminomethyl groups to the upper rim to give **8.16h** does not improve the catalytic efficiency of **8.16a**;[81] (c) for the transesterification of substrate **8.17** the calixarene **8.16d** ($M = Zn^{2+}$) carrying three chelating moieties on the upper rim is an even better catalyst ($k_{cat}/k_{uncat} = 32{,}000$) than **8.16a** ($M = Zn^{2+}$) ($k_{cat}/k_{uncat} = 23{,}000$);[82] (d) the aminomethyl groups in calixarene **8.16i** ($M = Cu^{2+}$) assist in the formation of

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[77] (a) S. Shinkai, Y. Shirahama, T. Tsubaki and O. Manabe, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1859; (b) *idem*, *J. Am. Chem. Soc.* **1989**, 111, 5477.

[78] M. Komiyama, K. Isaka and S. Shinkai, *Chem. Lett.* **1991**, 937.

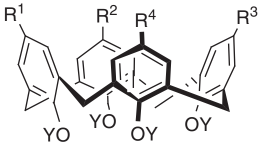
[79] P. Molenveld, S. Kapsabelis, J. F. J. Engbersen and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1997**, 119, 2948.

[80] P. Modenveld, J. F. J. Engbersen, H. Kooijman, A. L. Spek and D. N. Reinhoudt, *J. Am. Chem. Soc.* **1998**, 120, 6726.

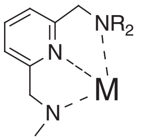
[81] P. Modenveld, J. F. J. Engbersen and D. N. Reinhoudt, *Eur. J. Org. Chem.* **1999**, 3269.

[82] P. Modenveld, W. M. Stikvort, H. Kooijman, A. L. Spek, J. F. J. Engbersen and D. N. Reinhoudt, *J. Org. Chem.* **1999**, 64, 3896.

the catalyst-substrate complex and can also serve as a handle for further functionalization;[83] (e) the vicinally substituted calixarene **8.16c** is more effective than the distally substituted calixarene **8.16a** in the transesterification of the RNA model substrate **8.17** but less effective in the hydrolysis of the DNA model substrate **8.18**;[84] (f) the calixarene **8.16d** ($M = Zn^{2+}$) is an effective catalyst for the methanolysis of the carboxylate substrate **8.19** ($k_{cat}/k_{uncat} = 24{,}000$), and a study of several other carboxylate substrates demonstrates the importance of a good match between the size of the substrate and the inter-metal distance;[85] (g) calixarenes **8.16f** ($M = Ba^{2+}$) and **8.16g** ($M = Ba^{2+}$) are comparable to or better than **8.16c** ($M = Zn^{2+}$) and **8.16a** ($M = Zn^{2+}$) in the ethanolysis of carboxylate substrates such as **8.19**;[86] and (h) among the calixarenes **8.16j,k,l** ($M = Cu^{2+}$) carrying one, two and three 1,5,9-triazacyclododecane moieties on the upper rim, **8.16l** ($M = Cu^{2+}$) is particularly effective in the cleavage of dinucleotide substrates such as **8.20** ($k_{cat}/k_{uncat} = 1.4 \times 10^5$).[87] These studies have demonstrated the utility of the calix[4]arene as a platform for affixing chelating moieties in fashioning effective catalysts for transesterification and hydrolysis reactions. They have also highlighted how critical are the identity, the number and the positioning of the chelating moieties on the *exo* rim of the calixarene as well as the dependence of the catalysis on the structure of the substrate molecule.



8.16



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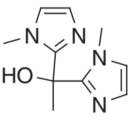
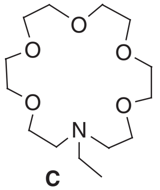
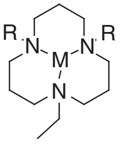


B



C



D

a) R^1, R^3 = **A**; R^2, R^4 = H
b) R^1 = **A;** $R^{2,3,4}$ = H
c) $R^{1,2}$ = **A**; $R^{3,4}$ = H
d) $R^{1,2,3}$ = **A**, R^4 = H)
e) $R^{1,3}$ = **B**; $R^{3,4}$ = H

f) $R^{1,3}$ = **C**; $R^{2,4}$ = H
g) $R^{1,2}$ = **C;** $R^{2,4}$ **= H**
h) $R^{1,3}$ = **A**; $R^{2,4}$ = CH_2NMe_2
i) $R^{1,3}$ = **B**; $R^{2,4}$ = CH_2NH_2

j) $R^{1,2}$ = **D**; $R^{3,4}$ = H
k) $R^{1,3}$ = **D**; $R^{2,4}$ = H
l) $R^{1,2,3}$ = **D**; R^4 = H
m) $R^{1,3}$ = NO_2; R^2 = CH_2OH; R^4 = H, Y = Pr

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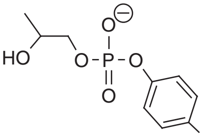
[83] P. Modenveld, J. F. J. Engbersen and D. N. Reinhoudt, *J. Org. Chem.* **1999**, 64, 6337.

[84] R. Cacciapaglia, A. Casnati, L. Mandolini, D. N. Reinhoudt, R. Salvio, A. Sartori and R. Ungaro, *J. Org. Chem.* **2005**, 70, 624.

[85] R. Cacciapaglia, A. Casnati, L. Mandolini, D. N. Reinhoudt, R. Salvio, A. Sartori and R. Ungaro, *J. Org. Chem.* **2005**, 70, 5398.

[86] R. Cacciapaglia, A. Casnati, S. DiStefano, L. Mandolini, D. Pulemili, D. N. Reinhoudt, A. Sartori and R. Ungaro, *Chem. Eur. J.* **2004**, 10, 4436.

[87] R. Cacciapaglia, A. Casnati, L. Mandolini, D. N. Reinhoudt, R. Salvio, A. Sartori and R. Ungaro, *J. Am. Chem. Soc.* **2006**, 128, 12322.



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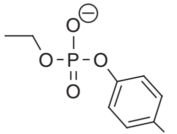

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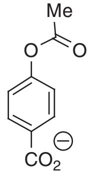

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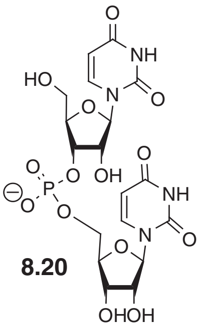

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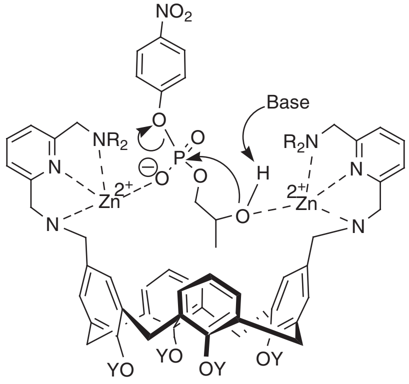

8.21

Several examples of selective "olysis" reactions of calixarenes involve intramolecular catalytic phenomena. In the conversion of the 1,3-dibenzoate of *p-tert*-butylcalix[4]arene to the monobenzoate with imidazole in a $CHCl_3$/MeCN solution, the kinetics of the process suggest that two or more imidazoles are involved, one acting as a base to form a calixarene oxyanion and another acting as the nucleophilic receptor for the departing 3,5-dinitrobenzoyl moiety.[88] In what might be called "pseudo intramolecular catalysis" the tetraesters **8.2a** in $CHCl_3$ or benzene solution undergo CF_3CO_2H catalyzed hydrolysis of a single ester moiety to yield the corresponding triester monoacids.[89] The termination of hydrolysis after the excision of a single ROH group is attributed to a change in conformation (supported by an X-ray crystal structure of the monoacid) and the consequent lower affinity of the cavity for complexation with the hydronium ion. In still another interesting example of pseudo intramolecular catalysis,[90] the half-time for the methanolysis of the calixarene monoacetate **8.22** with $Me_4N^+OMe^-$ in MeOH at 25 °C is reduced from 34 weeks to 8 seconds by the addition of Ba^{2+}. The reactive species is thought to be the Ba^{2+} complex of the calixarene in which Ba^{2+} intramolecularly coordinates with the acyl carbonyl group to activate it toward attack by MeO^-. Advantage is taken of

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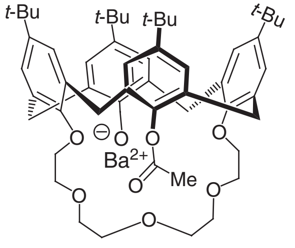
[88] K. A. See, F. R. Fronczek, W. H. Watson, R. P. Kashyap and C. D. Gutsche, *J. Org. Chem.* **1991**, 56, 7256.

[89] G. Barrett, V. Böhmer, G. Ferguson, J. F. Gallagher, S. J. Harris, R. G. Leonard, M. A. McKervey, M. Owens, M. Tabatabai, A. Vierengel and W. Vogt, *J. Chem. Soc Perkin Trans. 2* **1992**, 1595; V. Böhmer, W. Vogt, S. J. Harris, R. G. Leonard, E. M. Collins, M. Deasy, M. A. McKervey and M. Owens, *J. Chem. Soc. Perkin Trans. 1* **1990**, 431.

[90] R. Cacciapaglia, A. Casnati, L. Mandolini and R. Ungaro, *J. Chem. Soc. Chem. Commun.* **1991**, 1291.

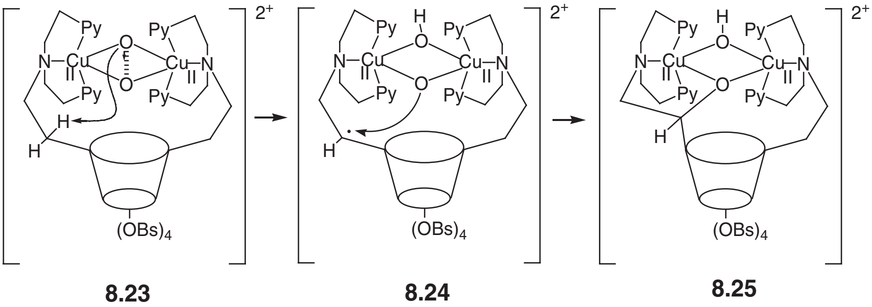
this phenomenon in the design of a nucleophilic catalyst with transacylase activity.



8.22

Using *p*-nitrophenyl acetate as the substrate, Ungaro and coworkers[91] showed that the methanolysis to *p*-nitrophenol and methyl acetate in MeCN-MeOH solution with R_3N buffer is catalyzed by formation of the Ba^{2+} complex **8.22**. The kinetics of the reaction are commensurate with the formation of an intermediate, and the overall reaction is a true catalytic process although the turnover number of $5.5 \times 10^{-3}\,min^{-1}$ (*i.e.* 8 per day) is very small.

With the exception of the hydration of 1-benzyl-1,4-dihydronicotinamide, the reactions described above are subtractive rather than additive processes. Much less success has been achieved in fashioning calixarene-based biomimetic catalysts for this latter group. One attempt is represented by the calixarene **8.22** carrying a pair of bis-pyridine-based chelating moieties on the upper rim, the goal being to mimic an oxidase, adding an oxygen atom to a benzene molecule captured in the cavity.[92] Instead, intramolecular oxidation occurred, as represented in the sequence **8.23** → **8.24** → **8.25**. The quest for an aldolase mimic likewise remains to be realized. Aldolase catalyses the addition process whereby glyceraldehyde phosphate and dihydroxyacetone phosphate combine to form fructose-1,6-diphosphate. A putative mimic represented by the calix[6]arene **8.26** has been constructed, but little, if any, catalysis was observed (*Apndx A-1, p. 15*).



8.23 **8.24** **8.25**

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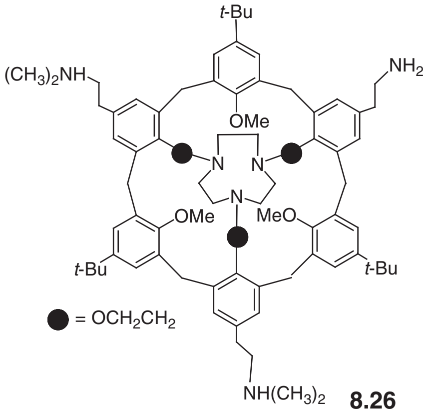
[91] R. Cacciapaglia, A. Casnati, L. Mandolini and R. Ungaro, *J. Am. Chem. Soc.* **1992**, 114, 10956.

[92] D. Xie and C. D. Gutsche, *J. Org. Chem.* **1998**, 63, 9278.



8.26

8.3.2 Non-biomimetic Catalysts (*Apndx A-1, p. 259; A-2, p. 513, 536*)

An example of a catalytic phenomenon in which the phenolic OH groups play a part is the "autoaccelerative" diazo coupling between calix[4]arene and aryldiazonium compounds in which the tetra-*p*-phenylazo-calixarene is almost the exclusive product even when starting material still remains.[93] Phenolic substrates are reported to be regioselectively hydroxylated with H_2O_2 in the presence of a cerium(IV)-calix[8]arene complex.[94]

A reaction involving what might be called "proximity catalysis" involves calix[4]arene **8.16m**, which undergoes an acid-catalyzed reaction with toluene in which the hydroxymethyl group on the *exo* rim becomes a tolylmethyl group with a 78% *ortho*/9% *para*/13% *meta* distribution of isomers,[95] attributable to the methyl-group-in-the-cavity orientation of the toluene molecule.

Nomura and coworkers have studied the phase transfer catalytic capability of the hexa-(3,6,9-trioxadecyl) ether of *p*-*tert*-butylcalix[6]arene in several reaction systems,[96] including (a) $ArOM + ArCH_2Br \rightarrow ArCH_2OAr$; (b) $RCO_2M + p\text{-}O_2C_6H_4CH_2Br \rightarrow RCO_2CH_2C_6H_4NO_2$; (c) $R_2C{=}CR_2 + [:CCl_2] \rightarrow$ dichlorocyclopropanes; (d) $RCH{=}CH_2$ or $RC{\equiv}CH$ or $RCH_2OH + KMnO_4 \rightarrow RCO_2H$. Under certain conditions the effectiveness of the calixarene is generally equal to or greater than that of the tetraalkylammonium salts or 18-crown-6 compounds. Thus, reactions *a*, *b* and *d* are catalyzed in CH_2Cl_2 solution but not in benzene solution, and a small amount of H_2O facilitates the reactions (except for the oxidation of $RC{\equiv}CH$). Rate studies of reactions *b* and *c* indicate that Michaelis–Menten kinetics are followed, from which the conclusion is drawn that the

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[93] S. Shinkai, K. Araki, J. Shibata, D. Tsugawa and O. Manabe, *J. Chem. Soc. Perkin Trans 1* **1990**, 3333.

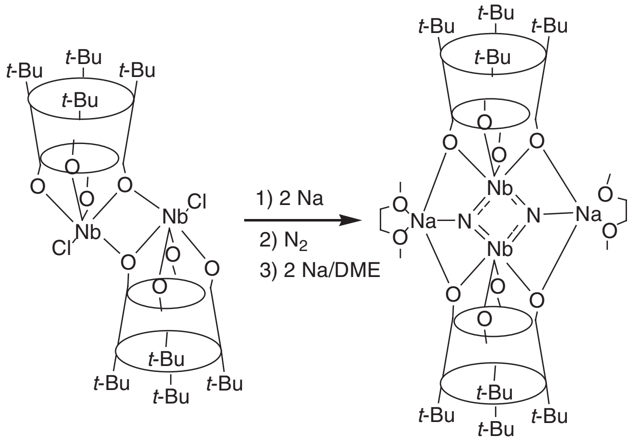
[94] H. M. Chawla, U. Hooda and V. Singh, *J. Chem. Soc. Chem. Commun.* **1994**, 61, 7.

[95] O. Struck, J. P. M. van Duynhoven, W. Verboom, S. Harkema and D. N. Reinhoudt, *J. Chem. Soc. Chem. Commun.* **1996**, 1517.

[96] H. Tanaguchi and E. Nomura, *Chem. Lett.* **1988**, 1773; E. Nomura, H. Taniguchi, K. Kawaguchi and Y. Otsuji, *Chem. Lett.* **1991**, 2167; E. Nomura, H. Taniguchi and Y. Otsuji, *Bull. Chem. Soc. Jpn.* **1994**, 67, 309, 792; H. Taniguchi, Y. Otsuji and E. Nomura, *ibid.* **1995**, 68, 3563.

reactions occur within the cavity of the calixarene (however, *cf.* ref. 97). Water soluble calixarenes have been studied for their application as inverse phase transfer catalysts[98] and have been shown to be effective, *inter alia*, in alkylation reactions of active methylene compounds, alcohols and phenols[99] and in the Wacker oxidation of alkenes[100] (*Apndx A-2, p. 407*).

The *endo* rim of the calixarenes, particularly the calix[4]arenes, has been seized on by the inorganic chemists as an ideal platform to which to affix various metal atoms. Foremost among the practitioners in this niche of calixarene chemistry are Carlo Floriani and his coworkers at the University of Lausanne, Switzerland. The full scope of their work (*Apndx A-2, p. 536; D-7*), however, is far too extensive to present in any detail in this short chapter, so only one representative, but quite dramatic, example is discussed.[101] Treatment of *p*-*tert*-butylcalixarene with a stoichiometric amount of $NbCl_5$ yields the niobium complex **8.27**. Treatment of **8.27** with sodium followed by nitrogen and then with more sodium in dimethoxyethane solution results in a four-electron reduction of the nitrogen to yield the complex **8.28** in which the strong N≡N bond has been broken.



8.27

8.28

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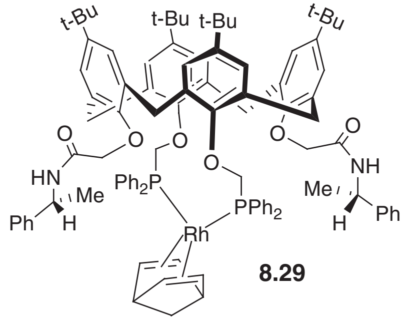
[97] K. Araki, A. Yanagi and S. Shinkai, *Tetrahedron* **1993**, 49, 6763.

[98] M. Baur, M. Frank, J. Schatz and F. Schildbach, *Tetrahedron* **2001**, 57, 6985.

[99] S. Shimizu, T. Suzuki, S. Shirakawa, Y. Sasaki and C. Hirai, *Adv. Synth. Catal.* **2002**, 344, 370.

[100] E. A. Karakhanov, Y. S. Kardasheva, A. I. Maximov, E. A. Runova, T. A. Buchneva, M. A. Gaevskiy, A. Y. Zhuchkova and T. Y. Filippova, *Polym. Adv. Technol.* **2001**, 12, 161.

[101] A. Zanotti-Gerosa, E. Solari, L. Giannini, C. Floriani, A. Chiesi-Villa and C. Rizzoli, *J. Am. Chem. Soc.* **1998**, 120, 437; A. Caselli, E. Solari, R. Scopelliti, C. Floriani, R. N. Re, C. Rizzoli and A. Chiesi-Villa, *ibid.* **2000**, 122, 3652. For a short review of this and other reactions *cf.* C. Floriani, *Chem. Eur. J.* **1999**, 5,19.



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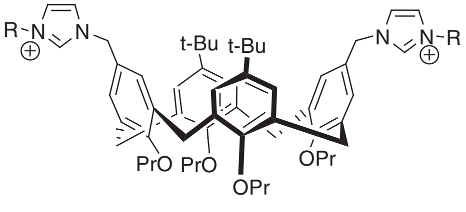

8.30

Floriani is by no means alone in the pursuit of metallocalixarene-catalyzed reactions. Other workers have shown that (a) the rhodium complex **8.29** catalyzes the hydroformylation of styrene to 2-phenylpropanal and 3-phenylpropanal in a 95:5 ratio;[102] (b) the hydroformylation of terminal alkenes is catalyzed by the rhodium complex of the monophosphanylcalix[6]arene **8.31d**[103] and (c) a similar rhodium complex catalyzes the hydroformylation of *n*-octene to nonal with as high as 99.5% regiospecificity.[104] Calix[4]arene-molybdenum(VI) compounds have been synthesized as putative catalysts for organometallic transformations.[105] Calixarene-based titanium catalysts have found application in several varieties of reactions. The aldol condensation of aldehydes with the bis-trimethylsilyl ether of $CH_3COCH_2CO_2Me$ (acetoacetic ester) is catalyzed by the titanium complexes of the monomethyl and 1,3-dimethyl ethers of *p*-*tert*-butylcalix[4]arene.[106] These same catalysts have been used in the epoxidation of allylic alcohols, where it was noted that the catalytic properties are greatly enhanced by the incorporation of 4 Å molecular sieves in the reaction mixture.[107] Dinuclear titanium complexes of *p*-*tert*-butylthiacalix[4]arene have been used as Lewis acid catalysts, for example in the cyclotrimerization of terminal alkynes to benzenes.[108] The zinc complex of the 1,3-dipropyl ether of *p*-*tert*-butylcalix[4]arene has been studied in the catalysis of the polymerization of L-lactide.[109] The Suzuki–Miyaura reaction (coupling of an aryl halide with an arylboronic acid to form a biaryl) has been studied by Schatz and coworkers who found the palladium complexes of the water-soluble **8.30** compounds to be effective catalysts.[110]

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[102] C. Loeber, C. Wieser, D. Matt, A. De Cian, J. Fischer and L. Toupet, *Bull. Soc. Chim. Fr.* **1995**, 132, 166.

[103] Y. Obora, Y. K. Liu, S. Kubouchi, M. Tokunaga and Y. Tsuji, *Eur. J. Inorg. Chem.* **2006**, 222.

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[105] L. Liu, L. N. Zakharov, J. A. Golen, A. L. Rheingold, W. H. Watson and T. A. Hanna, *Inorg. Chem.* **2006**, 45, 4247.

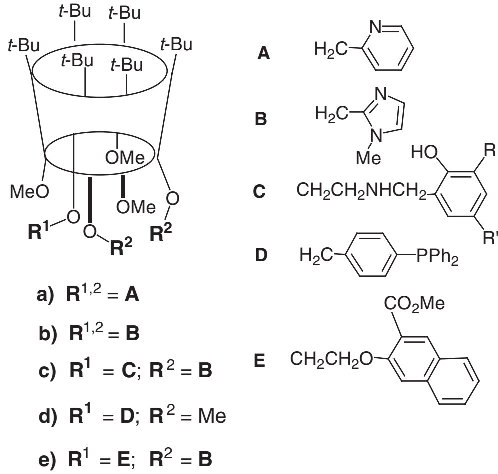
[106] A. Soriente, M. Fruilo, L. Gregoli and P. Neri, *Tetrahedron Lett.* **2003**, 44, 6195; A. Soriente, M. De Rosa, M. Fruilo, L. Lepore, C. Gaeta and P. Neri, *Adv. Synth. Catal.* **2005**, 347, 816.

[107] A. Massa, A. D'Ambrosi, A. Proto and A. Scettri, *Tetrahedron Lett.* **2001**, 42, 1995.

[108] N. Morohashi, T. Hattori, K. Yokomakura, C. Kabuto and S. Miyano, *Tetrahedron Lett.* **2002**, 43, 7769; *idem*, *ibid.* **2006**, 47, 1157.

[109] E. Bukhaltsev, L. Frish, Y. Cohen and A. Vigalok, *Org. Lett.* **2005**, 7, 5123.

[110] M. Frank, G. Maas and J. Schatz, *Eur J. Org. Chem.* **2004**, 607; T. Brendgen, M. Frank and J. Schatz, *ibid.* **2006**, 2378.



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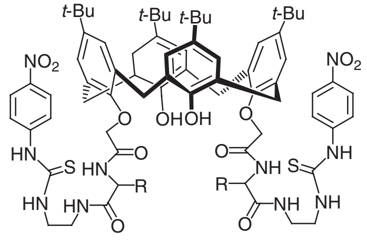

8.32

8.4 Calixarenes as Biomimetic and Physiological Compounds (*Apndx A-2, p. 496*)

In addition to the biomimetic catalyst systems described in Section 8.3.1, the mimicking of the receptor sites of metalloenzymes is being vigorously studied, in some instances with a calixarene as the central motif. Reinaud and coworkers have used a calix[6]arene as a platform to which to affix various chelating moieties and metal atoms on the lower rim. For example, **8.31a,b** form complexes with Cu^+ in which the role of the three pyridine or imidazole moieties is to anchor the copper ions, and the role of the calixarene is to protect the metal center from interaction with another metal center and to operate as a means of selection based on its size and nature.[111] In similar fashion **8.31b** interacts with Zn^{+2} to mimic a different class of metalloenzymes, producing what is referred to as a "molecular funnel".[112] The more elaborately functionalized **8.31c** likewise was designed to form complexes with Zn^{2+}, three different types of which were characterized.[113]

Numerous examples of the complexation of molecules of biological interest have been studied, several already having been cited in this chapter and the preceding chapter. Other examples, progressing from small to large guests, include: (a) the calixarene **8.32**, which is a chromogenic chiral sensor for α-phenylglycine anions;[114] (b) mono-*p*-ureidocalix[5]arene as an efficient receptor

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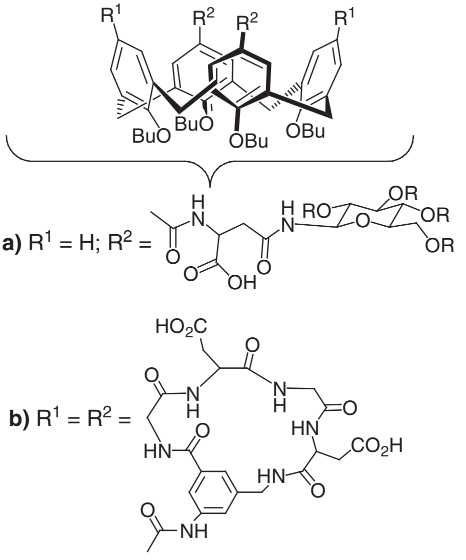
[111] S. Blanchard, L. Le Clainche, M.-N. Rager, B. Chansou, J.-P. Tuchagues, A. F. Duprat, Y. Le Mest and O. Reinaud, *Angew. Chem. Intl. Ed. Engl.* **1998**, 37, 2732; O. Sénéque, M. Campion, B. Douziech, M. Giorgi, E. Riviére, Y. Journaux, Y. Le Mest and O. Reinaud, *Eur. J. Inorg. Chem.* **2002**, 2007.

[112] O. Sénéque, M.-N. Rager, M. Giorgi and O. Reinaud, *J. Am. Chem. Soc.* **2000**, 122, 6183.

[113] O. Sénéque, M.-N. Rager, M. Giorgi, T. Prange, A. Tomas and O. Reinaud, *J. Am. Chem. Soc.* **2000**, 127, 14833.

[114] G.-Y. Qing, V.-B. He, Y. Zhao, C.-G. Hu, S.-Y. Liu and X. Yang, *Eur. J. Org. Chem.* **2006**, 1574.

for ω-amino acids and biogenic amines;[115] (c) *p*-sulfonatocalix[4,6,8]arenes as ion channel blockers;[116] (d) a peptidocalix[4]arene (*Apndx A-1, p. 233; D-4*) library containing 1000 hosts for peptides in aqueous media;[117] (e) calixarene **7.36** (*cf.* Chapter 7, p 201) for the complexation of carbohydrates;[118] (f) calixarenes carrying glycosyl moieties,[119] sometimes in combination with peptide moieties (*e.g.* **8.33a**), for cell surface recognition;[120] (g) calixarene **8.33b** carrying four peptide loops on the upper rim for the recognition of protein surfaces[121] (*Apndx A-1, p. 287; B-2*); (h) "color fingerprinting" of proteins by basic and acidic amphiphilic calixarenes embedded in lipid/polydiacetylene vesicles;[122] (i) the tetramethyl and tetrapropyl ethers of *p*-guanidiniumcalix[4,6,8]arenes for binding to plasmid DNA;[123] (j) the calix[4]arene dimer **8.34** carrying six ammonium groups on the *exo* rims which recognizes double stranded DNA.[124]



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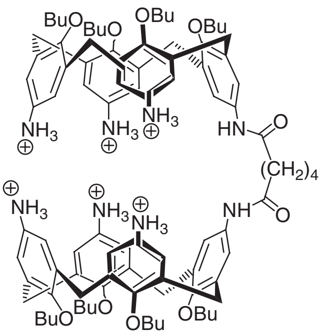

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[115] F. P. Ballistreri, A. Notti, S. Pappalardo, M. F. Parisi and I. Pisagatti, *Org. Lett.* **2003**, 5, 1071.

[116] G. Droogmans, C. Maertens, J. Prenen and B. Nilius, *Br. J. Pharmacol.* **1999**, 128, 35.

[117] H. Hioki, M. Kubo, H. Yoshida, M. Bando, Y. Ohnishi and M. Kodama, *Tetrahedron Lett.* **2002**, 43, 7949; M, Kubo, E. Nashimoto, T. Tokiyo, Y. Morisaki, M. Kodama and H. Hioki, *ibid.* **2006**, 47, 1927.

[118] M. Segura, B. Bricoli, A. Casnati, E. M. Muñoz, F. Sansone, R. Ungaro and C. Vicent, *J. Org. Chem.* **2003**, 68, 6296.

[119] A. Marra, M.-C. Scherrmann, A. Dondoni, A. Casnati, P. Minari and R. Ungaro, *Angew Chem. Int. Ed. Engl.* **1994**, 33, 2479; A. Dondoni, A. Marra, M.-C. Scherrmann, A. Casnati, F. Sansone and R. Ungaro, *Chem. Eur. J.* **1997**, 1774; F. Sansone, E. Chierici, A. Casnati and R. Ungaro, *Org. Biomol. Chem.* **2003**, 1802.

[120] U. Schädel, F. Sansone, A. Casnati and R. Ungaro, *Tetrahedron* **2005**, 61, 1149.

[121] Y. Hamuro, M. C. Calama, H. S. Park and A. D. Hamilton, *Angew. Chem. Intl. Ed. Engl.* **1997**, 36, 2678.

[122] S. Kolusheva, R. Zadmard, T. Schrader and R. Jelinek, *J. Am. Chem. Soc.* **2006**, 128, 13592.

[123] M. Dudic, A. Colombo, F. Sansone, A. Casnati, G. Donofrio and R. Ungaro, *Tetrahedron* **2004**, 60, 11613.

[124] R. Zadmard and T. Schrader, *Angew. Chem. Intl. Ed. Engl.* **2006**, 45, 2703.

Phenolic compounds are well known for possessing physiological properties. Good examples are the urishiols, which are long chain alkyl-substituted catechols present in the active vesicant principle of poison ivy. Qualitatively comparable dermatic responses have been noted for *p*-*tert*-butylphenol-formaldehyde resins, particularly the linear tetramer.[125] Although *p*-*tert*-butylcalix[4,8]arenes give negative responses in the Ames test for mutagenicity, this might simply reflect their great insolubility.

A considerable medical and biochemical literature has arisen concerning the oxyalkyl derivatives of simple phenols as well as phenol-formaldehyde condensates. It was the quest of such compounds, in fact, that led Cornforth to explore the Zinke reaction in the 1950s and to lay some of the groundwork for subsequent developments in calixarene chemistry. In Cornforth's initial work[126] he oxyethylated his phenol-formaldehyde condensates by treating them with ethylene oxide, which yielded a product called a "macrocyclon". In a follow-up investigation some years later,[127] a more carefully controlled set of experiments was carried out using the high-melting compound from the condensation of *p*-*tert*-octylphenol and formaldehyde (Cornforth's HOC compound, subsequently shown to be the cyclic octamer). A more recent study has reawakened interest in these compounds by showing that *in vivo* inhibition of *Mycobacterium tuberculosis* can be induced inside microphages by a calixarene carrying short polyethyleneoxy chains on the *endo* rim.[128]

Macrocyclons have also been tested in the therapy of parasitic diseases[129] and have been used to induce fusion of erythrocytes.[130] In a study[131] of the effects of macrocyclons on phospholipase A_2 it was found that the same Cornforth's HOC compound mentioned above (*ca*. 12.5 oxyethylene units/oxygen) inhibited the action of phospholipase A_2, while those having longer polyoxyethylene chains (*ca*. 60 oxyethylene units/oxygen) stimulated its action. Looking to the future of the carcerands, Donald Cram said[132] that "large metabolizable molecular cells might be used in drug or agricultural chemical delivery systems or in systems in which very slow release of compounds chemically shielded from their environment are needed".

The antibiotic vancomycin causes cell lysis by binding to the cell wall of mucopeptide precursors terminating in the sequence **D**-alanyl-**D**-alanine. The calixarene-based vancomycin mimic **8.35** containing alanyl residues shows

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[125] H. Schubert and G. Agatha, *Dermatosen in Beruf und Umwelt* **1979**, 27, 49.

[126] J. W. Cornforth, P. D'Arcy Hart, G. A. Nicholls, R. J. W. Rees and J. A. Stock, *Br. J. Pharmacol.* **1955**, 10, 73.

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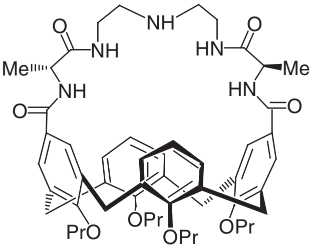
[131] M. R. Jahn and D. V. Jahagirdar, *Biochem. J.* **1988**, 222, 789.

[132] D. J. Cram, S. Karbach, Y. H. Kim, T. Baczynskyj, K. Marti, R. M. Simpson and G. W. Kalleymeyn, *J. Am. Chem. Soc.* **1988**, 110, 2554.

qualitatively similar though quantitatively somewhat inferior antimicrobial action against Gram-positive organisms.[133]



8.35

8.5 Miscellaneous Applications

A Langmuir–Blodgett (LB) multilayered film showing a strong pyroelectric effect has been prepared using calix[8]arenes carrying $OCH_2CH_2CH_2NH_2$ or carboxyl groups on their *endo* rims. The temperature-dependent proton transfer between the carboxyl and amino groups, detected by FTIR, is thought to provide the mechanism for the pyroelectric effect.[134] Mono- and multilayer LB films that are electrically conducting have been prepared[135] from the CH_2CO_2Me ether of *p-tert*-octylcalix[4]arene and Na^+TCNQ^-. The change in permeability of oriented monolayers of **8.2a,b** induced by alkali cations has been studied,[136] the magnitude of the response falling in the order $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$.

Taking note of the high luminescence quantum yield and long luminescence lifetime of the Tb^{3+} complex of **8.2** ($R = H$ or $COCH_3$; $Y = CH_2CONEt_2$; $n = 4$)[137] and also the demonstration that one of the amide groups can be replaced by a sensitizer group such as phenacyl (OCH_2COPh), Reinhoudt and coworkers designed a system based on the delayed luminescence properties of the Tb^{3+} and Eu^{3+} complexes of a *p-tert*-butylcalix[4]arene carrying an *endo* rim OCH_2COR group, where R = naphthalene, phenanthrene or triphenylene.[138] The triphenylene "antenna" proved to be the most effective, sensitizing the luminescence of both the Tb^{3+} and Eu^{3+} complexes and allowing the use of excitation wavelengths up to 350 nm. Attachment of a boronic

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[133] A. Casnati, M. Fabbi, N. Pelizzi, A. Pochini, F. Sansone, R. Ungaro, R. E. Di Modugno and G. Tarzia, *Bioorg. Med. Chem. Lett.* **1996**, 6, 2699.

[134] T. Richardson, M. B. Greenwood, F. Davis and C. J. M. Stirling, *Langmuir* **1995**, 11, 4623.

[135] C. B. McArdle, S. J. Harris, J. Guthrie and V. Casey, *Key Eng. Mater.* **1992**, 72–74, 359.

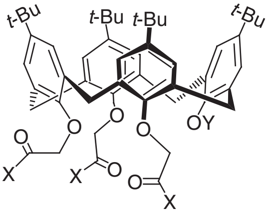
[136] K. Yagi, S. B. Khoo, M. Sugawara, T. Sakaki, S. Shinkai, K. Odashima and Y. Umezawa, *Electroanalytical Chem.* **1996**, 401, 65.

[137] N. Sabbatini, A. Mecati, M. Guardigli, V. Balzani, J.-M. Lehn, R. Zeissel and R. Ungaro, *J. Luminescence* **1991**, 48 & 49, 463; H. Matsumoto and S. Shinkai, *Chem. Lett.* **1994**, 901. For a review *cf*. H. M. Widner, *Anal. Methods. Instrum.* **1993**, 1, 3.

[138] F. J. Steemers, W. Verboom, D. N. Reinhoudt, E. B. van der Tol and J. W. Verhoeven, *J. Am. Chem. Soc.* **1995**, 117, 9408; F. J. Steemers, H. G. Meuris, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.* **1997**, 62, 4229.

acid-containing moiety to the *endo* rim to give **8.36c** provides a compound for which the luminescence of the Tb^{3+} complex is sensitive to the presence of saccharides.[139] A study of energy-transfer processes in Tb^{3+} and other lanthanide dinuclear complexes of *p-tert*-butylcalix[8]arene shows them to be dipole-dipole in character.[140] In a somewhat different vein *p*-carboxymethyl and carboxyethyl calixarenes have been shown to form thin films on porous silicon to produce systems that are selective for photoluminescence quenching by Cu^{2+} or amines.[141]

Molecules capable of reversibly switching between two distinct states are currently receiving considerable attention.[142] Photoresponsive molecules, for example, are of interest for their potential uses in optical data storage systems, and calixarenes are among the substances being investigated for this purpose. Shinkai and coworkers have shown that the calix[4]arene **8.37**, carrying a pair of anthracene moieties on the lower rim, undergoes intramolecular ring formation to **8.37** when irradiated with 350 nm light, and that **8.38** reverts to **8.37** when irradiated with 280 nm light.[143] It is interesting to note that **8.38** shows a considerably higher affinity for ions than does **8.37**, particularly for Na^+, which suppresses its thermal reversion to **8.37**. Another system taking advantage of a light-induced transformation is **8.39** carrying an azobenzene moiety on the lower rim, which undergoes *syn*/*anti* interconversion upon irradiation.[144] The *anti* isomer shows significantly higher binding capacity for the cations studied (Na^+, K^+, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Al^{3+}) than does the *syn* isomer.

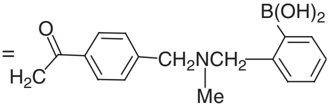


8.36

a) $X = NR_2$; $Y = CH_2COC_6H_5$

b) $X = OH$; $Y = CH_2CONHCH_2Ar$

c) $X = NEt_2$; $Y =$



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[139] H. Matsumoto, A. Ori, F. Inokuchi and S. Shinkai, *Chem. Lett.* **1996**, 301.

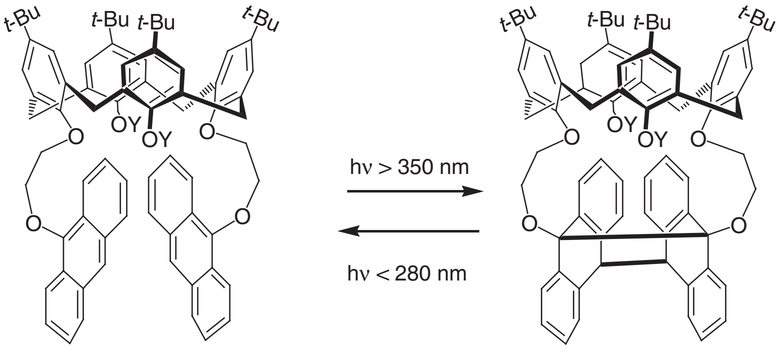
[140] P. Froidevaux and J.-C. G. Bünzli, *J. Phys. Chem.* **1994**, 98, 532.

[141] L. Zhang, J. L. Coffer, J. Wang and C. D. Gutsche, *J. Am. Chem. Soc.* **1996**, 118, 12840.

[142] For a general review *cf.* P. Gütlich, A. Hauser and A. Spiering, *Angew. Chem. Intl. Ed. Engl.* **1994**, 33, 2024.

[143] G. Deng, T. Sakaki, Y. Kawahara and S. Shinkai, *Tetrahedron Lett.* **1992**, 33, 2163; G. Deng, T. Sakaki, K. Nakashima and S. Shinkai, *Chem. Lett.* **1992**, 1287; G. Deng, T. Sakaki and S. Shinkai, *Journal of Polymer Science: Part A: Polymer Chemistry* **1993**, 31, 1915; G. Deng, T. Sakaki, Y. Kawahara and S. Shinkai, *Supramol. Chem.* **1993**, 2, 71.

[144] F. Hamada, T. Masuda and Y. Kondo, *Supramol. Chem.* **1995**, 5, 129.



Y = $CH_2CH_2CO_2Et$

8.37 **8.38**

A calixarene-based redox switch **8.40** has been constructed by placing pairs of hydroxamate and bipyridyl moieties on the *endo* rim of a calix[4]arene to provide "hard" and "soft" binding sites, respectively.[145] In the presence of Fe^{3+} the "hard" binding site comes into play, causing the hydroxamate groups to converge and *bipyridyl* groups to diverge. Conversely, when Fe^{3+} is reduced to Fe^{2+} the "soft" binding site comes into play, causing the *hydroxamate* groups to diverge with a concomitant color change from orange to pink. Bipyridyl groups have also been used to modulate the through-space exchange interaction between nitroxo radicals attached to the *endo* rim of calix[4]arene **8.7c**,[146] the magnitude depending on the presence or absence of Zn^{2+}.

Calixarenes substituted in the *p*-positions with arylazomethine groups or arylazo groups carrying long alkyl chains may possess liquid crystal properties (*Apndx D-20*). For example, **8.2h** ($R' =$ *p*-octyl to *p*-hexadecyl)[147] and the tungsten-oxo complex **8.41** are thermotropic, showing phase transitions attributed to the "melting" first of the aliphatic chains and then of the calix[4]arene bowl.[148] The liquid crystalline state of the tungsten-oxo complex **8.41** (red in the solid-state, yellow in solution) can be disrupted by the addition of DMF or pyridine, the guest molecules displacing the neighboring calixarene moieties in the columnar array (*cf.* **6.24** in Chapter 6, p 160). Another construction of a calixarene-based liquid crystal system employs **8.2i** mixed with a benzoic acid carrying a long chain alkoxy group in the *p*-position.[149]

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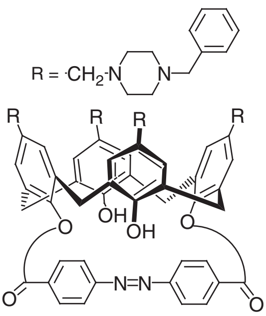
[145] C. Canevet, J. Libman and A. Shanzer, *Angew. Chem. Intl. Ed. Engl.* **1996**, 35, 2657.

[146] G. Ulrich, P. Turek and R. Zeisel, *Tetrahedron Lett.* **1996**, 37, 8755.

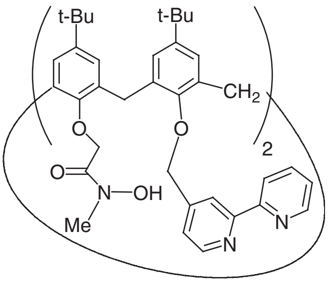
[147] T. Komori and S. Shinkai, *Chem. Lett.* **1993**, 1455.

[148] B. Xu and T. M. Swager, *J. Am. Chem. Soc.* **1993**, 113, 1159.

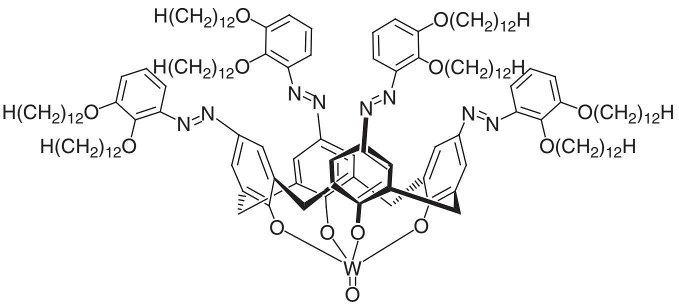
[149] K. N. Koh, K. Araki, T. Komori and S. Shinkai, *Tetrahedron Lett.* **1995**, 36, 5191.



8.39



8.40



8.41

The phenomenon of gelation has been observed with calixarenes.[150] Particularly effective are calixarenes carrying long chain *p*-acoyl groups such as *p*-dodecanoylcalix[8]arene,[151] which form gels with a variety of solvents, including benzene, toluene, CCl_4, CS_2, hexane, decane, cyclohexane, isopropanol, butanol and hexanol; but not, however, with $CHCl_3$, CH_2Cl_2, acetone, methanol and ethanol. The three-dimensional self association network giving rise to the gel, observable as a pattern by using a microscope equipped with crossed Nicol prisms, is attributed to intermolecular hydrogen bonding between the phenolic and carbonyl groups along with moderate affinity for the solvent.

A molecular printboard (*Apndx A-1, p. 213*), defined as "a self assembled monolayer on a surface that has recognition sites to which molecules can be anchored through specific interactions" has been constructed[152] using a cyclodextrin monolayer on a gold surface as the foundation. Sitting above the foundation is a calix[4]arene carrying guanidinium moieties on the *exo* rim and oxyalkylene chains on the *endo* rim that terminate in adamantyl moieties which fit into the annuli of the cyclodextrins. This, in turn, is capped with an anionic

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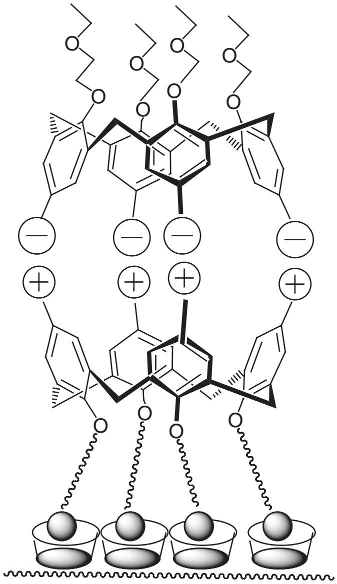
[150] H. Kawabata, M. Aoki, K. Mujrata and S. Shinkai, *Supramol. Chem.* **1993**, 2, 33.

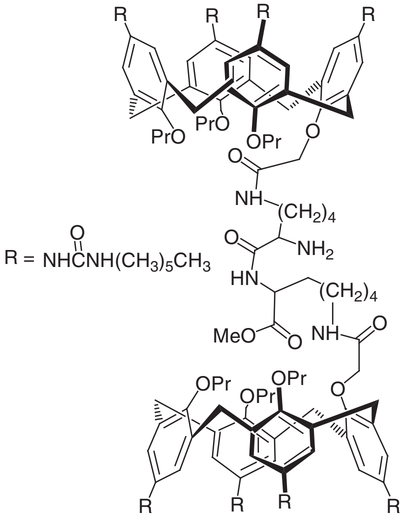
[151] M. Aoki, K. Murata and S. Shinkai, *Chem. Lett.* **1991**, 1715; M. Aoki, K. Nakashima, H. Kawabata, S. Tsutsui and S. Shinkai, *J. Chem. Soc. Perkin Trans 2* **1993**, 347.

[152] F. Corbellini, A. Mulder, A. Sartori, M. J. W. Ludden, A. Casnati, R. Ungaro, J. Huskens, M. Crego-Calama and D. N. Reinhoudt, *J. Am. Chem. Soc.* **2004**, 126, 17050.

p-sulfonatocalix[4]arene, which forms electrostatic bonds with the cationic calixarene to form a capsule, as illustrated in **8.42**. Applications of this intriguing and potentially useful assembly remain to be investigated. A rather different kind of polymeric capsular assembly involves the bis-calixarene **8.43** carrying ureido moieties on the *exo* rims, which, through intermolecular hydrogen bonding, leads to a polymeric array[153] which reversibly binds CO_2.



8.42



8.43

The hexaacetate of *p*-methylcalix[6]arene has been tested as a high-resolution negative resist for electron beam lithography, showing sufficient resolution to be useful for nanoscale device processing.[154] Quantum confined cadmium sulfide clusters are stabilized by *p*-dialkylamnomethylcalixarenes.[155]

Although there are numerous examples of calixresorcarenes being used as containers for guest molecules undergoing reaction, there are almost none with the phenol-derived calixarenes. One of the few is the phototransformation of stilbene in what is styled as a "van der Waals Nanocapsule", *viz*. a crystal obtained from a solution containing *p*-hexanoylcalix[4]arene and *trans*- or *cis*-stilbene, which X-ray crystallography shows in the latter case to be a stacked π–π dimer located in the center of the capsule.[156] UV irradiation of the crystals

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[153] H. Xu, S. P. Stampp and D. M. Rudkevich, *Org. Lett.* **2003**, 5, 4583; H. Xu and D. M. Rudkevich, *ibid.* **2005**, 7, 3223.

[154] J. Fujita, Y. Ohnishi, Y. Ochiai and S. Matsui, *Appl. Phys. Lett.* **1996**, 68, 1297; J. Fujita, Y. Ohnishi, Y. Ochiai, E. Nomura and S. Matsui, *J. Vacuum Sci. & Tech B* **1996**, 14, 4272; Y. Ohnishi, J. Fujita, Y. Ochiai and S. Matsui, *Microelectronic Engineering* **1997**, 35, 117.

[155] J. L. Coffer, R. R. Chandler, C. D. Gutsche, I. Alam, R. F. Pinizzoto and H. Yang, *J. Phys. Chem.* **1993**, 97, 696.

[156] G. S. Ananchenko, K. A. Udachin, J. A. Ripmeester, T. Perrier and A. W. Coleman, *Chem. Eur. J.* **2006**, 12, 2441.

induces the rapid establishment of a photoequilibrium between the *cis* and *trans* isomers followed by slower reactions to form dihydrophenanthrene (which irreversibly oxidizes to phenanthrene) and small amounts of two of the stereoisomers of tetraphenylcyclobutane, the results generally mirroring those observed in solution photochemistry.

8.6 Patent Literature

Two hundred or more patents have been issued for a variety of practical applications of calixarene-based molecules. Many of these, not surprisingly, involve the chemistry that is discussed in this book, especially the use of calixarenes in systems in which selective ion complexation plays the central role. A number, however, deal with quite different sorts of applications including, *inter alia*, the use of calixarenes as adhesion promoters,[157] electrophotographic photoreceptors,[158] photographic toners,[159] hair dyes,[160] diesel fuel additives,[161] curing agents,[162] antistatic agents,[163] antioxidants,[164] stabilizers,[165] temperature sensing devices,[166] pressure sensitive recording material,[167] flame proofing compounds,[168] safety glass compositions,[169] optical recording materials[170] and antibacterial agents.[171] The patents listed here were

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[157] R. G. Leonard and S. J. Harris, US, US 4,695,615, Sept **1987**.

[158] S. Maeda, Jpn. Kokai Tokkyo Koho, JP 05,323,632, May **1992**.

[159] S. Kuramoto, M. Orihara and T. Hagiwara, Jpn. Kokai Tokkyo Koho, JP 04,295,862, March **1991**; M. Yasuno and M. Kobayashi, Jpn. Kokai Tokkyo Koho, JP 05,127,426, Nov **1991**; S. Yamanaka, K. Sukata and S. Sugawara, Eur. Pat. Appl., EP 514,867, Nov **1992**; K. Iwasa, O. Mukushiro and J. Matsura, Jpn. Kokai Tokkyo Koho, JP 07,234,547, Sept **1995**; L. H. Ueda, Jpn. Kokai Tokkyo Koho, JP 05,119,534, May **1993**; K. Isawa, O. Mukushiro and J. Matsura, Jpn. Kokai Tokkyo Koho, JP 07,234,544, Sept **1995**; T. Hagiwara, S. Kuramoto and K. Kawasaki, Jpn. Kokai Tokkyo Koho, JP 05,216,278; S.-I. Yamanaka and K. Sukata, Eur. Pat. Appl., EP 712,049, Nov **1994**; M. Tomita, Y. Asahina, F. Sasaki, F. Kondo, C. Mochizuki, Y. Iwamoto and T. Minamitani, Jpn. Kokai Tokkyo Koho, JP 05,341,577; T. Takahashi, T. Nagatsu and K. Tanaka, Jpn. Kokai Tokkyo Koho, JP 07,295,299, Apr **1994**.

[160] H. Noack, H. L. Weinelt and B. Noll, B. Ger. Offen., DE 4,135,760, Oct **1991**.

[161] R. L. Sung, T. F. Derosa and B. J. Kaufman, US, US 5,199,959, Mar **1992**; I. Alam and R. L. Sung, US, US 5,482,520, Jun **1994**.

[162] W. M. Rolfe and M. R. Thoseby, Eur. Pat. Appl., EP 503,764, Feb **1991**.

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[164] D. Ehrhardt, S. Hauptmann and G. Mann, Ger. (East), DD 290,427, Dec **1989**; D. Ehrhardt, S. Hauptmann, G. Mann, W. Mertens, B. Noll, F. Weinelt and H. Weinelt, Ger. (East), DD 291,088, Sept **1988**; D. Ehrhardt, S. Hauptmann, G. Mann, W. Mertens, B. Noll, F. Weinelt and G. Weinelt, Ger. (East), DD 290,412, May **1991**.

[165] D. Ehrhardt, S. Hauptmann, G. Mann, F. Weinelt, G. Noll, H. Weinelt, H. G. Fuchs, I. Solf and L. Wever, Ger. (East), DD 290,429, May **1991**; G. Goermar, M. Schulz, K. Seiffarth and J. Bachmann, Ger. (East), DD 290,905, Jul **1985**; K. Seiffarth, M. Schulz, G. Goermar and J. Bachmann, Ger. (East), DD 273,844, Feb **1986**.

[166] T. Komori and S. Shinkai, Jpn. Kokai Tokkyo Koho, JP 05,271,175, Oct **1993**.

[167] H. Sato, K. Yoshikawa, O. Mukushiro and M. Kanasugi, Jpn. Kokai Tokkyo Koho, JP 088,192,573, Jan **1995**.

[168] A. Petri, Eur. Pat. Appl., EP 350,092, Jan **1990**.

[169] H. Shobi, N. Ueda and A. Bando, Jpn. Kokai Tokkyo Koho, JP 07,237,944, Feb **1994**; A. Bando, H. Shobi and N. Ueda, Jpn. Kokai Tokkyo Koho, JP 07,247,140, Mar **1994**.

[170] T. Nobori and S. Shinkai, Jpn. Kokai Tokkyo Koho, JP 06,95,292, Sept **1992**.

[171] S. J. Harris, PCT Int. Appl., WO 95,19,974, Jan **1994**.

issued between the years 1986 and 1995. No attempt has been made to include the more recent patent literature, and these examples are given simply to illustrate the scope of this facet of calixarene chemistry.

8.7 Concluding Remarks

Clarence S. Day says "*The world of books is the most remarkable creation of man... Even the books that do not last long, penetrate their own times at least, sailing farther than Ulysses even dreamed of, like ships on the seas*." Ulysses, in turn, as portrayed in Tennyson's poem, says "*all experience is an arch wherethrough gleams that untravelled world whose margin fades forever and forever as I move*". The present volume has strived to provide an updated and modestly detailed chart of the oceans through which sails the Ulyssian calixarenes. It has painted pictures of the important ports of call that have been visited, it has enumerated the various techniques for making safe passages, and is has limned the vast reserve of minutiae that make a voyage interesting and memorable. To what undreamed of supramolecular territories with ever fading margins this voyage next will go remains an intriguing question. As William Shakespeare's Antonio says in *The Tempest*, "Whereof what's past is prologue, what to come in yours and my discharge".

Appendices

Appendix A: Books

1. *Calixarenes in the Nanoworld*, ed. J. Harrowfield, P. Beer and J. Vicens, Kluwer Academic Publishers, **2006**.
2. *Calixarenes 2001*, ed. Z. Asfari, V. Böhmer, J. Harrowfield and J. Vicens, Kluwer Academic Publishers, **2001**.
3. *Calixarenes for Separations*, ed. G.J. Lumetta, R.D. Rogers and A.S. Gopalan, American Chemical Society Symposium Series 757, **2000**.
4. *Calixarenes in Action*, ed. L. Mandolini and R. Ungaro, Imperial College Press, London, **2000**.
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6. *Calixarenes 50th Anniversary*, ed. J. Vicens, M.-Z. Asfari and J. Harrowfield, Kluwer, Dordrecht, **1995**.
7. D.J. Cram and J.M. Cram, "Container Molecules and Their Guests", in *Monographs in Supramolecular Chemistry*, ed. J.F. Stoddart, Royal Society of Chemistry, London, **1994**.
8. *Calixarenes, A Versatile Class of Macrocyclic Compounds*, ed. J. Vicens and V. Böhmer, Kluwer, Dordrecht, **1991**.
9. C.D. Gutsche, "Calixarenes", in *Monographs in Supramolecular Chemistry*, ed. J.F. Stoddart, Royal Society of Chemistry, London, **1989**.

Appendix B: Long Reviews

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3. V. Böhmer, "Chapter 19: Calixarenes" in *The Chemistry of Phenols*, ed. Z. Rappoport, John Wiley & Sons, Ltd., **2003**, p. 1369–1441.
4. D.M. Rudkevich, "Nanoscale Molecular Containers", *Bull. Chem. Soc. Jpn.*, **2002**, 73, 393–413.

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11. E.B. Brouwer and J.A. Ripmeester, "Structural and Dynamic Properties of Solid Calixarenes", in *Advances in Supramolecular Chemistry*, ed. G.W. Gokel, Jai Press, Inc., **1999**, 121–155.
12. A. Jasat and J.C. Sherman, "Carceplexes and Hemicarceplexes", *Chem. Rev.*, **1999**, 99, 931–968.
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16. P. Timmerman, W. Verboom and D.N. Reinhoudt, "Resorcinarenes", *Tetrahedron*, **1996**, 52, 2663–2704.
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