NEIGHBOURING GROUP PARTICIPATION IN BICYCLIC SYSTEMS

PROEFSCHRIFT

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Aan mijn ouders
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A good neighbour is better
than a far friend

CONTENTS

CHAPTER I

General introduction

The most widely investigated effects of a substituent in an organic molecule are electronic effects transmitted through the carbon skeleton and steric effects. However, some substituents may influence a reaction by becoming bonded or partially bonded to the reaction centre, thus lowering a transition state or stabilizing an intermediate. This behaviour is called neighbouring group participation[1]. If the transition state of a rate-determining step is lowered in this way, an increased reaction rate occurs; the neighbouring group is then said to provide anchimeric assistance. One of the steps in such a reaction is

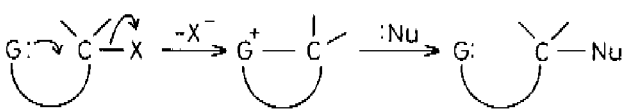


Fig. 1.1. Neighbouring group participation

an intramolecular nucleophilic displacement. Therefore, two requirements must be fulfilled. The neighbouring group must provide a pair of electrons and must be at a favourable distance from the reaction site.

Three principal methods can be used to detect neighbouring group participation. If anchimeric assistance is significant in a given system, the rate of solvolysis must be greater than

the rate of reaction in the absence of such participation. Consequently, a rate enhancement is one criterion for participation. The application of this criterion obviously requires some means of estimating the expected rate without participation. Reaction of the intermediate can give rise to isomeric products caused by rearrangement. The isolation of rearranged products constitutes a second criterion for the involvement of intermediates which result from neighbouring group participation. The stereochemical course of the reaction is a further mechanistic criterion. Finally, the intermediates can often be prepared and observed directly by spectroscopic techniques in highly acidic solvents with low nucleophilicity.

The first important evidence for the existence of neighbouring group participation was the demonstration by *Winstein*[2] that racemic *erythro* 3-bromo-2-butanol when treated with HBr gave *meso* 2,3-dibromobutane while either of the two *threo* isomers gave the racemic mixture. Since then many anchimeri-

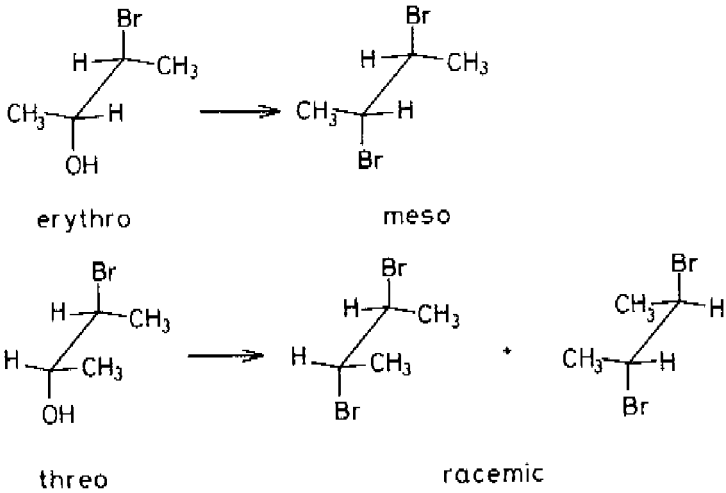


Fig. 1.2. Neighbouring group participation in 3-bromo-2-butanol

cally assisted reactions have been presented in the literature[3] Some of the more important neighbouring groups are COO^-, OCOR,

COOR, OR, OH, O^-, NR_2, SH, SR, S^-, Cl, Br and I. Besides lone-pair electrons also π- and even σ-electrons can provide anchimeric assistance. Some examples of neighbouring group participation by hetero-atoms will be discussed individually.

Neighbouring oxygen

The anchimeric assistance by oxygen is well documented. Participation by carbonyl, hydroxyl and ether groups has been described[3,4]. An example of remote oxygen participation in a

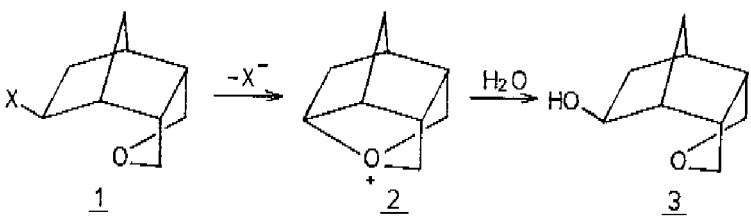


Fig. 1.3. Remote oxygen participation

rigid system was presented by *Wilder et al.*[4]. In the solvolysis of 1 oxygen was shown to participate *via* oxonium ion 2, leading to a moderate rate enhancement with respect to the *exo* annulated species. The anchimeric assistance of the carbonyl group is highly efficient in the hydrolysis of phtalamic acid[5]. In

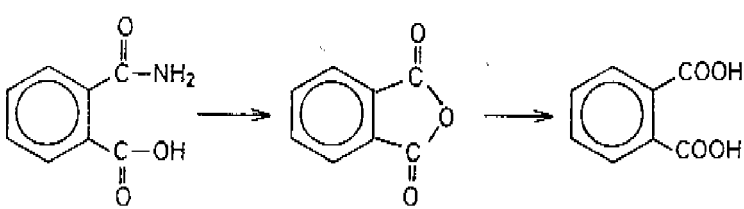


Fig. 1.4. Hydrolysis of phtalamic acid

10^{-3} M hydrochloric acid the rate is 75,800 times greater than that for benzamide. The reaction involves intramolecular nucleophilic participation with phtalic anhydride as an intermediate.

Neighbouring nitrogen

The nitrogen atom has a large effect on solvolytic displacement reactions. Many reactions proceeding through ammonium ions as intermediates have been studied[3,6]. Special interest was given to the intramolecular catalysis of nitrogen in ester hydrolysis, particularly in biochemical and enzymological reactions[7]. The participation by an imidazole group is of particular interest because of the analogy with the participation of histidine in reactions catalyzed by several esterases and proteinases. Intramolecular imidazole participation occurs in the hydrolysis of 4-(2-acetoxyethyl)-imidazole 4[8]. The rate

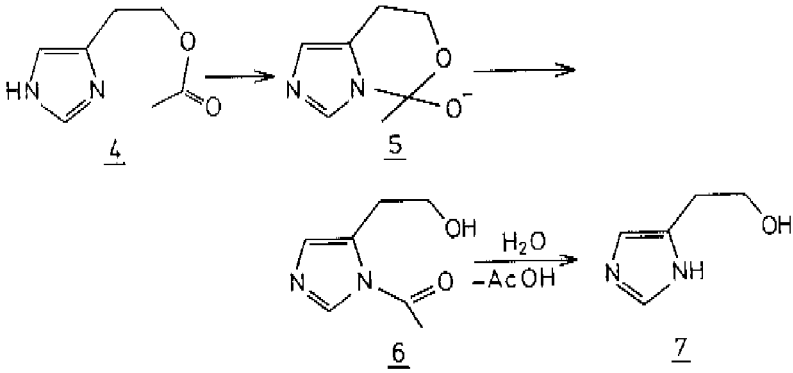


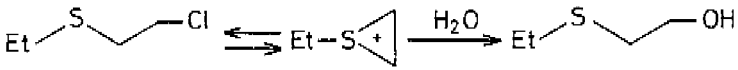
Fig. 1.5. Hydrolysis of 4-(2-acetoxyethyl)-imidazole

enhancement is caused by the occurrence of the tetrahedral intermediate 5, thus facilitating the acyl-oxygen bond fission.

Neighbouring sulphur[9]

Probably the first and most thoroughly studied reactions involving participation by a thio-ether group are those of 2,2'-bischloroethyl sulphide[3]. The effect of sulphur partici-

pation as compared with oxygen participation is shown by the fact that β-chloroethyl sulphide 8 is hydrolyzed 10^4 times more rapidly than the corresponding ether. Apparently,



8 9 10

Fig. 1.6. Hydrolysis of β-chloroethyl ethyl sulphide

the sulphonium ion 9 is easily formed. The effect of neighbouring group participation on the course of a reaction is demonstrated by the bromination of 2-thianorbornenes. The bromination was found to proceed with rearrangement with

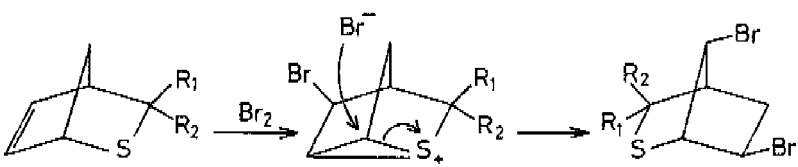


Fig. 1.7. Bromination of 2-thianorbornenes

formation of the 6,7-dibromides[10], indicating the preferential attack of the bromide ion on the 1-position. Sulphur is also a highly efficient intramolecular catalyst. Thus carbamate ester 11 cyclizes rapidly at 25° C with release of p-nitrophenol. The effective molarity of the neighbouring thiol group is 1.4×10^5 M in comparison with the bimolecular attack of a thiol on the unsubstituted phenyl carbamate ester (fig. 1.8)[11].

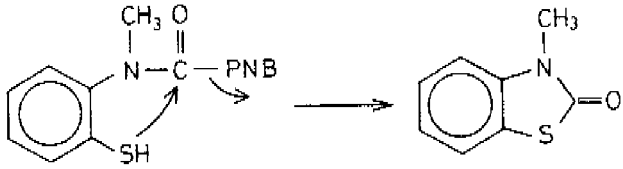


Fig. 1.8. Sulphur as an intramolecular catalyst

Neighbouring group participation in enzyme catalysis

Many reactions that ordinarily occur only under extreme conditions, proceed rapidly and quantitatively under mild conditions in the presence of the appropriate enzyme. In the enzymatic reactions several distinct functional groups are involved. These groups are usually distant from one another along the backbone of the enzyme, but are near each other in space. The initial step in enzymatic reactions involves the binding of one or more reactants to the enzyme surface. Such a process makes it possible to bring the substrate near the active site of the enzyme creating optimal reaction conditions. In other words, one of the principals of enzymatic catalysis is based on neighbouring group participation. For example, in the hydrolysis of peptides by α-chymotropsin[12] the active site consists of Asp. 102, His. 57 and Ser. 195 (see fig. 1.9). By interaction with the histidine unit, the conjugate base of the serine unit is formed, enabling the latter to attack the carbonyl group of the peptide. Thus the enzyme is acylated with departure of the amine fragment of the peptide. The hydrolysis of the acylated enzyme is in fact the reverse of the acylation process, leading to the liberation of the acid fragment of the peptide.

The aim of this thesis is to offer a better insight into the effects of neighbouring group participation in bicyclic

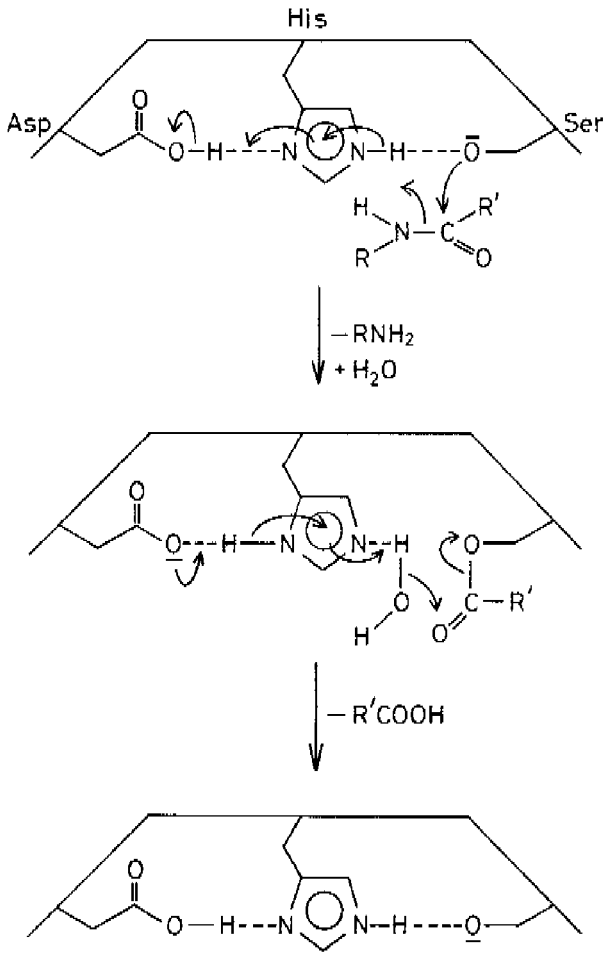


Fig. 1.9. Hydrolysis of peptides catalyzed by α-chymotropsin

systems. Special attention was paid to some aspects of anchimeric assistance of sulphur in nucleophilic displacement reactions and to the effect of positioning functional groups in such a manner as to facilitate intramolecular catalysis.

In Chapters II and III the mechanism for the solvolysis of 2,6-dichloro-9-thiabicyclo [3.3.1] nonane is discussed. It was established that the key intermediate in solvolysis is a sulphurane, oriented in a square pyramid, in which two positions are coordinated by a chloronium ion. This intermediate offers an explanation for the enhanced reactivity of the first chlorine atom with respect to the second one.

Chapter IV deals with some intramolecular reactions in 9-thiabicyclo [3.3.1] nonanes. It was shown that substituents on the 2- and 6-positions are ideally positioned to achieve 100% selectivity in ring closure reactions leading to oxa-thia-twistanes.

Some criteria for the participation of sulphur in the formation of carbocations are presented in Chapter V. The structural requirements for sulphur participation are discussed on the basis of the NMR spectra of several 2,6-disubstituted 9-thiabicyclo [3.3.1] nonanes in acidic solutions. Dimethyl-oxa-thia-twistane was shown to protonate on oxygen and therefore proved to be a model compound for the chloronium ion which appears in the solvolysis of 2,6-dichloro-9-thiabicyclo [3.3.1] nonane.

Finally, in Chapter VI a model for the dynamics of enzyme-substrate complexes is presented based on the principals of neighbouring group participation. As is demonstrated in this thesis, substituents in the 2- and 6-positions of the 9-thiabicyclo [3.3.1] nonane skeleton are oriented in such a way that an effective catalytic process can result. This intramolecular catalysis shows a striking resemblance to enzyme catalyzed reactions.

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CHAPTER II

Neighbouring group participation in the solvolysis of 2,6-dihalo-9-thiabicyclo[3.3.1]nonanes[1]

II.1 *Introduction*

It is well known that sulphur, not directly bonded to the reaction centre, may strongly effect the rate of a reaction by neighbouring group participation. Quite a few of these anchimerically assisted reactions have been studied, but only few of the intermediates have been characterized by spectroscopic techniques.

In 1966 *E.J. Corey et al.*[2] and *E.D. Weil et al.*[3] reported the synthesis of 2,6-dichloro-9-thiabicyclo[3.3.1]nonane 1 by the transannular addition of SCl_2 to cyclooctadiene. Both

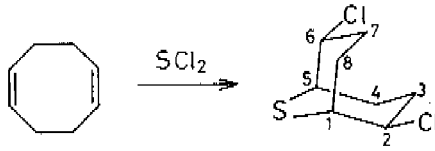

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Fig. 2.1. Synthesis of 2,6-dichloro-9-thiabicyclo[3.3.1]nonane

authors found that 1 is very reactive in nucleophilic substitution reactions, leading to a variety of 2,6-disubstituted 9-thiabicyclo[3.3.1]nonanes. Not only the high reaction rates, but also the stereochemistry is rather intriguing. All reaction products were shown to have the 3.3.1 skeleton with the substituents in the *endo* position. Based on these facts the intermediacy of sulphonium ion 2 was proposed. Attack of one of the lone pairs of sulphur towards C_2 assists in the release of chlorine with formation of a cyclic sulphonium ion 2. Addition

of a nucleophile (*e.g.* methanol) would then lead to 3. In a second step dimethoxide 5 is formed *via* a similar intermediate 4. Though this mechanism seems to be reasonable, some facts cannot be explained by it.

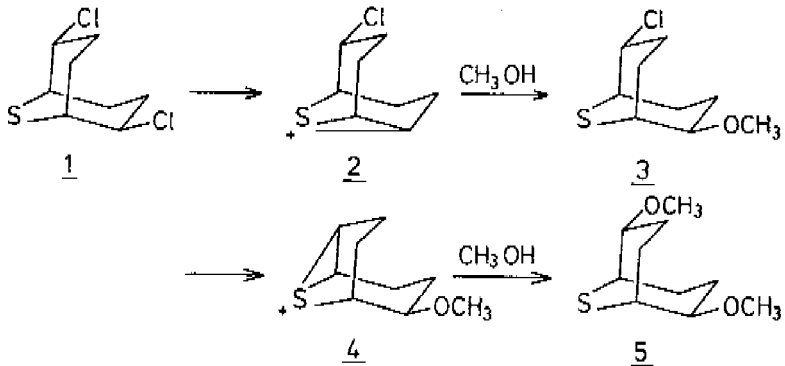


Fig. 2.2. Proposed mechanism for the solvolysis of 1

The chlorine atoms of 1 are unequally reactive towards replacement by the methoxy group. When 1 was boiled in methanol for several minutes, an oil was obtained in which the ratio of methoxy to chlorine as determined by NMR was 1:1; after seven hours of refluxing 1 in methanol this ratio was 3:1. If both chlorines were substituted *via* the same mechanism, one would not expect such a difference in the reaction rate of both steps. In order to give an explanation for the observed reactivity, the intermediates in the reaction sequence were trapped and characterized.

In generating the intermediate ions as long lived stable species, strong anhydrous acids were used as solvents, usually at low temperatures. Either Brönsted acids (*e.g.* H_2SO_4, HF, HSO_3F or CF_3SO_3H) or Lewis acids (*e.g.* SbF_5, $SbCl_5$ or $AlCl_3$) or mixtures of these (the so-called "super acids" such as HSO_3F/SbF_5) are suitable in carbocation chemistry because of the very low nucleophilicity of their conjugated bases. Liquid SO_2 or SO_2ClF and in some cases CH_2Cl_2 may be used as diluents.

II.2 *The intermediates in the solvolysis*

Dissolution of 1 in a mixture of HSO_3F and liquid SO_2 at -60° C gives rise to species 6. At -30° C 6 isomerizes to sulphonium ion 7, which is stable even at elevated temperatures. The structural assignments of both 6 and 7 are based on the NMR data and the chemical behaviour (see Chapter III).

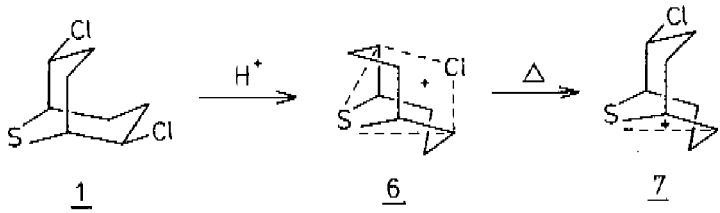


Fig. 2.3. Reaction of 1 with HSO_3F in liquid SO_2

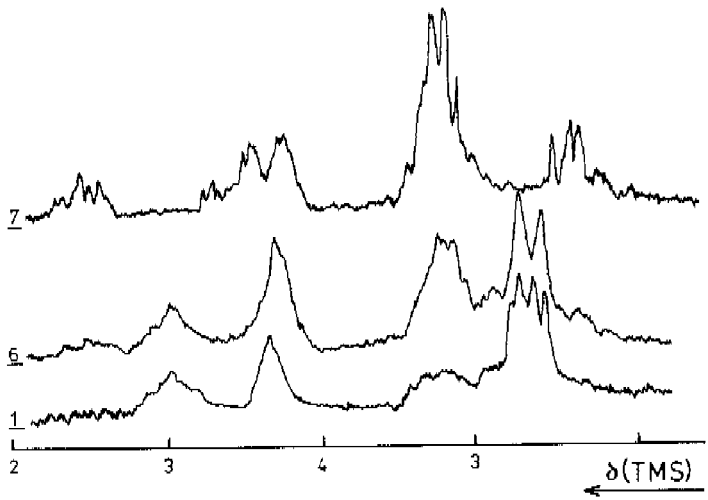


Fig. 2.4. PMR spectra of 1 in HSO_3F/liquid SO_2

Upon quenching either 6 or 7 in water only compounds 1 (*ca* 80% by internal return), 8 and 9 are formed. This indicates that in the formation of 6 and 7 no skeletal rearrangements are involved. Ions 6 and 7 are also formed in aprotic media.

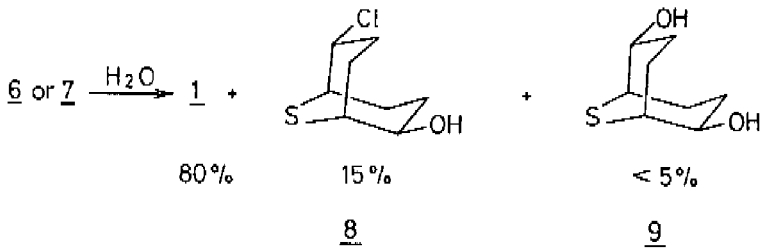


Fig. 2.5. Quenching of ions 6 and 7 in water

Addition of 1 in CD_2Cl_2 to a solution of SbF_5 in liquid SO_2 or to a suspension of $AlCl_3$ in liquid SO_2 led to 6, which again rearranged to 7 at elevated temperatures.

For comparison the spectra of several other 2,6-disubstituted 9-thiabicyclo [3.3.1] nonanes in acidic solutions were studied. Reaction of 1 with HBr in acetic acid leads to 2,6-dibromo-9-thiabicyclo [3.3.1] nonane 10; with NaI in acetone the corresponding diiodide 11 is formed. Hydrolysis of 1 with NaOH in water/dimethoxyethane gives dihydroxide 9, whereas methanolysis with $NaOCH_3$ in methanol furnishes dimethoxide 5[3]. The 2-chloro-6-methoxide 3 was prepared by boiling 1 in methanol during several minutes. In consequence of the enhanced reactivity of the first chlorine with respect to the second one 3 is formed in *ca* 95% yield. The synthesis of 2-chloro-6-hydroxy-9-thiabicyclo [3.3.1] nonane 8 was achieved by quenching a solution of 1 in HSO_3F with a suspension of water in liquid SO_2. The yield of 8 was poor, due to the high percentage of recovered 1 caused by internal return of chlorine (*vide supra*). This high

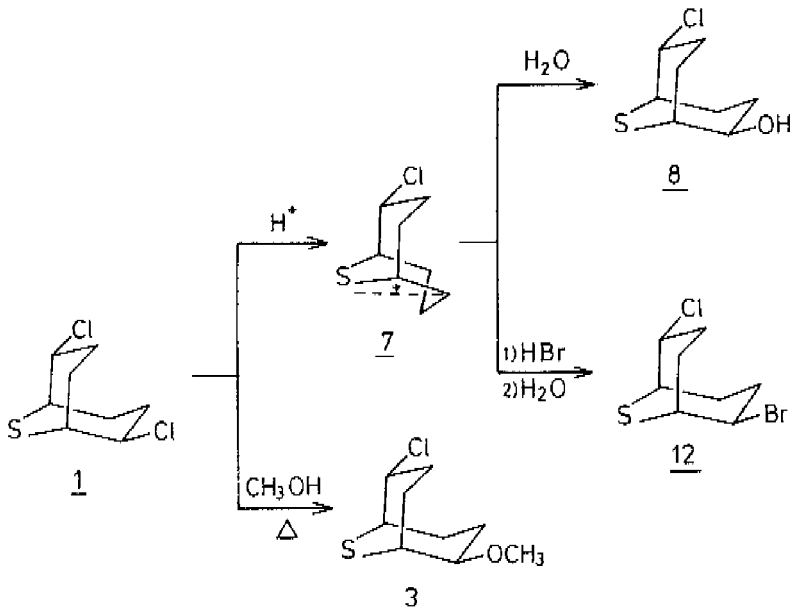


Fig. 2.6. Synthesis of some bicyclo [3.3.1] nonanes

degree of internal return was used favourably in the preparation of 2-chloro-6-bromo-9-thiabicyclo [3.3.1] nonane 12. Leading HBr through a solution of 1 in HSO_3F during half an hour followed by quenching in water gives the mixed halide 12, which was obtained in 70% yield, the rest being dibromide 10. This mixture was used as such in further experiments without separation.

The reaction course of 2,6-dibromo-10 and 2,6-diiodo-9-thiabicyclo [3.3.1] nonane 11 is similar to that of dichloride 1. In HSO_3F/liquid SO_2 at -60° C a symmetric bromonium ion 13 and an iodonium ion 15 are formed, respectively. At elevated temperatures 13 and 15 isomerize to the asymmetric sulphonium ions 14 and 16. The thermal stability of the iodonium ion 16 is higher than that of the bromonium ion 14 which in turn is higher than that of the chloronium ion 6. This order of stability is in agreement with the well known ability of Cl, Br

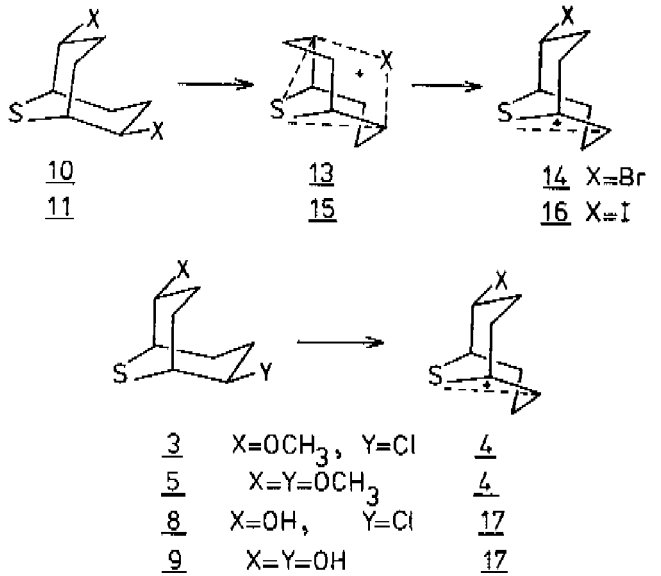


Fig. 2.7. Reaction of bicyclo [3.3.1] nonanes with HSO_3F

and I to increase their valency. Reaction of the 2-chloro-6-bromide 12 with HSO_3F in liquid SO_2 gives rise to both the chloronium ion 6 and the bromonium ion 13. The spectrum of this solution is identical to that of a mixture of dichloride 1 and dibromide 10 in HSO_3F/liquid SO_2. Solutions of the 2,6-dihydroxide 9, the 2,6-dimethoxide 5 as well as the 2-chloro-

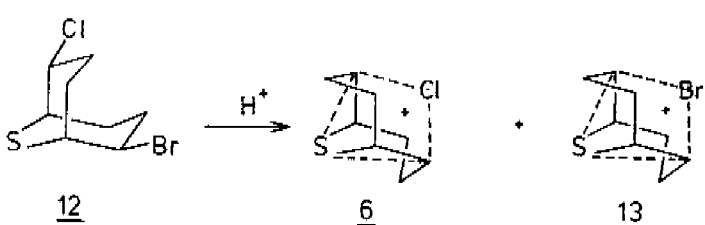


Fig. 2.8. Ions derived from 2-chloro-6-bromide 12

6-hydroxide 8 and the 2-chloro-6-methoxide 3 only show the presence of asymmetric sulphonium ions (17 and 4, respectively).

II.3 *Discussion*

The occurrence of 6 in the solvolysis of 2,6-dichloro-9-thiabicyclo [3.3.1] nonane 1 in methanol explains the fact that the first chlorine is released much faster than the second one. In the first step the chlorine on C_2 assists in the release of the chlorine on C_6 with formation of a chloronium ion. Apparently, a methoxy group cannot participate in solvolysis to the same extent. This is confirmed by the fact that with 2-chloro-6-methoxy-9-thiabicyclo [3.3.1] nonane 3 no bridged oxonium ion is formed.

Evidence for the nucleophilic participation by halogeno groups comes both from kinetic measurements and the direct observation of the intermediate halonium ions. A well known example is the reaction of 3-bromo-2-butanol 18 with HBr which

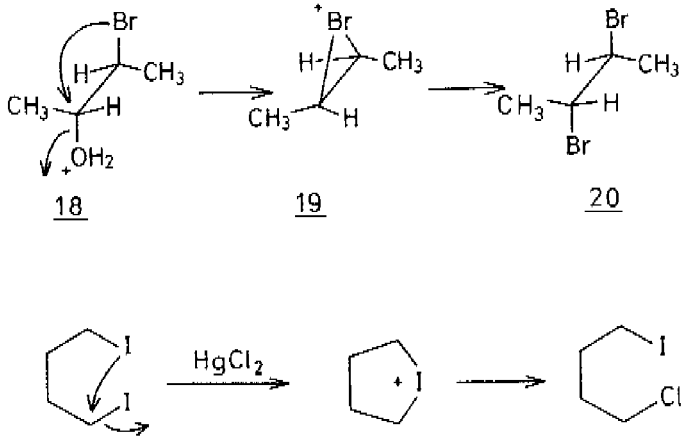


Fig. 2.9. Neighbouring group participation by halogens

proceeds *via* bromonium ion 19[4]. Nucleophilic participation by a more remote iodo group is provided by the observation that treatment of several 1,4-diiodoalkanes with $HgCl_2$ in chloroform replaces one of the iodo groups with chloride, but that the second iodo group is inert. With the development of highly acidic solvents, such as SbF_5/SO_2 solutions, the preparation and direct observation and in some cases even isolation of stable halonium ions have become possible. Both acyclic and cyclic halonium ions have been studied. The cyclic halonium ions include three-membered ring ethylenehalonium ions[5], five-membered ring tetramethylenehalonium ions[6] and six-membered ring pentamethylenehalonium ions[7] (see Fig. 2.10).

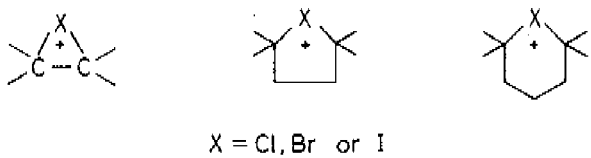


Fig. 2.10. Cyclic halonium ions

It was found that both the ease of formation and the stability of the halonium ions increase in the order Cl < Br < I. Fluoronium ions have never been observed. *Olah et al.*[8] have carried out a comprehensive study of the structure of cyclic halonium ions by CMR spectroscopy.

The chloronium ion formed in the solvolysis of 1 is stabilized by electron donation from sulphur to C_2 and C_6. Thus the positive charge is delocalized on C_1, C_2, C_5, C_6 and S.

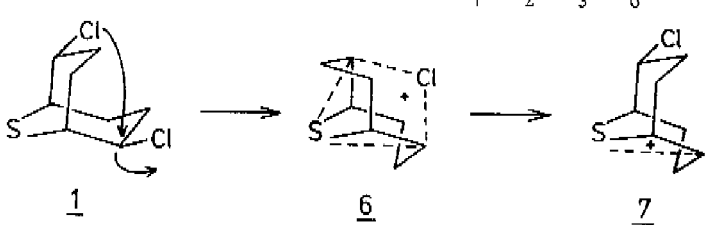
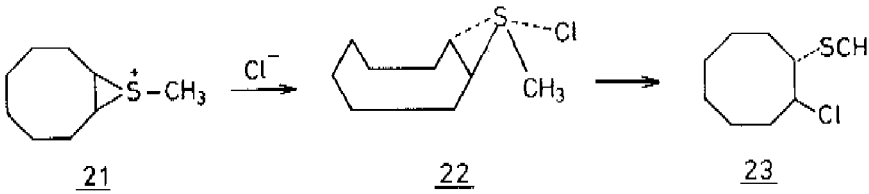


Fig. 2.11. The first step in the solvolysis

Therefore, 6 is best described as a sulphurane, oriented in a *square pyramid*, in which two positions are coordinated by a chloronium ion. This configuration increases the stability of the chloronium ion.

The occurrence of a sulphurane as an intermediate in the reaction of cyclooctene-5-methylepisulphonium-2,4,6-trinitrobenzenesulphonate 21 with nucleophiles has been demonstrated by *Owsley et al.*[9]. Thus a chloride ion attacks at sulphur

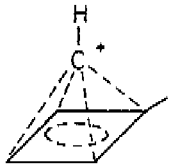


21 22 23

Fig. 2.12. Reaction of cyclooctene episulphonium ion with chloride ion

with formation of sulphurane 22 which was characterized by NMR in CD_3NO_2 at -5^{o} C and is stable for at least 30 minutes. At room temperature 22 rapidly decomposes to *trans*-1-chloro-2-(methylthio)cyclooctane 23. Sulphurane 22 was proposed to have a square pyramidal configuration based on extended Hückel MO calculations.

Chloronium ion 6 has another interesting feature; the carbon atoms C_2 and C_6 are five-coordinated. The first suggestion of a higher coordination number than four for the carbon atom was made by *Wilson*[10] and *Winstein*[11]. Since then nonclassical ions with a pentacoordinated carbon atom have become common phenomena in the literature. Among these are the more recently described carbocations such as 24[12,13,14], which have a square pyramidal configuration involving a pentacoordinated carbon atom. Even a hexacoordinated carbon atom



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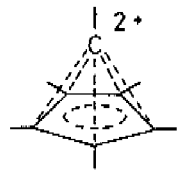

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Fig. 2.13. Pyramidal carbocations

has been shown to occur in dication 25 by *Hogeveen et al.*[15]. In chloronium ion 6 a pyramidal configuration for C_2 and C_6 would make the best fit.

At elevated temperatures 6 isomerizes to sulphonium ion 7. Evidently, the driving force for this rearrangement is the rehybridization of sulphur. Ion 7 is best characterized as a cyclic sulphonium ion in which the positive charge is mainly delocalized on sulphur and C_2. This is based on the CMR data (see Chapter III). The displacement of the second chlorine in 1 by methoxy is achieved *via* sulphonium ion 4 by anchimeric assistance of sulphur. Apparently, the activation energy for this process is higher than that of the process described above. This causes the second chlorine to be replaced much slower than the first one.

Since the first step in the solvolysis is enhanced by anchimeric assistance of the neighbouring group (*e.g.* chlorine), reaction of 1 with a nucleophile leading to the introduction of a better neighbouring participating group (*e.g.* a thioether), must lead to a process in which the second chlorine is replaced faster than the first one. Indeed, when 1 was allowed to react with thiourea, the second thiouronium group was introduced much faster than the first one: upon reaction of 1 with 1 eq. thiourea, only ½ eq. disubstituted product 27 together with ½ eq. unchanged 1 was isolated. No

mono thiouronium salt could be detected indicating that the second step is much faster than the first.

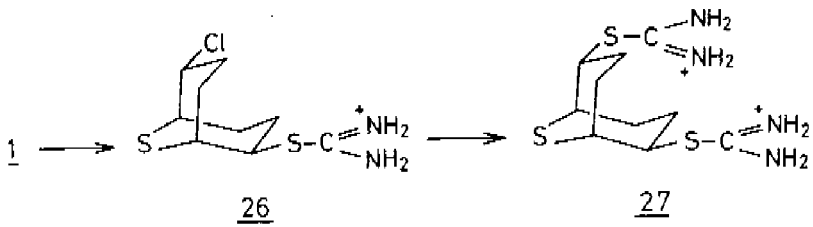

Fig. 2.14. Reaction of 1 with thiourea

A priori sulphonium ion 7 can open in three different manners. Attack of a nucleophile (*e.g.* methanol) at C_5 would lead to a cyclooctene episulphide (path a), whereas with substitution on C_1 (path b) a bicyclo [4.2.1] nonane would be formed. Since the positive charge is mainly on C_2 all products have the 3.3.1 skeleton by the attack of the nucleophile on C_2 (path c).

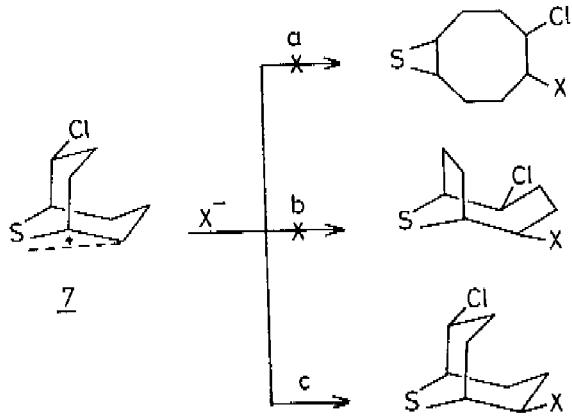

Fig. 2.15. Possible reactions of 7 with a nucleophile

II.4 *Experimental*

1 was synthesized following the procedure of *Corey*[2]. Compounds 5, 9, 10, 11, 18, and 19 are described by *Weil*[3].

► 2-Chloro-6-methoxy-9-thiabicyclo [3.3.1] nonane (3)
10 g (0.047 mol) 1 in 150 ml methanol was refluxed until TLC indicated the absence of starting material (10-15 min). The solution was concentrated; chromatography on silica/$CHCl_3$ yielded 9.3 g (95%) 5, b.p. 75-80°/0.01 mm.

► 2-Chloro-6-hydroxy-9-thiabicyclo [3.3.1] nonane (8)
5 g (0.024 mol) 1 was dissolved in 15 ml HSO_3F. The resulting solution of the sulphonium salt 7 was poured into a suspension of water in liquid SO_2 at -60° C. CH_2Cl_2 was added and the mixture was allowed to warm up to room temperature. The organic layer was washed with water, 10% aqueous $NaHCO_3$ and water, dried and concentrated. Chromatography on silica with $CHCl_3/CH_3OH$ 10:1 as eluent gave 3.3 g (65%) recovery of 1 and 1.4 g (30%) 8.

► 2-Chloro-6-bromo-9-thiabicyclo [3.3.1] nonane (12)
A stream of HBr was passed through a solution of 1 g (0.005 mol) 1 in 10 ml HSO_3F during 30 min. The solution was poured into ice-water and extracted with CH_2Cl_2. The organic layer was washed with 10% $NaHCO_3$ and water. Removal of the solvent gave 1.2 g of a mixture of 12 (*ca* 70%) and dibromide 10 (*ca* 30%). This was used as such without purification.

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CHAPTER III

Structural assignment of the intermediates;

a CMR and quantumchemical study

III.1 *Introduction*

Neighbouring group participation of sulphur in nucleophilic displacement reactions is known to occur when a three-, five-, six- or seven-membered cyclic sulphonium ion can be formed. γ-Chloro sulphides which on cyclization would form a four-membered ring are no more reactive than *n*-hexyl chloride. That five-, six- and seven-membered sulphonium rings are formed has been demonstrated by the isolation of cyclic sulphonium salts from the corresponding ω-chloro sulphides[1]. Three-membered ring ethylene sulphonium ions have been proposed as intermediates long ago. Recently, some of these episulphonium ions have been isolated and characterized[2-5]. Different methods have been used to prepare episulphonium ions. The stable episulphonium complexes of cyclooctene[2] and *cis*-di-*tert.*-butylethene[3] have been synthesized by alkylation of the corresponding episulphides. More general methods were reported

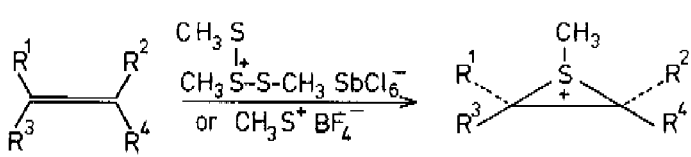


Fig. 3.1. Preparation of episulphonium ions

by *Smit et al.*[4] and *Capozzi et al.*[5] by the alkylthiolation of alkenes. The structural assignment of these ions is based on NMR data and chemical evidence. CMR spectroscopy has proved to be particularly useful in understanding the structure of carbonium ions. The effect of introducing a formal positive charge on sulphur is reflected in a moderate downfield shift in the CMR spectrum of the adjacent carbon atoms[3]. Although some NMR data have been presented[2,3,5], little is known about the structure of unsymmetrically substituted episulphonium ions.

III.1 *Structure of the intermediate ions in the solvolysis of 2,6-dichloro-9-thiabicyclo [3.3.1] nonane*

The structural assignment of the intermediates in the solvolysis of 2,6-dihalo-9-thiabicyclo [3.3.1] nonanes is based on the following considerations.

The CMR spectrum of 2 shows four absorption signals. This points to a symmetric structure. *A priori*, three feasible

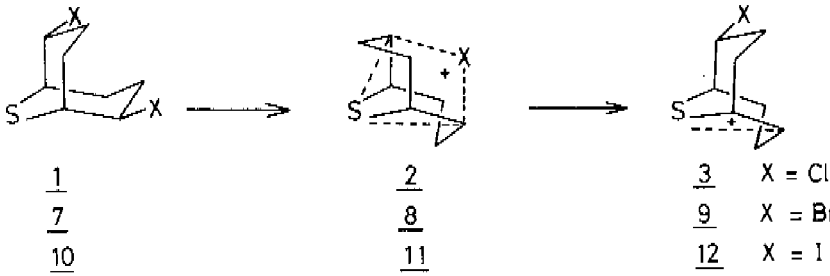


Fig. 3.2. Intermediates in the solvolysis of 2,6-dihalo-9-thiabicyclo [3.3.1] nonane

structures fulfill the requirement of symmetry.
Complexation of both chlorines with the acid used would result in a downfield shift of the adjacent carbon atoms in the CMR spectrum. On the contrary, an upfield shift is observed. Fur-

thermore, one would expect a temperature and solvent dependent spectrum which is not observed. The carbon chemical shifts are the same with the different acids (HSO_3F, SbF_5 and $AlCl_3$) used in the generation of the intermediates as long lived species. *Protonation or complexation on sulphur*. This possibility would require a fast exchange of the proton on sulphur between both sites as shown in fig. 3.3. Proton inversion can be obtained

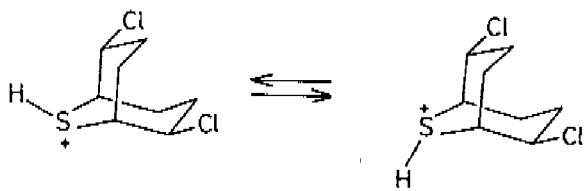
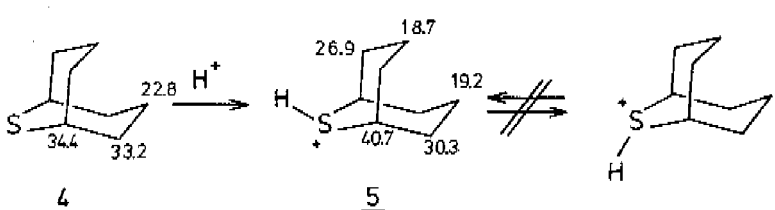


Fig. 3.3. Inversion of the proton on sulphur

via an intra- or intermolecular pathway. In the latter case proton exchange with the solvent is involved. Proton inversion in protonated sulphides is slow relative to the NMR time scale. For example, protonation of diisopropyl sulphide gives rise to the observation of diastereotopic methyl groups in the NMR spectrum[6]. The CMR spectrum of protonated 9-thiabicyclo[3.3.1]-nonane 5 shows five absorptions, because the proton is not located in the plane of symmetry through sulphur. This indeed



4 5

Fig. 3.4. Protonation of 9-thiabicyclo[3.3.1]nonane
CMR chemical shifts are given in the figure

points to a relatively high energy barrier for proton inversion on sulphur. Apparently, the basicity of sulphur in 1 is lowered by the presence of both chlorine atoms. This implies that a proton or another electrophile will attack on chlorine. The lowered basicity of sulphur in 1, with respect to 4, reflects itself in the unreactivity towards methylating agents. Whereas 4 reacts readily with methyl iodide under formation of sulphonium iodide 6, no reaction of 1 occurs even with strong methylating reagents such as trimethyl oxonium salts and methyl

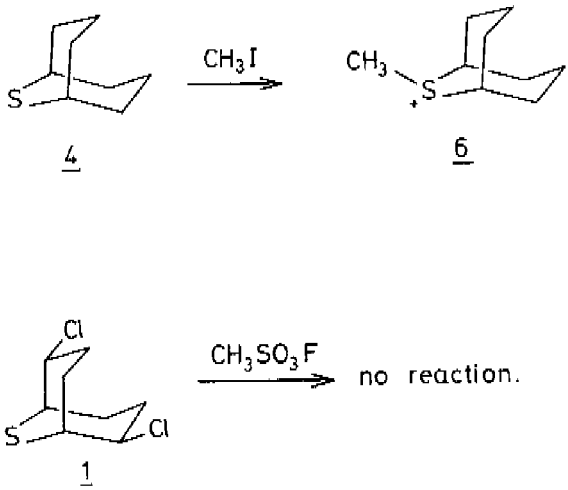
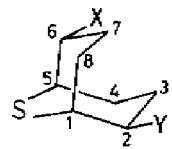


Fig. 3.5. Methylation on sulphur

fluorosulphonate. Protonation on sulphur can also be eliminated by comparison of the CMR spectra for different media. The spectrum of ion 2 in HSO_3F/liquid SO_2 and in the aprotic media SbF_5/CD_2/liquid SO_2 or $AlCl_3/CD_2Cl_2$/liquid SO_2 are identical. This is not the case for the unsubstituted sulphide 4. *Structure 2 as depicted in figure 3.2* offers a good explanation for the CMR spectra and the chemical behaviour. In the CMR spectrum of 2, C_2 and C_6 show an upfield shift compared with 1 of 8.1 ppm (Table III.2). The CMR spectra of the 2,6-disubsti-

Table III.1

CMR spectra of 2,6-disubstituted 9-thiabicyclo [3.3.1] nonanes
Shifts in ppm relative to external TMS



X	Y	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8		Solvent
Cl	Cl	38.5	63.8	33.8	29.9						$CDCl_3$
Br	Br	38.8	57.0	34.7	31.3						$CDCl_3$
I	I	39.9	37.6	37.1	33.7						$CDCl_3$
Br	Cl	37.7	62.9	32.9	29.5	38.0	56.3	33.9	30.3		$CDCl_3$
OH	OH	38.0	71.9	31.6	27.2						DMF
OCH_3	OCH_3	34.5	81.4	29.4	27.7					56.4(OCH_3)	$CDCl_3$

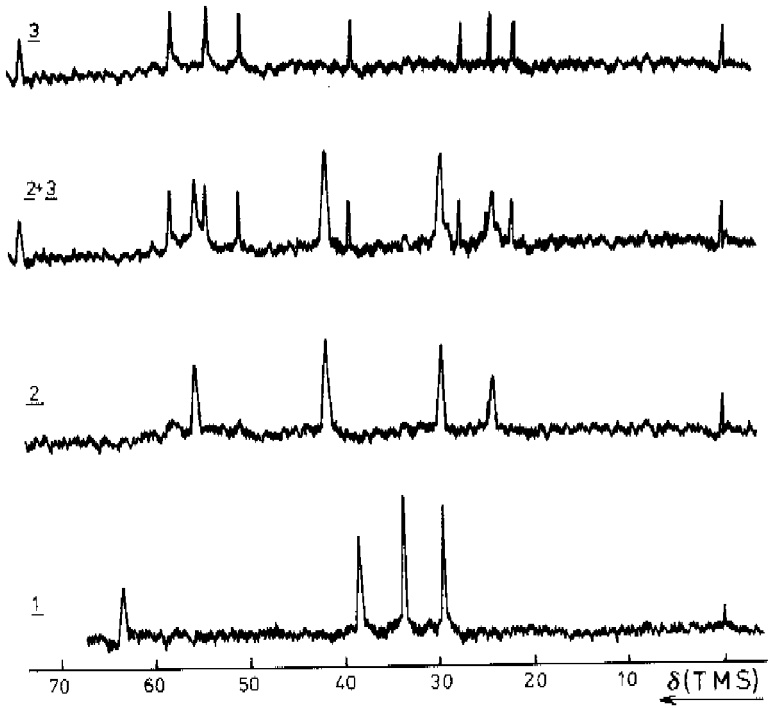


Fig. 3.6. CMR spectra of 1 in $CDCl_3$ and HSO_3F/liq. SO_2

tuted 9-thiabicyclo [3.3.1] nonanes are given in Table III.1. This upfield shift can be explained by an increase in carbon coordination at these positions which offsets the effect of a positive charge induced by chloronium coordination. The effect of increased coordination at carbon on the chemical shift has been demonstrated clearly for the 2-norbornyl cation[7] (fig. 3.7). The CMR spectrum shows that the norbornyl cation is a nonclassical ion with a pentacoordinated carbon atom. Due to the increase in coordination this methylene carbon atom is not deshielded (δ=22.4 ppm). The tetracoordinated carbons to which

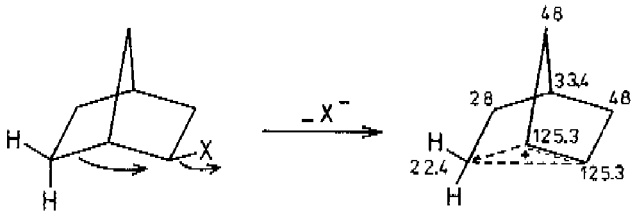


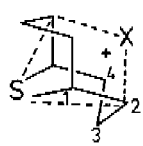
Fig. 3.7. The 2-norbornyl cation
CMR chemical shifts are given in the figure

bridging takes place show more deshielding (δ=125.3 ppm), but are still much more shielded than expected for a classical ion.

The small downfield shift (3.4 ppm) for the bridgehead carbons in 2 is caused by a partial positive charge on sulphur. The introduction of a formal positive charge on sulphur would result in a downfield shift of at least 6 ppm as can be seen from the chemical shifts in 4 and 5 (fig. 3.4). The upfield shifts for the other carbon atoms might be ascribed to changing steric interaction. The CMR spectra of both the bromonium ion

Table III.2

CMR spectra of halonium ions derived from 2,6-dihalo-9-thiabicyclo [3.3.1] nonanes



X	C_1	C_2	C_3	C_4
Cl	42.0	55.7	29.7	24.2
Br	42.6	45.8	30.5	26.3
I	42.9	44.9	30.4	25.4

8 and the iodonium ion 11 can be explained along the same lines as for the chloronium ion 2. In the bromonium ion 8 C_2 and C_6 show an upfield shift of 11.2 ppm. The downfield shift for the bridgehead carbons (3.7 ppm) is comparable with the corresponding shift in the chloronium ion. This indicates that the positive charges on sulphur in both cases are comparable. In the iodonium ion 11, C_2 and C_6 shift downfield (7.4 ppm) as compared with the diiodide 10. In contrast with bromine and chlorine, iodine has an upfield effect on the α-carbon. Apparently, in going from diiodide 10 to the iodonium ion 11 the loss of this upfield effect causes C_2 and C_6 to shift downfield. Again the downfield shift of C_1 and C_5 (3.1 ppm) is of the same magnitude as for 2 and 8. In comparing the chemical shifts for these halonium ions with those for the tetramethylene halonium ions published by *Olah et al.*[8], one can conclude that the positive charge is indeed delocalized on sulphur.

Table III.3

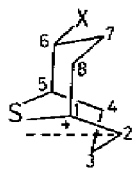
Tetramethylene halonium ions[a]

	X	C_1	C_2		X	C_1	C_2
13	Cl	44.7	30.3	16	Cl	77.8	33.8
14	Br	33.6	31.8	17	Br	70.7	36.3
15	I	8.3	34.9	18	I	51.0	38.7

The CMR spectrum of 2-chloro-6-bromo-9-thiabicyclo[3.3.1]-nonane 19 in HSO_3F/liquid SO_2 at -60° C reveals the formation of both chloronium ion 2 and bromonium ion 8. This spectrum is the same as that of a mixture of the dichloride 1 and the dibromide 7 under identical conditions. This also is in good agreement with the proposed structure. Thus one may conclude that 2 is indeed best described as a sulphurane, oriented in a

Table III.4

CMR spectra of episulphonium ions in HSO_3F/liq. SO_2
Shifts in ppm relative to external TMS



X	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
Cl	54.5	74.8	39.6	22.2	51.3	58.4	27.8	24.5
Br	58.5	75.2	40.7	22.8	52.2	45.2	28.1	25.6
I	57.6	74.9	42.5	20.5	53.5	28.0	27.5	22.6
OH	59.7	75.6	39.6	19.8	47.6	76.6	27.5	21.6
OCH_3	58.0	75.3	39.0	19.3	46.0	81.9	27.8	21.7

square pyramid, in which two positions are coordinated by a chloronium ion (see Chapter II).

Ion 3 is best characterized as a sulphonium ion in which the positive charge is mainly delocalized on sulphur and C_2. This is based on the CMR spectra which show a downfield shift for C_2 of *ca* 42 ppm with respect to 9-thiabicyclo [3.3.1] nonane 4. If the positive charge were localized on C_2, one would expect a chemical shift of at least 300 ppm (compare for example the *iso* propyl cation; δ=319.6 ppm). The observed chemical shift is 74.8 ppm, indicating that the positive charge is delocalized on sulphur. The other carbon of the episulphonium ring (C_1) shifts *ca* 20 ppm downfield. This indicates that C_1 bears much less positive charge than C_2. This downfield shift for C_1 might be ascribed mainly to an inductive effect of both sulphur and C_2. The positive charge localized on sulphur can also be seen from the downfield shift of 12.7 ppm for C_5 as compared with 1. In measuring these shifts one half of the molecule is compared with the unsubstituted sulphide 4, the other half with the dichloride 1, in order to eliminate the chlorine substitution effects.

The structures of the several episulphonium ions derived from 9-thiabicyclo [3.3.1] nonanes are comparable (Table III.4). In all these ions the chemical shifts of one half of the molecule are equivalent. This shows that the charge distribution in the episulphonium ions is the same in each case.

III.3 *Quantumchemical calculations*

In order to verify the experimental results on the intermediates in the solvolysis of 2,6-dichloro-9-thiabicyclo [3.3.1] nonane, semi-empirical CNDO/2 calculations[9] have been performed on 1, 2 and 3[10]. The bond distances, bond angles and torsion angles are given in Table III.5. The bond distance and angles indicated by an asterisk were optimized. It was found that 2 and 3 are indeed energy minima. The results of the calculations are summarized in Table III.6. The calculated energy for 3 is

Table III.5

Bond distances, bond angles and torsion angles

Bond distances, Å	1	2	3
S-C	1.80	1.80	1.80
C-C	1.54	1.54	1.54
C-H	1.09	1.09	1.09
C-Cl	1.76	1.885*	1.76
Bond angles, deg.			
C_5-S -C_1*	109.85	108.38	117.84
C_5-S -C_6*	40.94	49.1	40.94
C_1-S -C_2*	40.94	49.1	49.1
S -C_1-C_8	111	111	111
S -C_5-C_4	111	111	111
C_5-C_6-C_7	114	114	114
C_6-C_7-C_8	114	114	114
C_7-C_8-C_1	114	114	114
C_5-C_4-C_3	114	114	114
C_4-C_3-C_2	114	114	114
C_3-C_2-C_1	114	114	114
H -C -C	109.5	109.5	109.5
Torsion angles, deg.			
C_2-S -C_1-C_5*	295	288.5	288.5
C_6-S -C_5-C_1*	295	288.5	295
C_4-C_5-S -C_6	240	240	240
C_8-C_1-S -C_2	240	240	240
C_3-C_2-C_4-C_5	146	230	230
C_7-C_6-C_8-C_1	146	230	230
Cl_{10}-C_2-C_1-C_3	239.9		
Cl_{11}-C_6-C_5-C_7	239.9		239.9

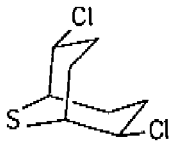
*These values were optimized

Table III.6

CNDO/2 results

	Total energy, a.u.		Charge densities					
	E	$E+E_{HCl}$	S	C_1	C_2	C_5	C_6	Cl
1	-109.88034		-0.16	+0.01	+0.12	+0.01	+0.12	-0.19
2	- 93.43520	-110.28873	+0.18	+0.10	-0.09	+0.10	-0.09	-0.15
3	- 93.28192	-110.13545	+0.10	+0.02	+0.09	+0.08	+0.01	-0.10

	Dipole moments, D	Overlap populations			
		$S-C_1$	$S-C_2$	$S-C_5$	$S-C_6$
1	1.50	0.74	0.11	0.74	0.11
2	4.93	0.66	0.46	0.66	0.46
3	5.58	0.86	0.60	0.78	0.18



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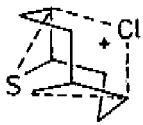

2

3

higher than that for 2. This is not in agreement with the experimental results which show that 3 is more stable than 2. Apparently, the energy of 3 is lowered by solvation. It is to be expected that the solvation energy for 3 is higher than that for 2, since the positive charge is less delocalized. This is also indicated by the higher calculated dipole moment of 3 as compared with 2.

The calculated negative charge density on chlorine in 1 is higher than that on sulphur. This indicates that an electrophile will attack on chlorine and not on sulphur, which is in agreement with the unreactivity of 1 towards methylating agents (see Section III.2). In 2 and 3 sulphur bears a positive charge.

The effect of sulphur participation is nicely demonstrated by the calculated overlap populations[11]. In chloronium ion 2 sulphur forms a strong bond with C_2 and C_6 showing that sulphur indeed has a sulphurane configuration. In going from 2 to 3 the overlap between sulphur and C_2 is increased at the cost of the S-C_6 bond. This is in good agreement with an episulphonium ion structure for 3.

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CHAPTER IV

Neighbouring Group effects in the formation of twistanes[1]

IV.1 *Introduction*

In the previous chapters the occurrance of a chloronium ion in the solvolysis of 2,6-dichloro-9-thiabicyclo [3.3.1] nonane is discussed. The formation of this ion implies the intramolecular attack of chlorine on C_6 at the incipient carbonium ion on C_2. In order to demonstrate this ring closure, thia-oxa-twistanes were synthesized directly from suitably functionalized 9-thiabicyclo [3.3.1] nonanes (Fig. 4.1).

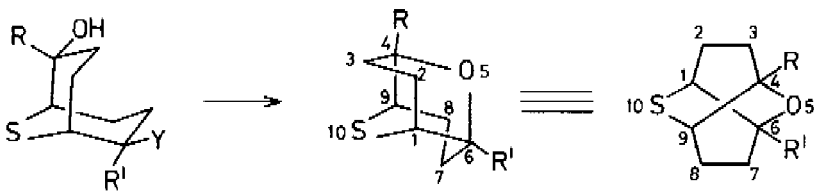
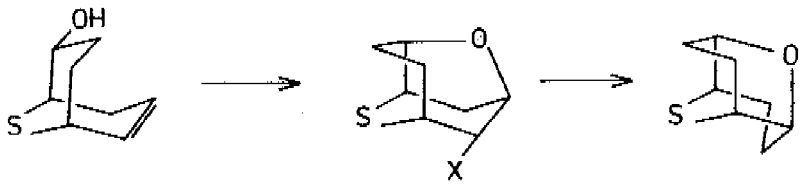


Fig. 4.1. Ring closure of 2,6-disubstituted 9-thiabicyclo-[3.3.1] nonanes

The synthesis of oxa-thia-twistane (3) has been reported by *Ganter et al.*[2] starting from 2-hydroxy-9-thiabicyclo [3.3.1] -non-6-ene (1). Reaction of 1 with *t*-BuOI led to iodo-*iso*-twistane (2, X=I) which could be transformed to the twistane (3) by $LiAlH_4$ reduction of the corresponding tosylate (2, X=OTs).

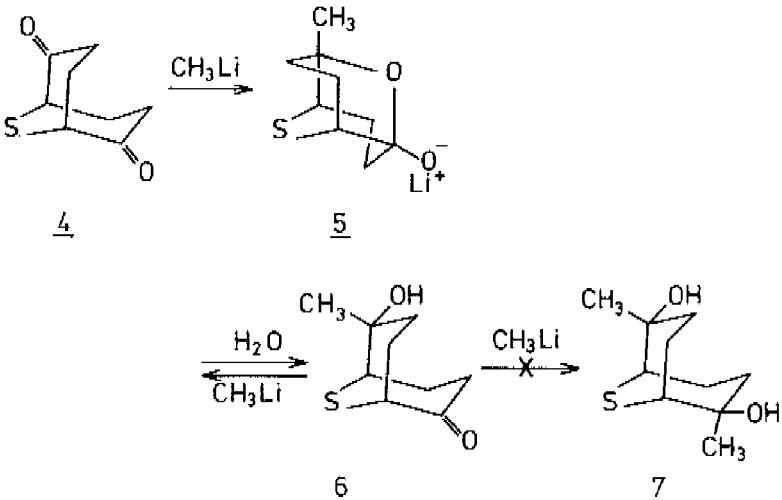


1 2 3

Fig. 4.2. Synthesis of oxa-thia-twistane

IV.2 *Intramolecular reactions in bicyclo [3.3.1] nonanes*

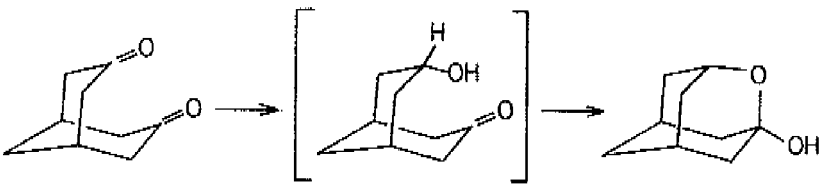
In an attempt to synthesize diol 7 diketone 4 was treated with 3 eq. CH_3Li in THF at -50° C. Aqueous work-up afforded the 1:1 adduct 6 as sole product in 90% yield. Apparently, the second keto group is unreactive towards CH_3Li. The occurrence of lactolate anion 5 would explain this behaviour.



4 5 6 7

Fig. 4.3. Reaction of diketone 4 with CH_3Li

The formation of a lactol from a keto-alcohol in a bicyclic system has a precedent. In the reduction of bicyclo-[3.3.1] nonane-3,7-dione 8 *Stetter* and co-workers[3] found that the resulting keto-alcohol 9 underwent a direct ring closure to the oxaadamantanol 10.

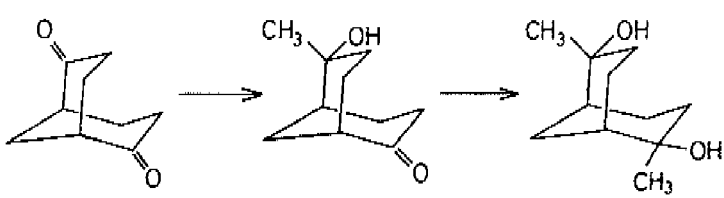


8 9 10

Fig. 4.4. Reduction of bicyclo [3.3.1] nonane-3,7-dione

The intermediacy of the lactolate anion 5 (an oxa-thia-twistane) formed by the CH_3Li addition to 4 was established by IR measurements in dioxane. The IR spectrum of 6 (0.5% in dioxane) showed characteristic absorptions at 3485 cm^{-1} (O-H) and 1695 cm^{-1} (C=O). Addition of 1 eq. CH_3Li caused both absorptions to disappear and an absorption appeared at 1620 cm^{-1}. This absorption can be assigned to an asymmetric O-C-O stretch in 5 as is the case in carboxylate anions. Upon addition of water 6 was recovered.

The reaction of CH_3Li with bicyclo [3.3.1] nonane-2,6-dione 11 led to both keto-alcohol 12 and diol 13. Seemingly in this



11 12 13

Fig. 4.5. Reaction of bicyclo [3.3.1] nonane-2,6-dione with CH_3Li

case no lactolate anion comparable with 5 is formed. Indeed in the IR spectrum of 12 no absorption appeared near 1620 cm^{-1} upon the addition of 1 eq. CH_3Li indicating the absence of a transannular interaction.

The fact that in the sulphur analogue a ring closure takes place, might be ascribed to a decrease in the distance between C_2 and C_6 by the bigger sulphur atom as compared with carbon. This would place the oxygen anion nearer to the carbonyl group, thus facilitating a transannular reaction. A second explanation might be found in an activating effect of sulphur on the keto group. Due to the extra polarization of the keto group *via* an orbital overlap with sulphur the equilibrium between the open

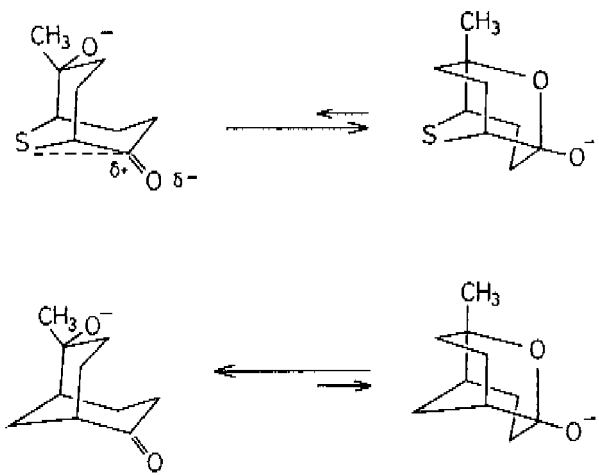


Fig. 5.6. Equilibria between open and closed structures; the effect of polarization by sulphur

structure and the lactolate anion might be shifted to the right (Fig. 5.6). In the carbon analogue this additional polarization is absent causing the open structure to predominate. Probably both these steric and electronic effects bring about the

remarkable difference in the reactivity of 4 and 11 towards CH_3Li.

The oxymercuration-demercuration of unsaturated alcohols is known to lead to cyclic ethers if the hydroxyl group is capable of quenching the incipient carbonium ion[2,4,5]. Thus reaction of α-terpineol 14 with $Hg(OAc)_2$ in anhydrous THF with subsequent demercuration of the organomercury compound with $NaBH_4$ in alkaline aqueous solution gives 1,8-eneole 15 in 90% yield[5]. In the presence of water the addition of $Hg(OAc)_2$ to α-terpineol proceeded to give terpin hydrate 16 after demercuration.

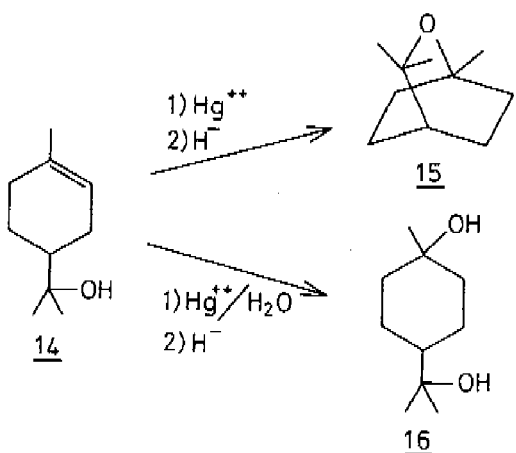


Fig. 4.7. Oxymercuration-demercuration of α-terpineol

Ganter et al.[2] showed that the oxymercuration-demercuration of 2-hydroxy-9-thiabicyclo[3.3.1]non-6-ene 1 leads exclusively to oxa-thia-*iso*-twistane 17 by the attack of the hydroxy group at C_7. Even though the mercuration step is carried out in aqueous solution, no diol is formed. In order to ensure the generation of a carbonium ion on C_6, the oxymercuration-demercuration reaction of the *exo* cyclic alkenes 20 and 21 and the *endo* cyclic alkene 22 was studied.

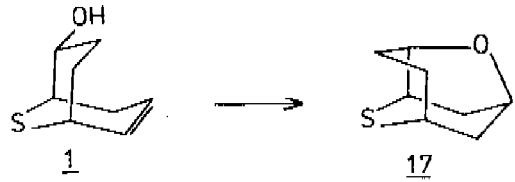


Fig. 4.8. Oxymercuration-demercuration of 2-hydroxy-9-thia-bicyclo[3.3.1] non-6-ene

Reaction of diketone 4 with methylene triphenyl phosphorane leads to both keto alkene 18 and bisalkene 19. CH_3Li

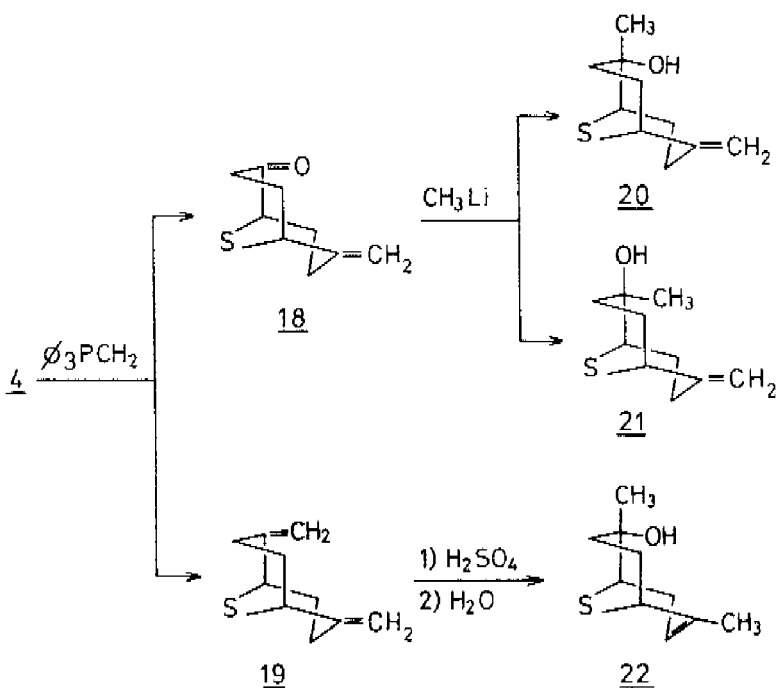


Fig. 4.9. Synthesis of starting materials

addition to 18 affords the isomeric unsaturated alcohols 20 and 21. *Endo* cyclic alkene 22 was prepared by dissolving diene 19 in concentrated H_2SO_4 followed by quenching in water.

Mercuration of 20 during two days at room temperature with $Hg(NO_3)_2$ in THF/1% HNO_3 1:1, followed by $NaBH_4$ reduction in alkaline solution, leads to 4,6-dimethyl-5-oxa-10-thiatwistane 23 in a clean reaction in 75% yield; 25% starting material was recovered. Under identical conditions *endo* cyclic alkene 22 is much less reactive and affords 23 in only 7% yield. In

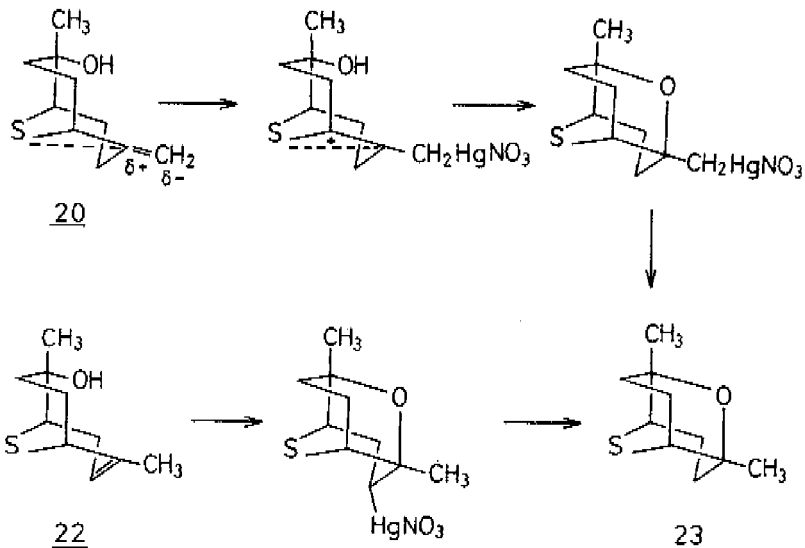
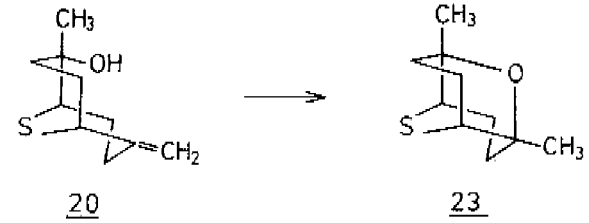


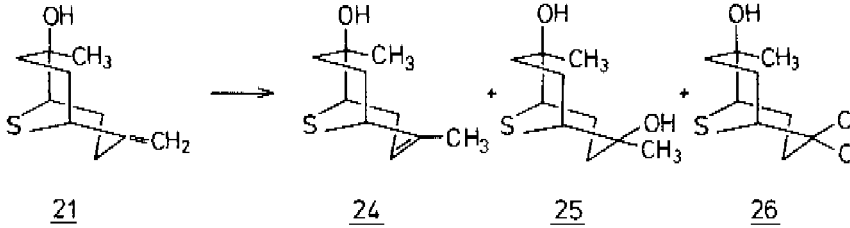
Fig. 4.10. Oxymercuration of unsaturated alcohols; effect of sulphur participation

20 the alkene is activated by sulphur. Polarization of the alkene by an orbital overlap with sulphur facilitates the attack of $Hg(NO_3)_2$ leading to a stabilized carbonium ion. Intramolecular attack of the hydroxyl group then completes the reaction. In the *endo* cyclic alkene 22 this effect is not

present as the orbital orientation of the alkene moiety is unfavourable. It is noteworthy that in these reactions only one product is formed. The initial attack of Hg^{++} might proceed from two sides of the molecule leading to two different stereoisomeric products. Seemingly, stereospecific attack of $Hg(NO_3)_2$ in both 20 and 22 is favoured by anchimeric assistance of the hydroxyl group. This is nicely demonstrated by comparison of the mercuration of the *endo* alcohol 20 with that of the *exo* isomer 21, in which the hydroxyl group cannot participate. Whereas 20 leads to only one product (*vide supra*), mercuration of 21 leads to a mixture of products. Also the



20 23



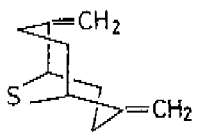
21 24 25 26

Fig. 4.11. Oxymercuration of unsaturated alcohols; effect of hydroxylic participation

rate of the latter reaction is much slower than the former one. After reaction of 21 with $Hg(NO_3)_2$ during five days 50% starting material is recovered, the products being *endo* cyclic alkene 24 - by a 1,3-H shift (*ca* 25%) - and diols 25 (*ca* 15%) and 26 (*ca* 15%) by the reaction of the intermediate mercuro-

nium ion with water. These experiments show that the neighbouring hydroxyl group has both an accelerating and a directing effect on the oxymercuration reaction. The effectiveness of hydroxyl participation can be seen from the fact that though the reactions are carried out in aqueous solution, no products are formed in which the mercuronium ion is quenched by the solvent.

Twistane 23 can also be synthesized directly from diene 19. Reaction of 19 with two eq. $Hg(NO_3)_2$ for two days followed by $NaBH_4$ reduction leads to oxa-thia-twistane 23 in 45% yield together with 20, 21, 24, 25, and 26.



19

1) $Hg(NO_3)_2$
2) $NaBH_4$

20 + 21 + 23 + 24 + 25 + 26

Fig. 4.12. Oxymercuration of diene 19

IV.3 *Experimental*

► 2-*endo*-Hydroxy-2-*exo*-methyl-9-thiabicyclo [3.3.1] nonan-6-one (6)

To a solution of 1 g (0.0059 mol) diketone 4[6] in 10 ml dry THF, 6.25 ml of a 2 M solution of CH_3Li in ether (*ca* 0.013 mol) was added at -50° C in an N_2 atmosphere. After stirring for 2 hr, excess CH_3Li was destroyed by addition of water. The reaction mixture was extracted with $CHCl_3$. The organic layer was washed with water, dried and concentrated. This afforded 1 g (95%) 6. NMR: see fig. 5.6.

► 2-*endo*-Hydroxy-2-*exo*-methylbicyclo [3.3.1] nonan-6-one (12)
► 2,6-di-*endo*-Hydroxy-2,6-di-*exo*-methylbicyclo [3.3.1] nonane (13)

1 g (0.0066 mol) 11[7] was treated with 6.25 ml 2 M CH_3Li in ether

as described for 6. Yield: 0.6 g (55%) 12 and 0.45 g (37%) 13.

- 6-Methylene-9-thiabicyclo [3.3.1] nonan-2-one (18)
- 2,6-Dimethylene-9-thiabicyclo [3.3.1] nonane (19)

To a solution of 22 g (0.006 mol) methyl triphenyl phosphonium bromide in 75 ml dry benzene was added 45 ml of a 15% solution of butyllithium in hexane under N_2 at 5° C. After 1 hr 3.5 g (0.02 mol) 4 in benzene was added and the mixture was stirred overnight. The reaction mixture was poured into water and extracted with ether. The ether extracts were washed with water dried and concentrated. Chromatography on silica gel using $CHCl_3$ as eluent yielded 2.5 g (72%) 18 and 0.8 g (24%) 19.

- 2-*endo*-Hydroxy-2-*exo*-methyl-6-methylene-9-thiabicyclo-[3.3.1] nonane (20)
- 2-*exo*-Hydroxy-2-*endo*-methyl-6-methylene-9-thiabicyclo-[3.3.1] nonane (21)

A solution of 1 g (0.006 mol) 18 in dry ether was treated with 3.3 ml CH_3Li (2 M in ether) at -50° C under N_2. After stirring for 1 hr water was added and the reaction mixture was extracted with ether. The ether extracts were washed with water, dried and concentrated. Chromatography on silica gel ($CHCl_3$ as eluent) gave 0.2 g (20%) 20, 0.55 g (50%) 21 and 0.3 g (30%) recovered 18.

NMR: see fig. 5.3 and fig. 5.4.

- 2-*endo*-Hydroxy-2-*exo*-methyl-9-thiabicyclo [3.3.1] non-6-ene (22

1 g (0.006 mol) diene 19 was dissolved in 10 ml concentrated H_2SO_4. This solution was quenched in water and extracted with CH_2Cl_2. The organic layer was washed with water, saturated $NaHCO_3$ and water. Drying and evaporation of the solvent gave 1.05 g (95%) 22.

Oxymercuration-demercuration reactions

The unsaturated alcohols 20, 21 and 22 were treated with 1 eq. $HgNO_3$ in a 1:1 mixture of THF and 1% HNO_3. After 2 days the mixture was rendered alkaline with 2 N NaOH and an excess of

2 M solution of $NaBH_4$ in 2 N NaOH was added. The products were extracted into CH_2Cl_2, washed, dried and concentrated. Separation was achieved by chromatography over silica gel with $CHCl_3$ as eluent.
Diene 18 was treated analogously with 2 eq. $HgNO_3$.

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CHAPTER V

9-thiabicyclo [3.3.1] nonanes in acidic solutions; an NMR study

V.1 *Introduction*

In the previous Chapters some aspects of the anichimeric assistance of sulphur in the formation of carbocations are discussed. It was shown that sulphur can participate in two different ways. In the chloronium ion described in Chapter II sulphur stabilizes two centres bearing a partial positive charge *via* a sulphurane configuration. In the other compounds sulphur participates *via* a three-coordinated sulphonium configuration. In order to gain a better insight in the structural requirements for sulphur participation in cations, the NMR spectra of several 2,6-disubstituted 9-thiabicyclo [3.3.1] nonanes in acidic solutions were studied. Oxa-thia-twistane is shown to protonate on oxygen and therefore proves to be a model compound for the chloronium ion which occurs in the solvolysis of 2,6-dichloro-9-thiabicyclo [3.3.1] nonane.

V.2 *Results and Discussion*

Reaction of 2,6-dimethylene-9-thiabicyclo [3.3.1] nonane 1 with HSO_3F in liquid SO_2 at -60° C leads to protonation of one of the alkene functions with formation of a carbonium ion, which can be considered as a sulphonium ion. This can be seen from the decrease of the methylene signal at δ=4.98 ppm and the appearance of a methyl signal at δ=2.17 ppm in the PMR spectrum. If the positive charge was localized on C_6 one would expect a chemical shift of *ca* 4 ppm for this methyl group (compare the chemical shift of 4.1 ppm for the *tert*.butyl

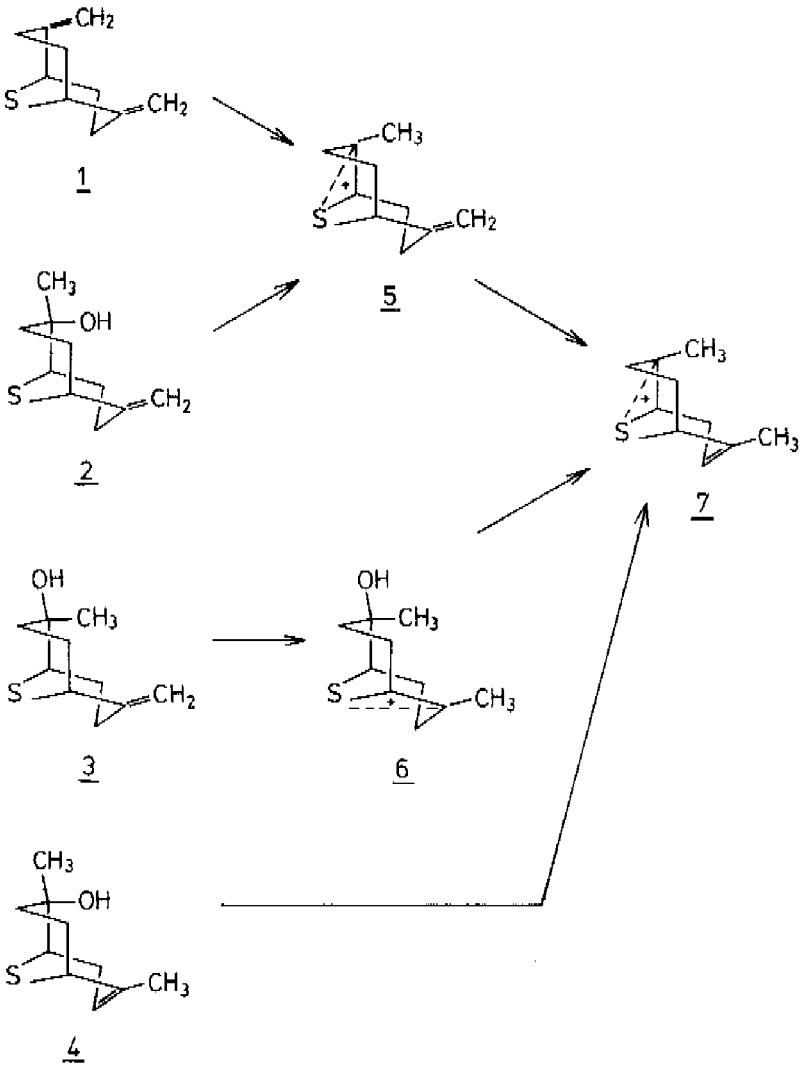


Fig. 5.1. Protonation of bicyclo [3.3.1] nonanes

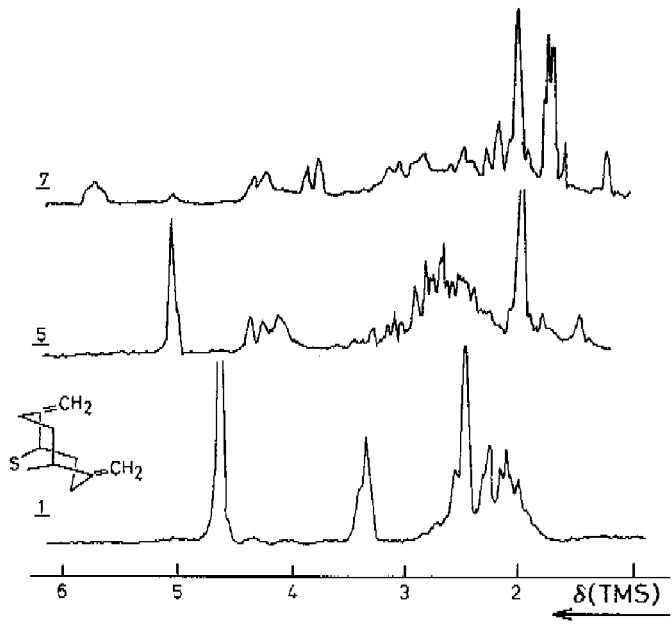


Fig. 5.2. PMR spectra of 1 in liquid SO_2 and HSO_3F/liquid SO_2

cation). The charge delocalization by electron donation from sulphur is also reflected by the relatively far downfield positions for the bridgehead protons. The downfield shift of 0.95 ppm for C_1 is due to the inductive effect of the partially positive sulphur. The downfield shift of 1.25 ppm for C_5 is caused by an inductive effect of sulphur as well as C_6. Thus *the chemical shifts for the bridgehead positions can be seen as a measure for the charge delocalization on sulphur.* In HSO_3F/liquid SO_2 the second methylene group is not protonated. The methylene protons in 5 absorb downfield as compared with those in 1. Apparently in 1 the methylene groups are polarized

by sulphur. In 5 sulphur stabilizes the cation by electron donation to C_6, so that the polarization of the remaining methylene group decreases. This effect can also be seen from the CMR spectra (*vide infra*). On warming up to -30° C 5 isomerizes to 7. This indicates that the methylene group on C_2 is protonated, followed by a rapid deprotonation of C_3 loading to an *endo*cyclic alkene. If one eq. acid is used, 5 is stable at -10° C for at least 30 minutes, showing that the isomerization is indeed acid catalyzed. The same process is encountered in the acid catalyzed 1,3-H shift in methylenecyclohexane leading to methylcyclohexene.

The structural assignment of ions 5 and 7 is also based on the CMR spectra (Table V.1). The chemical shifts of the episulphonium ring carbons are equivalent with those of the episulphonium ions described in Chapter III when corrected for methyl substitution. The difference in the chemical shift between the two methylene carbons in 1 indicates the polarization of the double bond by sulphur. This polarization is absent in 5 as can be seen from the much smaller chemical shift difference.

Table V.1

CMR spectra of 1 in liq. SO_2 and HSO_3F/liq. SO_2

	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_{10}	C_{11}
1	41.3	148.2	34.9	30.7	41.3	148.3	34.9	30.7	108.2	108.2
5	63.8	94.3	45.2	22.2	54.9	137.0	34.4	24.4	24.2	117.3
7	64.5	95.6	49.9	21.6	48.6	127.7	120.4	30.6	24.4	23.2

With HSO_3F in liquid SO_2 at -60° 6-*endo*-hydroxy-6-*exo*-methyl-2-methylene-9-thiabicyclo [3.3.1] nonane 2 is protonated on the hydroxyl group and leads to 5 by removal of a water molecule. The basicity of the hydroxyl group is higher than that of the methylene group. In contrast with an *exo*-hydroxyl group (*vide infra*) an *endo*-hydroxyl group can be activated by

anchimeric assistance of sulphur. Since sulphur in 2 is oriented favourably, the leaving ability of the *endo* substituent is increased. This offers an explanation for the reactivity of 2 in acidic solutions. It can also be seen that a ring closure, to an oxa-thia-twistane, comparable with the oxymercuration-demercuration reaction described in Chapter IV, cannot be achieved by proton-acid catalysis. The spectrum of 2 in

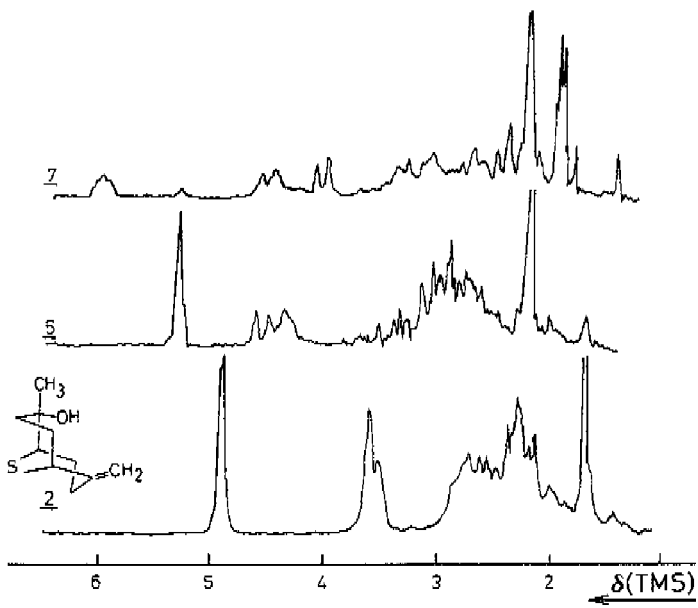


Fig. 5.3. NMR spectra of 2 in liq. SO_2 and HSO_3F/liq. SO_2

HSO_3F/liquid SO_2 (fig. 5.3) is identical to that of 1 under the same conditions (fig. 5.2). Again 5 isomerizes to 7 at elevated temperatures.

When 6-*exo*-hydroxy-6-*endo*-methyl-2-methylene-9-thiabicyclo [3.3.1] nonane 3 is treated with HSO_3F in liquid SO_2 the

methylene group is protonated leading to sulphonium ion 6. This is concluded from the disappearance of the methylene signal and the appearance of a methyl signal at δ=2.17 ppm. The hydroxyl group is also protonated which can be seen from the downfield shift for the adjacent methyl group. In 3 the hydroxyl group and sulphur are in a *cis* position with respect to one another. Therefore, sulphur cannot participate in the formation of a

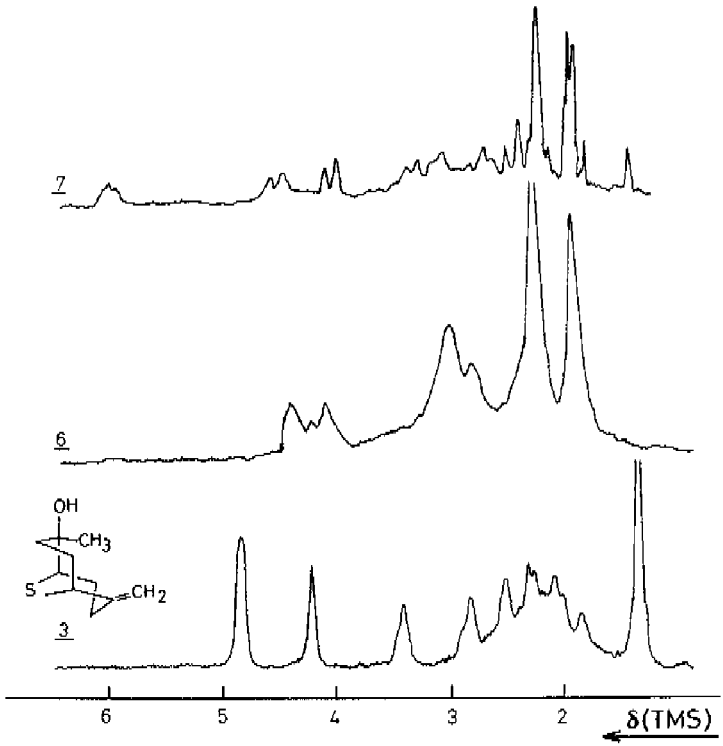


Fig. 5.4. PMR spectra of 3 in liq. SO_2 and HSO_3F/liq. SO_2

positive charge on C_6. Instead, the methylene group is protonated leading to a cation on C_2 which is stabilized by sulphur.

As in the former reactions 7 is formed at elevated temperatures. This is accomplished by the dehydratation of 6 leading to the *endo*-cyclic alkene. Ion 7 is also formed by the reaction of 6-*endo*-hydroxy-6-*exo*-methyl-2-methyl-9-thiabicyclo [3.3.1] non-2-ene 4 with HSO_3F in liquid SO_2.

In 6-*endo*-hydroxy-6-*exo*-methyl-9-thiabicyclo [3.3.1] nonan-2-one 9 the generation of a positive charge on C_6 is slowed down by protonation of the keto group. The first intermediate in the reaction of 9 with HSO_3F is the diprotonated species 12.

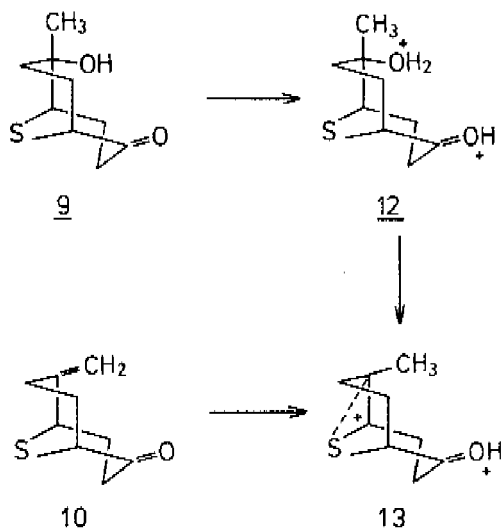


Fig. 5.5. Protonation of 9-thiabicyclo [3.3.1] nonanones

This can be seen from the downfield shifts for both the methyl and the bridgehead protons. At elevated temperatures 12 reacts further to sulphonium ion 13. The methyl signal absorbs farther downfield, indicating the formation of a positive charge on C_6 by removal of a water molecule. The chemical shift of the methyl protons is the same as those of the methyl group of 5.

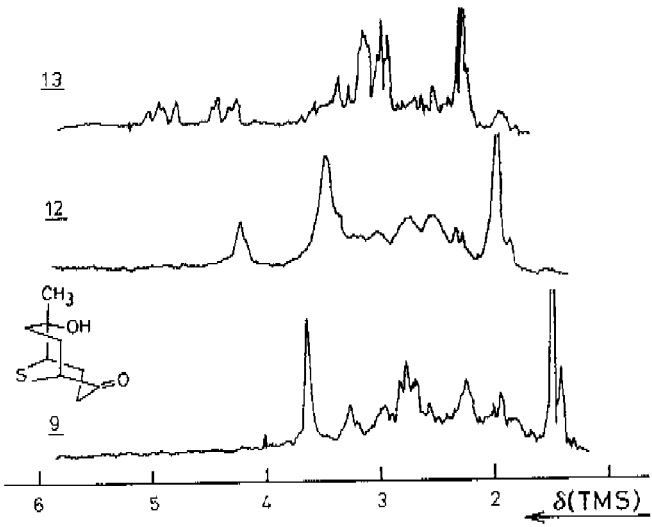
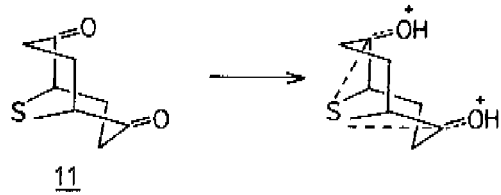


Fig. 5.6. PMR spectra of 9 in liq. SO_2 and HSO_3F/liq. SO_2

Again the downfield absorptions of the bridgehead positions indicate charge delocalization on sulphur. 13 is formed directly from 6-methylene-9-thiabicyclo [3.3.1] nonan-2-one 10 upon reaction with HSO_3F in liquid SO_2.

The experiments described above all lead to asymmetric sulphonium ions due to the fact that a formal positive charge is generated on C_6. The generation of a partially positive charge on both C_2 and C_6 might favour participation of sulphur *via* a sulphurane-like configuration, as was demonstrated in the chloronium ion described in Chapter II. A partial positive charge can be introduced by the protonation of a keto group[1]. Therefore, the NMR spectra of 9-thiabicyclo [3.3.1] nonan-2,6-dione 11 in acidic media were studied (fig. 5.7). Addition of HSO_3F to a solution of 11 in liquid SO_2 resulted in a downfield shift for both the bridgehead and methylene protons. This



11

Fig. 5.7. Protonation of diketone 11

indicates that both keto groups are protonated and that the positive charge is delocalized on sulphur. Apart from some viscosity broadening the spectrum remained identical in a temperature range of -90° C to -10° C. Since the spectrum shows a symmetric structure, one might conclude that sulphur stabilizes the positive charge on both the 2- and 6-position; in other words, sulphur participates *via* a sulphurane configuration.

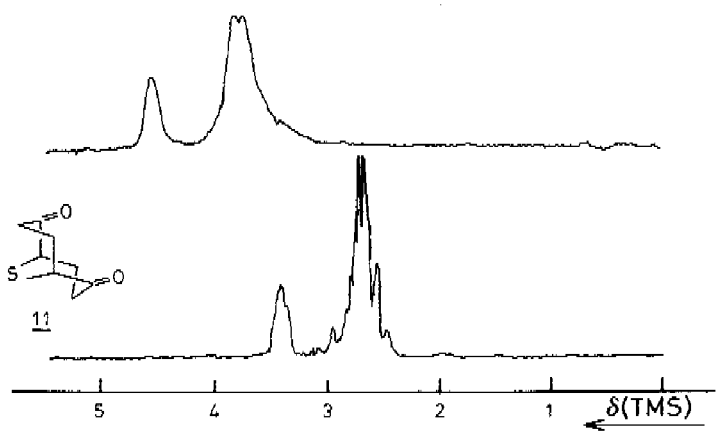


Fig. 5.8. PMR spectra of 11 in liq. SO_2 and HSO_3F/liq. SO_2

This is also indicated by the CMR spectra. Protonation of acetone leads to a downfield shift of *ca* 45 ppm for the carbonyl carbon. The downfield shift for the keto groups in 14 as compared with 11 is only 26.9 ppm. This points to delocalization of the positive charge by electron donation from sulphur.

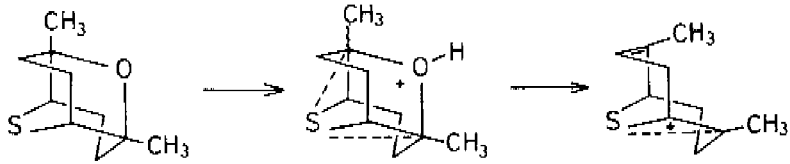
Table V.2

CMR spectra of diketone 11 in $CDCl_3$ and HSO_3F/liq. SO_2

	C_1	C_2	C_3	C_4
11	44.9	204.9	36.7	31.2
14	44.8	231.8	35.8	30.8
$(CH_3)_2C{=}O$	30.2	205.1		
$(CH_3)_2C{=}\overset{+}{O}H$	32.6	250.3		

V.3 *Protonated 4,6-dimethyl-6-oxa-10-thiatwistane; a model for the chloronium ion*

In Chapter IV the synthesis of 4,6-dimethyl-5-oxa-10-thiatwistane 15 was described. If in 15 oxygen is protonated,



15 16 7

Fig. 5.9. Reaction of 15 with HSO_3F in liq. SO_2

this would lead to a model system for the chloronium ion, which appears in the solvolysis of 2,6-dichloro-9-thiabicyclo-[3.3.1] nonane. Addition of a small amount of HSO_3F to a solution of 15 in liquid SO_2 indeed leads to formation of 16 in

which oxygen is protonated. This results in a downfield shift of 19.2 ppm for the adjacent carbon atoms in the CMR spectrum (fig. 5.10). The spectrum remains symmetric in acidic solutions. This shows that a fast proton exchange between 15 and the solvent is involved. Thus the observed spectrum results from rapidly equilibrating structures 15 and 16. The carbon atoms C_1 and C_9 show a downfield shift of 0.3 ppm, indicating that only a fraction of the positive charge is delocalized on sulphur. The further addition of small amounts of HSO_3F to the solution gives rise to a relative upfield shift for C_4 and C_6 (fig. 5.10). C_1 and C_9 shift further downfield. These data can be explained in terms of an increase of the acid concentration, leading to a higher contribution of the protonated structure 16 in the spectrum. In other words, increasing the acid concentration leads to an increase of the lifetime of 16. The gradual downfield shift for C_1 and C_9 is caused by an increasing positive charge on sulphur. At first C_4 and C_6 show a downfield shift; at higher acid concentrations these positions shift upfield. This can be assigned to the progressive increase in the coordination of C_4 and C_6 by electron donation from sulphur. In the resulting structure 16 the oxonium ion is stabilized by sulphur, oriented in a square pyramid. At first the positive charge on oxygen dominates the chemical shift of the adjacent carbon atoms. With increasing acid concentrations this inductive effect is gradually exceeded by the increase of carbon coordination. With these considerations in mind, the spectrum of 16 is analogous to that of the chloronium ion described in Chapter III.

The thermal stability of 16 is noteworthy. In general, the stability of protonated ethers depends on the ease of formation of the corresponding carbocations by carbon-oxygen bond cleavage. Qualitative data on the stability of protonated primary, secondary and tertiary ethers was presented by *Olah* and *O'Brien*[2] in terms of the temperatures of decomposition. It was shown that the protonated, primary ether 18 is stable up to 40° C whereas 19 decomposes at -30° C. The protonated, tertiary ether 20 is so unstable that it cannot be observed even at -70° C. Even

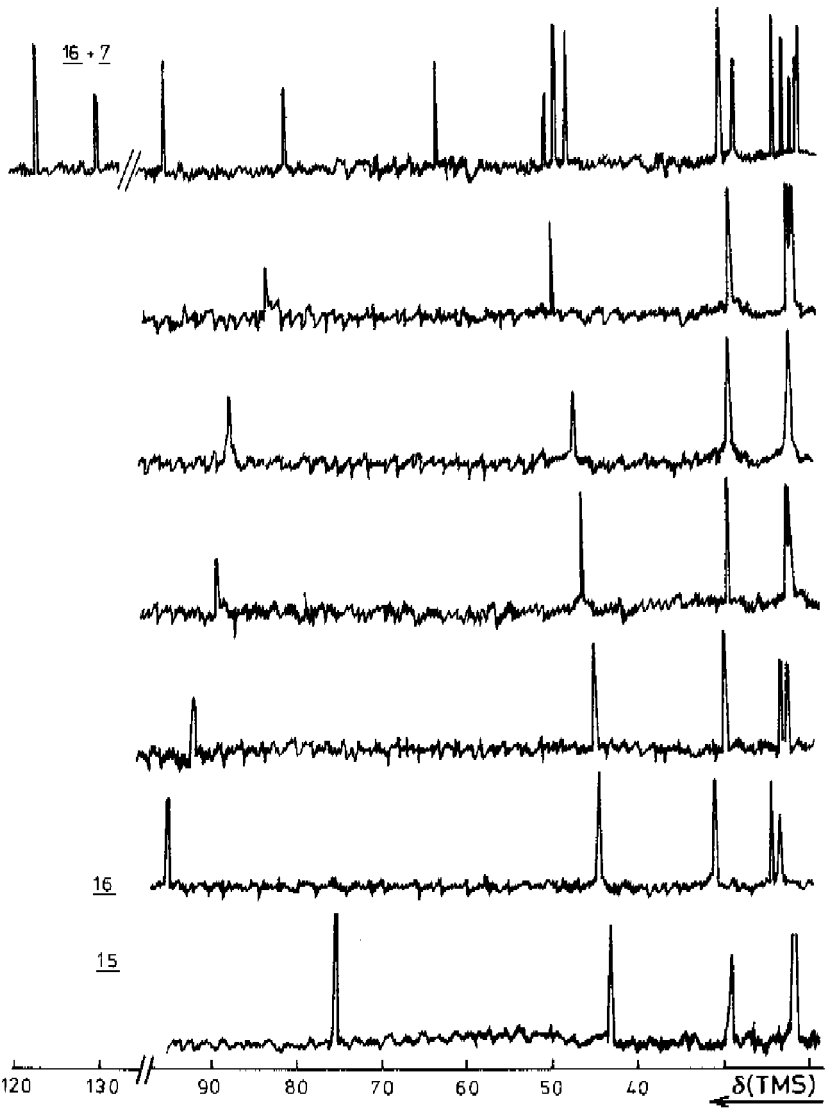


Fig. 5.10. CMR spectra of 15 in liq. SO_2 with increasing amounts of HSO_3F

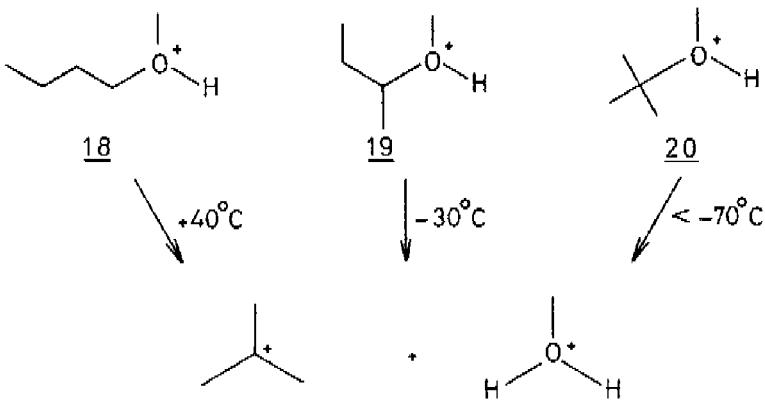


Fig. 5.11. Decomposition of protonated ethers

though 15 is a ditertiary ether the protonated species 16 is stable up to 0° C for several hours. After prolonged standing at elevated temperatures, 16 does decompose leading to sulphonium ion 7 *via* intermediate 17 (compare with protonation of 3 described in Section 5.2). After 5 weeks at -20° C *ca* 75%

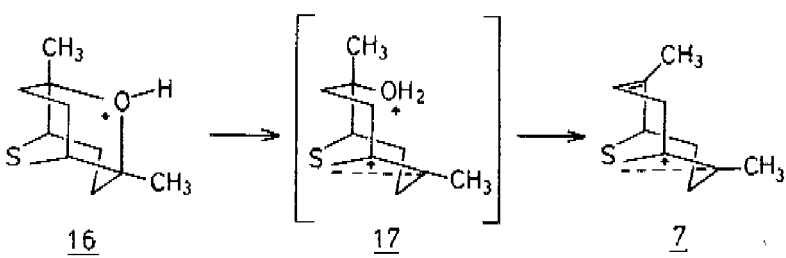


Fig. 5.12. Decomposition of oxa-thia-twistane 16

decomposition has occurred. In regarding the CMR spectrum of 16 one can decide upon the nature of the stabilization of the protonated ether. The bridgehead carbons show a downfield shift as compared with 16. This indicates that sulphur has a partial positive charge caused by electron donation to C_2 and C_6 (*vide supra*). Thus sulphur stabilizes the protonated ether *via* a sulphurane-like configuration, as is the case in the chloronium ion (Chapter III).

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CHAPTER VI

Neighbouring group participation as a model for the dynamics of enzyme-substrate complexes

VI.1 *Introduction*

The biochemical role of enzymes is their ability to effect the rates of a wide spectrum of reactions in a specific and efficient manner[1]. Enzymes are exceptional catalysts in several respects. The efficiency of enzymes is illustrated by the fact that under optimal conditions most enzymatic reactions proceed 10^8 to 10^{11} times more rapidly than the corresponding non-enzymatic reactions. The rates of certain steps are diffusion controlled. Thus, many reactions that ordinarily occur only under extreme conditions, proceed rapidly and quantitatively under mild conditions in the presence of the appropriate enzymes. Most enzymatic reactions are specific in terms of the reaction catalyzed and the structure of the substrate. Finally, enzymes catalyze a wide variety of reactions, for example hydrolytic reactions, polymerizations, oxidation-reductions, acyl transfer reactions, *etc.* Consequently, enzymes are exceptionally versatile catalysts.

The high catalytic efficiency and marked specificity exhibited by enzymatic reactions imply the participation of several distinct functional groups of the enzyme. This has been demonstrated by, for example, the X-ray diffraction studies of enzymes such as chymotropsin, papain and carboxypeptidase, which establish the involvement of several groups. These groups are usually distant from each other along the polypeptide chain, but near one another in space. Those parts of the enzyme which perform a direct function in the catalytic process, are called the active sites.

The initial step in enzyme-catalyzed reactions involves the binding of one or more reactants to the enzyme surface. Such a binding process makes it possible that one function of the enzyme may be to approximate and orient reactive sites in such a fashion as to permit the reaction to occur more readily. Such catalysis may therefore involve *proximity effects*, that is, rate increases due solely to bringing the reactants more closely together, and *orientation effects* which involve orienting groups into a configuration favouring reaction. *Koshland*[2] has calculated the rate increases expected from proximity and orientation effects. The results indicate that these effects alone cannot account for the rate of enzyme-catalyzed reactions. Although we must reckon with additional catalytic factors, it does seem reasonable that proximity and orientation effects do contribute to the rate of reaction. This point is emphasized by the comparison of the rates for reactions proceeding *via* intra- and intermolecular reaction paths. For example, the first-order rate constant for the loss of *p*-nitrophenol

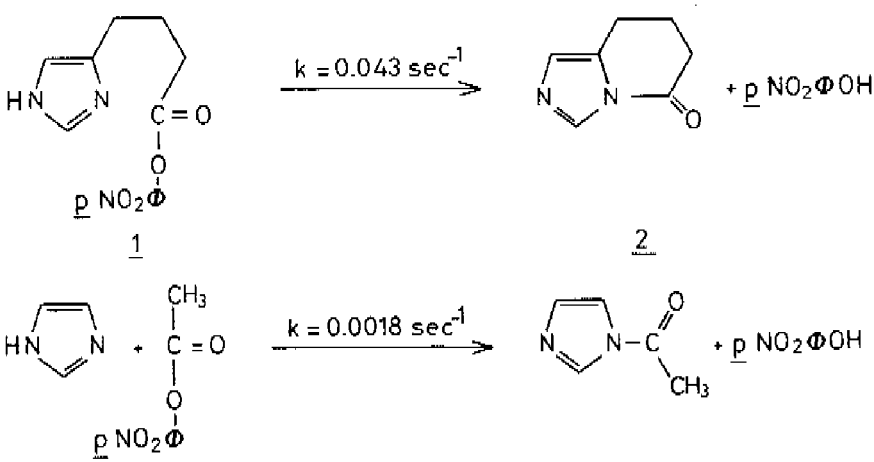


Fig. 6.1. Comparison of an intra- and intermolecular reaction

from *p*-nitrophenyl-γ-(4-imidazolyl)-butyrate 1 is 20-fold larger than the *pseudo*-first-order rate constant for the reaction of *p*-nitrophenylacetate with 1 M imidazole[1a]. This means that, due to the neighbouring group effect, the intramolecular reaction proceeds as if the imidazole group were present at an effective concentration of 20 M. Based on these considerations, an intramolecular reaction may be seen, within limitations, as a model for enzyme-catalyzed reactions. However, one must consider that the approximation and the orientation of the functional groups have been built into the molecule by chemical synthesis. The enzyme must perform this function of approximation and orientation itself in the formation of the enzyme-substrate complex. Therefore, the intramolecular reaction provides information of mainly the reaction within the enzyme-substrate complex and not of the overall reaction.

VI.2 *Intramolecular catalysis in bicyclo [3.3.1] nonanes*

In the previous Chapters several aspects of neighbouring group participation in 9-thiabicyclo [3.3.1] nonanes were discussed. It was shown that the substituents located at the 2- and 6-positions are at such a distance that the rate of reaction is increased and the reaction proceeds with high specificity.

In 2,6-dichloro-9-thiabicyclo [3.3.1] nonane 3 the first chlorine is released much faster than the second one, due to the occurrence of chloronium ion 4 (fig. 6.2). The second chlorine is released *via* intermediate 6. The first step in solvolysis implies the attack of the chlorine on C_6 at the distant carbon atom C_2. In other words, the displacement of the first chlorine is facilitated by intramolecular catalysis.

Several hetero-atoms are known to possess the ability to catalyze certain reactions in intramolecular processes[1,3]. Thus the introduction of such a neighbouring group should also lead to catalytic effects. Indeed the reaction of dichloride 3

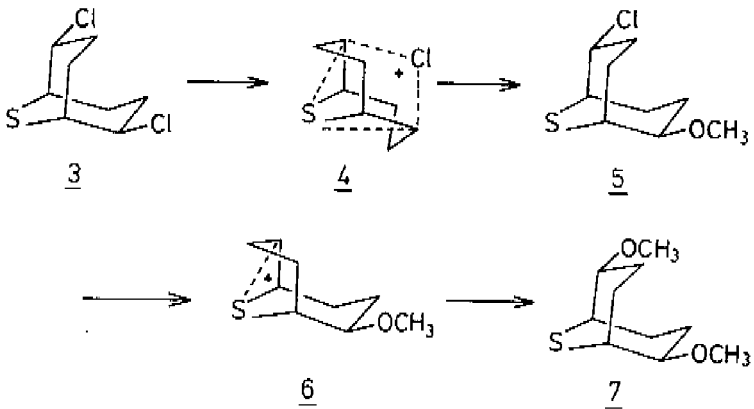


Fig. 6.2. Intramolecular catalysis in the solvolysis of 3

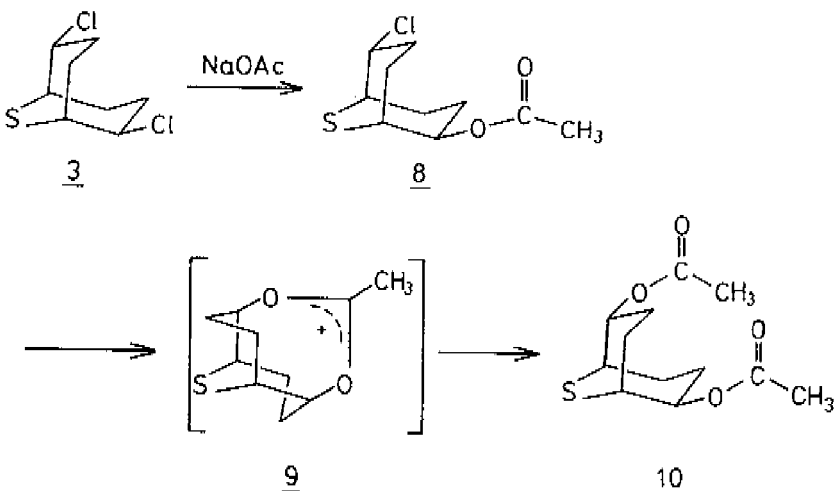
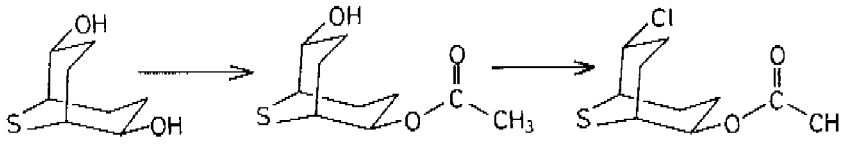


Fig. 6.3. Reaction of 3 with sodium acetate

with nucleophiles, leading to the introduction of good neighbouring groups (*e.g.* oxygen, nitrogen or sulphur containing groups), gives rise to a change in the reactivity of the chlorines. In the reaction of 3 with thiourea the second chlorine is substituted much faster than the first one (see Chapter II). A similar reactivity is encountered in the reaction with sodium acetate. When 3 was reacted with sodium acetate no monosubstituted product 8 could be isolated (fig. 6.3). Apparently, the second chlorine is far more reactive than the first one which is caused by the involvement of acetoxonium ion 9 in the second step. Therefore, monoacetate 8 cannot be prepared by a nucleophilic displacement reaction. The synthesis of 8 could be achieved *via* another route. Acylation of diol 11, with acetyl chloride in a mixture of pyridine and benzene, afforded 12



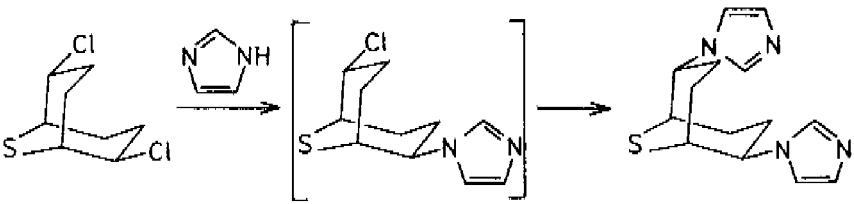
11 12 8

Fig. 6.4. Synthesis of 8

in *ca* 70% yield. Chlorination of 12 with thionyl chloride then gave 2-chloro-6-acetoxy-9-thiabicyclo [3.3.1] nonane 8. The chlorine in 8 is indeed very reactive in solvolysis. In methanol at 35° C chlorine is rapidly replaced by a methoxy group.

A further example of this kind of reactivity is the reaction of dichloride 3 with imidazole. Again the monosubstituted product 13 cannot be isolated due to the fact that the second step is faster than the first one (fig. 6.5).

That the substituents on C_2 and C_6 are ideally positioned is also demonstrated by the oxymercuration-demercuration reactions described in Chapter IV. The approximation of the



3 13 14

Fig. 6.5. Reaction of 3 with imidazole

functional groups makes it possible that these reactions proceed with a 100% selectivity. In the addition of methyl lithium to 9-thiabicyclo [3.3.1] nonane-2,6-dione this resulted in the unreactivity of the second keto group towards this reagent (see also Chapter IV).

VI.3 *Intramolecular reactions as a model for enzyme catalysis*

As was outlined in Section VI.1 several functional groups are involved in enzymatic reactions. Introduction of the appropriate functional groups into the 9-thiabicyclo [3.3.1] nonane skeleton might lead to active simulation models for enzyme catalysis. This assumption is based on the effects of neighbouring group participation in this system. It must be stated that the reactions described in this Section have not yet been carried out and will be subject to further research. The purpose of this Section is to offer a model for enzymatic reactions based on the principles of anchimeric assistance in intramolecular reactions.

One of the most thoroughly understood enzymes, from a mechanistic standpoint, is chymotropsin. This enzyme is an acyl group-transfer catalyst. It transfers the acyl group from a wide range of substrates such as esters, amides and acids to a number of acceptors such as water, alcohols and amines. A

simplified mechanism of the action of chymotropsin is given in fig. 1.6 (Chapter I). The main functional groups in the active site of the enzyme are an imidazole group of a histidine fragment and a serine hydroxyl group. 6-Hydroxy-2-(2-imidazolyl) 9-thiabicyclo [3.3.1] nonane 15 might function as a model for chymotropsin. Because of the proximity of both functional groups the hydroxylic function can be activated by the imidazole group In a pre-equilibrium step the anion of the alcohol is formed by proton transfer to imidazole. The imidazolium ion on C_6 may be stabilized by electron donation from sulphur. In this manner the nucleophilicity of the hydroxyl group is increased, enablin the attack on the carbonyl group. Thus the acylated product 17

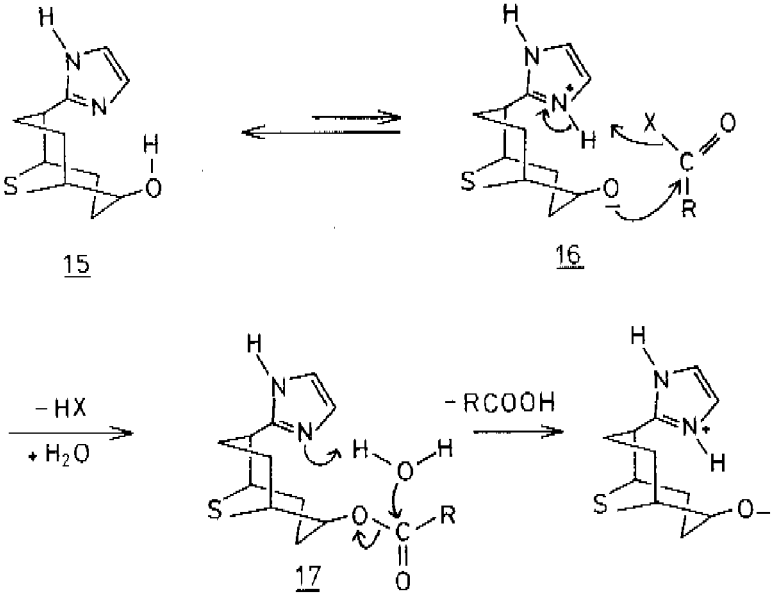
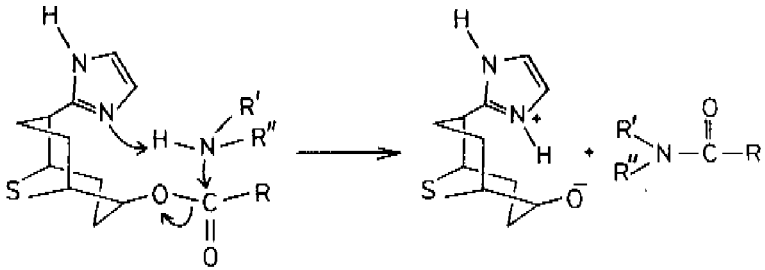


Fig. 6.6. Model for catalysis by chymotropsin

is formed with departure of the protonated leaving group X (for example an amine or alcoholic fragment). The hydrolysis of the acyl intermediate 17 can be seen as the reverse of the

acylation step. Upon hydrolysis the catalyst is recovered with liberation of the acid fragment.

The acyl intermediate 17 can also function as an acyl donor to, for example, amines in the synthesis of peptides. The amine is activated by the imidazole group to attack the



17

Fig. 6.7. Synthesis of peptides

carbonyl group (fig. 6.7). This process is in fact the reverse of the hydrolysis of an amide as is described in fig. 6.6 ($X=NR_2$).

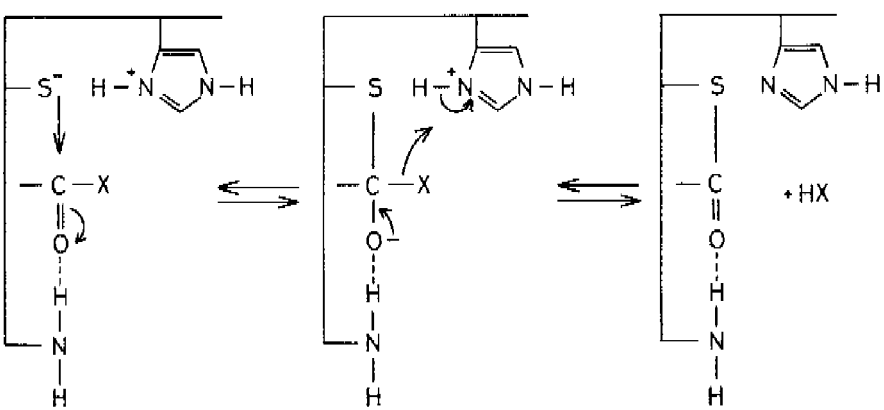
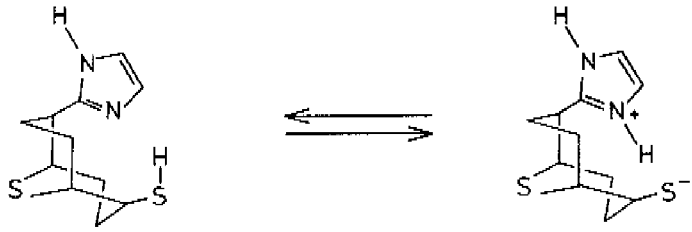


Fig. 6.8. *Drenth*'s mechanism for papain catalysis
The hydrolysis of the acylated enzyme is the reverse of this process

Recently, *Drenth et al.*[4] proposed a new mechanism for the mode of action of papain (fig. 6.8). The function of papain is similar to that of chymotropsin. One of the essential units is the thiol group of Cys 25. The nucleophilicity of this thiol is increased by proton transfer to the imidazole group of His 159. Based on *ab initio* calculations *Broer et al.*[5] found that the occurrence of the ImH^+S^- ion pair can be expected on theoretical grounds, although this does not seem likely, because the sulphur anion is a much stronger base than imidazole. It was calculated that the total energy for the ion pair in a model system is only 1.2 Kcal/mole^{-1} higher than that for the neutral species. Therefore, it seems reasonable that the ion pair is the active intermediate in papain catalyzed reactions. Based on these facts one can assume that in 18, which might serve as a model for papain, such a pre-equilibrium occurs.



18 19

Fig. 6.9. A model for papain; pre-equilibrium

Thus 19 would be an active catalyst in the hydrolysis of carbonyl compounds.

VI.4 *Experimental*

►6-Acetoxy-2-hydroxy-9-thiabicyclo[3.3.1]nonane (12)
1.7 g (0.01 mol) diol 11 was treated with 1 eq. acetyl chloride in a mixture of 50 ml pyridine and 50 ml benzene for 15 hr. The reaction mixture was washed with dilute hydrochloric acid and water. After drying and evaporation of the

solvent, the residue was chromatographed on silica gel with chloroform as eluent. This gave 1.5 g (70%) 12.
NMR: δ=5.27 (m,1,CHOAc), 4.22 (m,1,CHOH), 3.52 (s,1,OH), 2.67 (m,2,CH), 1.77-2.50 (m,8,CH_2), 2.08 (s,3,CH_3).

► 6-Acetoxy-2-chloro-9-thiabicyclo [3.3.1] nonane (8)
To a solution of 1 g (0.005 mol) 12 and 0.5 g pyridine in 25 ml ether was added 0.6 g (0.005 mol) thionyl chloride. After stirring for 1 hr at room temperature the reaction mixture was washed with water, sat. $NaHCO_3$ and water. Drying and evaporation of the solvent gave 1.1 g (95%) 8.
NMR: δ=5.27 (m,1,CHOAc), 4.67 (m,1,CHCl), 2.78 (m,2,CH), 1.83-2.50 (m,8,CH_2), 2.02 (s,3,CH_3).

► 2,6-Diimidazol-1-yl-9-thiabicyclo [3.3.1] nonane (14)
A solution of 2.1 g (0.01 mol) dichloride 3 and 2.7 g (0.04 mol) imidazole in 75 ml ether was stirred for 15 hr at room temperature. The ether was decanted from the precipitate. The latter was treated with 4 N NaOH and extracted with $CHCl_3$. The extracts were washed with water, dried and concentrated. The resulting solid was recrystallized from DMF/water. This gave 2.1 g (75%) 14.
NMR: δ=7.60 (s,1,Im), 7.03 (s,2,Im), 4.80 (m,2,CHIm), 2.87 (m,2,CH), 1.9-2.7 (m,8,CH_2).

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SUMMARY

In this thesis several aspects of neighbouring group participation in bicyclic systems are discussed. Special attention was paid to the anchimeric assistance of sulphur in nucleophilic displacement reactions and to the effect of positioning functional groups in such a manner as to facilitate intramolecular catalysis.

In the solvolysis of 2,6-dichloro-9-thiabicyclo [3.3.1] - nonane the first chlorine is replaced much faster than the second one. It was established that this is caused by the intermediacy of a sulphurane, oriented in a square pyramid, in which two positions are coordinated by a chloronium ion. This intermediate is responsible for the enhanced reactivity of the first chlorine. The substitution of the second chlorine takes place *via* an episulphonium ion. In this ion the positive charge is mainly delocalized on sulphur and C_2. These observations are confirmed by quantumchemical calculations on the proposed intermediates.

On the basis of the NMR spectra of 2,6-disubstituted 9-thiabicyclo [3.3.1] nonanes in acidic solutions, the structural requirements for sulphur participation in the formation of carbocations are discussed. Dimethyl-oxa-thia-twistane was shown to protonate on oxygen and proved to be a model compound for the chloronium ion which appears in the solvolysis of 2,6-dichloro-9-thiabicyclo [3.3.1] nonane.

Intramolecular reactions in 9-thiabicyclo [3.3.1] nonanes were shown to be highly efficient. In the addition of methyl lithium to 9-thiabicyclo [3.3.1] nonane-2,6-dione the second keto group is unreactive. This is explained by the formation

of a lactolate anion *via* a transannular interaction. It was also found that substituents in the 2- and 6-positions of the 9-thiabicyclo [3.3.1] nonane skeleton are ideally positioned to achieve 100% selectivity in oxymercuration-demercuration reactions leading to oxa-thia-twistanes.

Furthermore, it could be demonstrated that substituents in the 2- and 6-positions are oriented in such a way that an effective catalytic process can result. This intramolecular catalysis shows a striking resemblance to enzyme catalyzed reactions. Based on the principles of neighbouring group participation in bicyclic systems, a model for the dynamics of enzyme-substrate complexes is presented. Suggestions are made for simulation models for acyl transfer enzymes such as chymotropsin and papain.

SAMENVATTING

In dit proefschrift worden verscheidene aspecten van *neighbouring group participation* in bicyclische systemen beschreven. De aandacht werd vooral gericht op *anchimeric assistance* van zwavel in nucleofiele substitutiereacties en op het effect van de positie van functionele groepen op intramoleculaire reacties.

In de solvolyse van 2,6-dichloor-9-thiabicyclo [3.3.1] - nonaan blijkt de eerste chloor veel sneller vervangen te worden dan de tweede. Aangetoond werd, dat dit veroorzaakt wordt door het optreden van een sulfuraan, in een *square pyramidale* configuratie, waarin twee van de posities gecoördineerd worden door een chloronium ion. Dit intermediair komt voor in de eerste solvolyse-stap. Het tweede chlooratoom wordt vervangen via een sulfonium ion, waarin de positieve lading voornamelijk gedelocaliseerd is over zwavel en C_2. Deze resultaten werden bevestigd door quantumchemische berekeningen.

Aan de hand van de NMR spectra van 2,6-di-gesubstitueerde 9-thiabicyclo [3.3.1] nonanen, opgelost in protonzuren, zijn de factoren die van invloed zijn op de participatie van zwavel in de vorming van kationen, beschreven. Aangetoond werd, dat dimethyl-oxa-thia-twistaan op zuurstof geprotoneerd wordt en daardoor een model blijkt te zijn voor het chloronium ion, dat als intermediair voorkomt in de solvolyse van 2,6-dichloor-9-thiabicyclo [3.3.1] nonaan.

Intramoleculaire reacties in 9-thiabicyclo [3.3.1] nonanen blijken bijzonder selectief te zijn. In de reactie van 9-thiabicyclo [3.3.1] nonaan-2,6-dion met methyllithium is de tweede ketogroep inert. Dit wordt verklaard door de vorming

van een lactolaat anion via een intramoleculaire interactie. Tevens werd aangetoond, dat de substituenten op de 2- en 6-positie zodanig geplaatst zijn, dat oxymercurering-demercurerings-reacties 100% selectief verlopen naar oxa-thia-twistanen.

De positie en orientatie van de substituenten op de 2- en 6-plaats geven aanleiding tot intramoleculair gekatalyseerde processen. Deze intramoleculaire katalyse vertoont een grote overeenkomst met enzym-gekatalyseerde reacties. Op basis van *neighbouring group participation* in bicyclische systemen wordt een model gepresenteerd voor de dynamica van enzym-substraat complexen. Met name worden simulatiemodellen voor acyloverdracht voorgesteld, afgeleid van het werkingsmechanisme van chymotropsine en papaine.

CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren op 12 october 1949 te Helmond. Na het behalen van het diploma HBS-b aan het "Dr. Knippenbergcollege" te Helmond begon hij in 1967 met de ingenieursstudie op de afdeling der Scheikundige Technologie aan de Technische Hogeschool Eindhoven. In september 1972 behaalde hij het ingenieursdiploma met als afstudeerrichting Organische Chemie.

Vanaf 15 september 1972 is hij als wetenschappelijk medewerker verbonden aan de Technische Hogeschool Eindhoven.

Het in dit proefschrift beschreven onderzoek werd begonnen in maart 1974 en stond onder leiding van prof. dr. H.M. Buck.

DANKWOORD

Gedurende het onderzoek dat in dit proefschrift is beschreven heb ik veel steun ondervonden op het gebied van synthese, spectroscopie en quantumchemische berekeningen. Met velen heb ik bijzonder stimulerende discussies mogen voeren. Voor al deze hulp wil ik een ieder van harte bedanken.

Verder ben ik diegenen zeer erkentelijk, die een bijdrage hebben geleverd aan de uiteindelijke vormgeving van dit proefschrift.

DRUK: WIBRO HELMOND

STELLINGEN

1. Het mechanisme van de gemodificeerde Wittig-reactie zoals voorgesteld door *Schlosser* is niet in overeenstemming met de experimentele resultaten.

   M. Schlosser and K.F. Christmann,
   Ann. Chem., 708, 1 (1967)

2. De veronderstelling van *Dilling*, dat de acetolyse van *syn*- en *anti*-pentacyclo$[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]$dec-6-yl *p*-tolueensulfonaat verloopt via door σ-participatie gestabiliseerde kationen, is aanvechtbaar.

   W.L. Dilling and J.H. Alford,
   J. Amer. Chem. Soc., 96, 3615 (1974)

3. De methode, die *Gehrke* gebruikt om ketenoverdrachtsconstanten in anionische polymerisaties van butadieen te berekenen, is niet juist.

   K. Gehrke, C.H. Roth und G. Hünerbein,
   Plast. Kaut., 20, 667 (1973)

4. De NMR chemical shifts van gesubstitueerde allyl trifenyl fosfonium zouten kunnen worden verklaard uitgaande van een model gebaseerd op sterisch geïnduceerde polarisatie zonder de aanwezigheid van een p_π-d_π overlap.

   T.A. Albright, W.J. Freeman and E.E. Schweizer,
   J. Amer. Chem. Soc., 97, 2946 (1975)

5. De Haarhoff-methode voor de berekening van de dichtheid van vibrationele energieniveaus wordt vaak ten onrechte gebruikt.

P.A.M. v.d. Boogaardt, R.P.H. Rettschnick and J.D.W. van Voorst,
Chem. Phys. Letters, 41, 270 (1976)
R. v.d. Werf, E. Schutten and J. Kommandeur,
Chem. Phys., 16, 151 (1976)

6. De productverdeling bij de door phtalocyanine-metaalcomplexen gekatalyseerde oxidatie van thiolen wijst op activering van de thiolgroep; dit in tegenstelling tot de algemeen aanvaarde opvatting, dat bij dit soort reacties uitsluitend zuurstof geactiveerd wordt.

N.N. Kundo and N.P. Keier,
Kinetics and Catalysis, 11, 72 (1970)
N.N. Kundo, N.P. Keier, G.V. Glazneva and E.K. Mamaeva,
Kinetics and Catalysis, 8, 1119 (1967)

7. De NMR spectra van pentacyclo $[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]$nonan-9-ol in sterk zure media zijn meer in overeenstemming met een snelle uitwisseling van de gecomplexeerde alcoholfunctie dan met de vorming van een homoaromatisch carbonium ion.

R.M. Coates and E.R. Fretz,
J. Amer. Chem. Soc., 97, 2538 (1975)

8. Het verdient aanbeveling bij het verminderen van de personeelssterkte van universiteiten en hogescholen het aantal tijdelijke contracten zoveel mogelijk constant te houden.

9. De beklimming van de Hidden Peak (Himalaya-gebergte) zonder de gebruikelijke zekeringsmethoden moet gezien worden als anti-propaganda voor verantwoord alpinisme.

R. Messner, Die Herausforderung - Zwei und ein Achttausender. BLV Verlagsgesellschaft, München 1976

10. De Nederlandse pers is het blijkbaar niet eens met het devies "Zieh in die Berge, und komme wieder", aangezien zij geen aandacht heeft besteed aan de behouden terugkeer van de geslaagde Himalaya-expeditie 1976 van de Nederlandse Bergsport Vereniging.

J.A.J.M. Vincent

Eindhoven, 4 februari 1977