Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 4487–4494, July 1982
Review

Recent aspects of nitration: New preparative methods and mechanistic studies (A Review)

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Contributed by George A. Olah, April 13, 1982

ABSTRACT New preparative methods of electrophilic nitration and transfer nitration are reviewed, including reactions relating to the ambident reactivity of the nitronium ion. Recent aspects of the mechanism of electrophilic aromatic substitution are discussed.

Nitration is one of the most studied and best understood of organic reactions (for reviews, see refs. 1–4). Both aromatic and aliphatic compounds can be nitrated by various methods such as heterolytic (electrophilic and nucleophilic) and radical nitrations. Aromatic nitration is most frequently electrophilic; aliphatic is free radical. Nitroaromatic compounds are of substantial use as intermediates in the synthesis of plastics, pharmaceuticals, dyestuffs, explosives, insecticides, etc.; nitroaliphatics are used as solvents and synthons in organic synthesis.

In regard to aromatic nitration, Ingold and his associates published a series of papers in 1950 which ever since have been considered the most fundamental study in our understanding of electrophilic nitration reactions (for a review, see ref. 5). Despite this, many questions remained unanswered and many new aspects of nitration reactions have been discovered. Nucleophilic and free radical nitration of aromatics is considerably less studied. Aliphatic nitration, most frequently carried out in the gas phase under free radical conditions, is of increasing interest.

In the 1980s, the subject of nitration is still of substantial interest and activity. This is the case concerning new preparative aspects as well as mechanistic aspects with particular emphasis on the nature of the reactive intermediates involved. The following review summarizes results of our ongoing research on nitration in recent years.

PREPARATIVE ASPECTS

Nitration with Nitronium Salts. The Ingold group (5) clarified the nature of the salt obtained by Hantsch (6, 7) from the reaction of nitric and perchloric acids as a mixture of nitronium perchlorate and hydronium perchlorate. They subsequently prepared and studied (by Raman spectroscopy) pure nitronium perchlorate (5). This was a significant step because it directly proved the existence of the nitronium ion suggested by their kinetic studies. However, nitronium perchlorate was unstable (explosive) and therefore it was not further studied.

Preparation of stable nitronium salts as nitrating reagents necessitated the use of counterions that could give no unstable esters. Olah and Kuhn reported the preparation of nitronium tetrafluoroborate and its application as a nitrating agent (8–10).

Nitronium tetrafluoroborate is most conveniently prepared by adding anhydrous HF to HNO_3 in a solvent such as CH_3NO_2, CH_2Cl_2, or the like and then saturating the solution with BF_3:

$$HNO_3 + HF + 2BF_3 \rightarrow NO_2^+BF_4^- + BF_3\ H_2O.$$

Nitronium salts are colorless, crystalline, stable compounds. $NO_2^+BF_4^-$ decomposes at atmospheric pressure only above 170°C, without subliming, into its components—i.e., $NO_2F + BF_3$. The hexafluoroantimonate salt is even more stable. The higher thermal stability may be partially a consequence of the higher boiling point of the corresponding Lewis acid fluoride compared to boron trifluoride.

Nitronium salts can be stored at room temperature indefinitely without decomposition. Refrigeration is generally unnecessary and no other special precautions are required. However, all nitronium salts are very hygroscopic and must be stored and handled with precautions to avoid moisture.

Nitronium tetrafluoroborate and related nitronium salts are extremely active nitrating agents for aromatics:

$$ArH + NO_2^+BF_4^- \rightarrow ArNO_2 + HF + BF_3.$$

The nitrations are carried out under anhydrous conditions. This is of special advantage in dealing with compounds which, under the usual strongly acidic nitration conditions, may undergo hydrolysis or oxidation. Aryl nitriles, for example, are easily hydrolyzed under nitration conditions and no direct dinitration, requiring forceful conditions, was previously possible. The nitronium fluoroborate method enabled us to carry out mono- and dinitration of aryl nitriles in high yields without any hydrolysis of the -CN group.

Typical results of preparative nitrations of arenes, nitroarenes, arylcarboxylic acid esters and halides, and arylnitriles are summarized in Tables 1–4.

In mono- or dinitration of aromatics, nitronium salts generally react under quite mild conditions, and yields are 80–100%.

Trinitration of aromatics, particularly of benzene, represented a challenging problem. Although the preparation of 1,3,5-trinitrobenzene from *m*-dinitrobenzene has been reported in low yield (11), 1,3,5-trinitrobenzene is usually prepared by indirect methods (12). The nitration of *m*-dinitrobenzene to 1,3,5-trinitrobenzene with nitronium tetrafluoroborate in fluorosulfuric acid solution in contrast could be carried out with ease (62% yield).

Nitronium salts in strongly acidic solvents (such as FSO_3H or HF) are thus capable of effecting an efficient preparative nitration of benzene to 1,3,5-trinitrobenzene which, due to its increased stability relative to TNT, can be of significance.

Nitronium salts also readily nitrate aliphatics. Alkanes and cycloalkanes, such as cyclohexane or adamantane, give high yields. The difficulty is not in lack of reactivity but due to the fact that tertiary (and reactive secondary) nitroalkanes themselves can react further under acidic conditions via cleavage of the C—N bond. Thus, reaction conditions must be found to minimize further reaction; in contrast, this is not the case in aromatic nitrations. Primary nitroalkanes are less susceptible but nitration of their less reactive C—H bonds is also more difficult. The nitration of methane, for example, is feasible only in strongly acidic solution (such as FSO_3H).

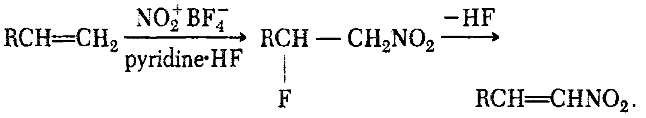
Nitronium salts also add readily to olefins in the presence of

Table 1. Nitration of arenes with $NO_2^+BF_4^-$

Substrate	Product	Reaction time, min	Yield of isolated mononitro product, %
Benzene	Nitrobenzene	10	93
Toluene	Nitrotoluenes	10	95
o-Xylene	Nitroxylenes	10	91
m-Xylene	Nitroxylenes	10	90
p-Xylene	Nitro-*p*-xylene	10	93
Mesitylene	Nitromesitylene	10	89
Ethylbenzene	Nitroethylbenzenes	10	93
n-Propylbenzene	Nitro-*n*-propylbenzenes	10	91
iso-Propylbenzene	Nitro-iso-propylbenzenes	10	93
n-Butylbenzene	Nitro-*n*-butylbenzenes	10	90
sec-Butylbenzene	Nitro-*sec*-butylbenzenes	10	92
tert-Butylbenzene	Nitro-*tert*-butylbenzenes	10	88
Naphthalene	Nitronaphthalenes	25	79
Anthracene	9-Nitro-anthracene	25	85

All nitrations were carried out in tetramethylene sulfone solutions at temperatures between 0°C and 5°C.

pyridinium hydrogen fluoride, giving vicinal fluoronitroalkanes:

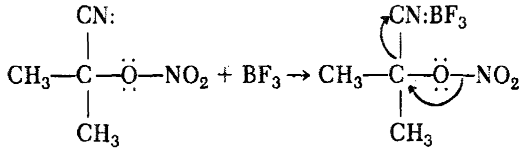


$$\mathrm{RCH{=}CH_2} \xrightarrow[\text{pyridine·HF}]{NO_2^+BF_4^-} \underset{\displaystyle \mathrm{F}}{\mathrm{RCH}} - \mathrm{CH_2NO_2} \xrightarrow{-HF} \mathrm{RCH{=}CHNO_2}.$$

These 1,2-fluoronitroalkanes then can be dehydrofluorinated to the corresponding nitroolefins.

Nitration with Alkyl Nitrates. In our studies of electrophilic nitrations, we also found alkyl nitrates (particularly CH_3NO_3) to be very effective nitrating agents in the presence of BF_3 as a catalyst (13, 14). The reaction was found to be particularly useful as a selective and mild nitration method—for example, allowing mononitration of durene and other highly alkylated benzenes which, when with mixed acid, usually undergo dinitration (Table 5). CH_3NO_3/BF_3 also can be used to achieve dinitration of tetramethylbenzenes by using a 2–3 molar excess of CH_3NO_3. Other Friedel–Crafts type catalysts can also be used, but BF_3 was found to be the most suitable. $AlCl_3$ and $Ti(IV)Cl_4$ in the nitration of pentamethylbenzene caused formation of significant amounts of chlorinated derivatives, whereas use of H_2SO_4 led to nitrodemethylation products.

Acetone cyanohydrin nitrate has enhanced reactivity compared to CH_3NO_3 for the synthesis of various ring-substituted phenyl nitromethanes (15). The incipient negative charge upon the formation of the nitronium ion is stabilized to a large extent by the ready expulsion of cyanide ion, thus providing the necessary driving force for the reaction to proceed:



$$\mathrm{CH_3}-\overset{\displaystyle \mathrm{CN:}}{\underset{\displaystyle \mathrm{CH_3}}{\mathrm{C}}}-\ddot{\mathrm{O}}-\mathrm{NO_2} + \mathrm{BF_3} \rightarrow \mathrm{CH_3}-\overset{\displaystyle \mathrm{CN{:}BF_3}}{\underset{\displaystyle \mathrm{CH_3}}{\mathrm{C}}}-\ddot{\mathrm{O}}-\mathrm{NO_2}$$

Using acetone cyanohydrin nitrate has certain practical advantages over other procedures that use alkyl nitrates. The former is more stable than CH_3NO_3 and is stored easily for longer periods of time. BF_3 etherate is easier to handle than the BF_3 gas used in other methods. Under similar conditions, this method provides cleaner products and higher yields than does a mixture of CH_3NO_3 and BF_3 etherate; only small amounts of BF_3 etherate are required.

Alkylbenzenes and anisole have been nitrated (16) by this method. Table 6 summarizes the data.

Nitration with Silver Nitrate. Topchiev *et al.* nitrated aromatic hydrocarbons with metal nitrates in the presence of various Lewis acids under heterogeneous conditions (17). A maximum yield of 58% of nitrobenzene was obtained with silver nitrate. Low yields and the heterogeneous nature of the reactions due to the limited solubility of metal nitrates in common organic solvents rendered the reaction of limited use. No studies of mechanism were reported either, probably for the same reasons. Because of the excellent solubility of $AgNO_3$ in CH_3CN, we have developed the $AgNO_3/BF_3$ system (18) for both preparative nitrations and for investigation of the reaction mechanism. The reactions are homogeneous and, if necessary, silver is easily recovered from the tetrafluoroborate salt:

$$\mathrm{ArH} \xrightarrow{AgNO_3/BF_3} \mathrm{ArNO_2}.$$

$AgNO_3$ is a highly efficient nitrating agent under these reaction conditions. We have been able to carry out selective mononitrations of polymethylbenzenes to obtain the corresponding nitroalkylbenzenes in excellent yields (Table 5).

Nitration with Solid Superacid Catalysts. Electrophilic aromatic nitration is generally carried out with HNO_3 or its metal salts, mixed anhydrides, or nitrate esters catalyzed by H_2SO_4 (1–5). Lewis acid catalysts have also been used in nitration (1–5). All of these methods require subsequent aqueous basic workup. The use of solid acid catalysts in nitration is limited to a recent report by Kameo *et al.* (19) on the use of polystyrenesulfonic acid catalysis in the nitration of aromatics with HNO_3. The method is of limited use because the catalyst is degraded by the strong acid.

Table 2. Nitration of nitroarenes and nitrohaloarenes with $NO_2^+BF_4^-$

Substrate	Product	Reaction Temp., °C	Reaction Time, min	Yield of nitro product, %
Nitrobenzene	*m*-Dinitrobenzene	25	20	81
α-Nitronaphthalene	Dinitronaphthalenes	25	20	85
p-Fluoronitrobenzene	2,4-Dinitrofluorobenzene	30	30	78
o-Fluoronitrobenzene	2,4-Dinitrofluorobenzene	30	30	84
2,4-Dinitrofluorobenzene	Picryl fluoride	120	720	40
p-Nitrochlorobenzene	2,4-Dinitrochlorobenzene	30	1,800	75
o-Nitrochlorobenzene	2,4-Dinitrochlorobenzene	30	1,200	77
2,4-Dinitrochlorobenzene	Picryl chloride	100	600	80

Tetramethylene sulfone was used as the solvent in all cases except that for 2,4-dinitrofluoro- and 2,4-dinitrochlorobenzene 100% H_2SO_4 was used.

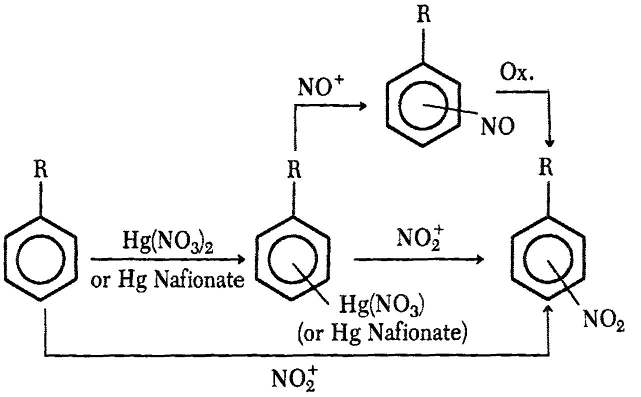
Table 3. Nitration of arylcarboxylic acid esters and halides with $NO_2^+BF_4^-$

Substrate	Product	Reaction Temp., °C	Reaction Time, min	Yield of mononitro product, %
Methyl benzoate	*m*-Nitromethyl benzoate	30	20	88
Ethyl benzoate	*m*-Nitroethyl benzoate	30	20	79
Propyl benzoate	*m*-Nitropropyl benzoate	30	20	82
m-Nitroethyl benzoate	3,5-Dinitroethyl benzoate	85–90	120	60
Benzoyl fluoride	*m*-Nitrobenzoyl fluoride	50	30	69
Benzoyl chloride	*m*-Nitrobenzoyl chloride*	50	30	70

All nitrations were carried out in tetramethylene sulfone solutions.
* Halogen exchange to acid fluoride takes place with byproduct HF.

Our studies showed that preparative nitrations with *n*-butyl nitrate and acetone cyanohydrin nitrate catalyzed by a perfluorinated resin-sulfonic acid (Nafion-H) provide the cleanest method yet known for nitrations of aromatics (20). All of the byproducts are volatile organic materials. Nitro compounds therefore can be isolated simply by removal of the catalyst by filtration, without the need of any aqueous basic washing or work-up.

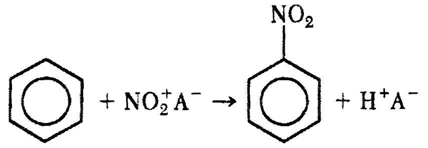
When nitrations of aromatics are performed with mixed acid, the rate of reaction slows with time. This is due to water produced in the reaction mixture, which dilutes the acid. In preparative nitrations, consequently, a large excess of acid is needed, with much of the acid being wasted because of its dilution. Disposal of spent acid also represents increasing environmental problems. It was therefore of interest to study the Nafion-H catalyzed nitration of aromatics with fuming and concentrated HNO_3 under conditions of azeotropic removal of water. Fuming and concentrated HNO_3 were found to be equally effective. The yields of nitro compounds, however, varied depending upon the nature of the aromatic substrate (20).



When the Nafion-H catalyst is modified by impregnation with $Hg(NO_3)_2$, the isomer ratios of product nitroalkylbenzenes show significant differences from conventional acid-catalyzed nitrations, yielding larger amounts of the less-hindered isomer (21) (Table 7). The nitroarenes are formed under the reaction conditions both by direct nitration (catalyzed by Nafion-H) and by nitrodemercuration (or nitrosodemercuration-oxidation) of initially formed arylmercuric nitrates (or surface arylmercuric Nafionates). Nitrodemercuration regenerates the $Hg(NO_3)_2$ (or Nafionate), which reenters the catalytic cycle.

Because the water is removed azeotropically from the reaction vessel, the catalyst (mercury-impregnated Nafion-H) can be recovered without loss of activity and reused.

Transfer Nitrations. Electrophilic aromatic nitrations are usually carried out with acid systems, and an equivalent amount of acid is also produced as a by-product due to proton elimination from the aromatic, even in nitronium salt nitrations.



It was therefore of interest to carry out nitrations under essentially neutral conditions, by tying up the acid product with a suitable base. This has led to work on transfer nitrations with *N*-nitropyridinium and *N*-nitroquinolinium salts (22, 23).

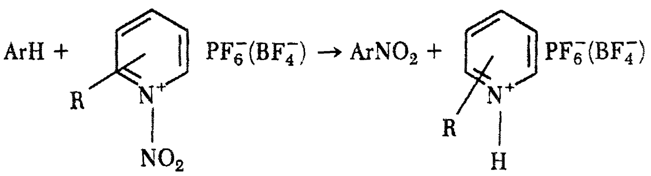
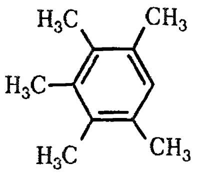
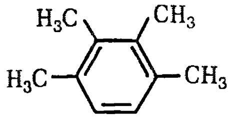
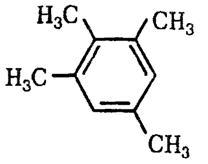
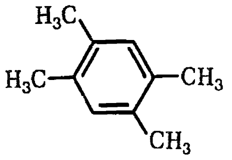


Table 4. Nitration of aryl and aralkyl nitriles with $NO_2^+BF_4^-$

Substrate	Product	Reaction Temp., °C	Reaction Time, min	Yield of nitro product, %
Benzonitrile	3-Nitrobenzonitrile	20–35	30	85
o-Toluonitrile	2-Methyl-5-nitrobenzonitrile	20–35	30	90
m-Toluonitrile	Nitrotoluonitriles	20–35	30	85
p-Toluonitrile	4-Methyl-3-nitrotoluonitrile	20–35	30	92
Nitro-*o*-toluonitrile	3,5-Dinitro-*o*-toluonitrile	100	60	93
Nitro-*m*-toluonitrile	Dinitro-*m*-toluonitriles	100	60	84
Nitro-*p*-toluonitrile	3,5-Dinitro-*o*-toluonitrile	100	60	89
p-Fluorobenzonitrile	4-Fluoro-3-nitrobenzonitrile	40–50	30	90
p-Chlorobenzonitrile	4-Chloro-3-nitrobenzonitrile	50–55	40	92
1-Naphthonitrile	Nitronaphthonitrile	20–35	30	91
Benzyl cyanide	Nitrobenzyl cyanides	0–15	15	84

All nitrations were carried out in tetramethylene sulfone solutions with a ratio of $ArCN/NO_2BF_4$ of 1:1.25 in mononitrations and a ratio of $ArNO_2CN/NO_2BF_4$ of 1:2 in dinitrations.

Table 5. BF_3-catalyzed mononitration of polymethylbenzenes

Polymethylbenzene	Yield of mononitro product, %	
	CH_3NO_3 in CH_3NO_2	$AgNO_3$ in CH_3CN
	99	92
	95.4	86
	97.5	83
	97.0	87

Nitrations with these salts can be carried out under essentially neutral conditions because the only acid present, due to proton elimination from the nitration of aromatics, will bind with the liberated heterocyclic base. At the same time, the reactivity of the nitrating agent can be varied by altering the electron demand as well as the steric crowding of the pyridine ring with suitable substituents.

N-Nitropyridinium and *N*-nitroquinolinium salts were prepared by the method of Olah *et al.* (24). Addition of the corresponding pyridine derivative to an equivalent amount of the nitronium salt in CH_3CN, CH_3NO_2, or sulfolane solution gives the corresponding *N*-nitropyridinium ions in practically quantitative yield. The reverse addition should be avoided because it can lead to ring-opening reactions.

The *N*-nitropyridinium salts can be isolated as stable (although hygroscopic), crystalline salts or generally can be used *in situ* in solution. Except for *N*-nitropyridinium hexafluorophosphate, other substituted salts are readily soluble in CH_3NO_2 or sulfolane, whereas the former is soluble only in CH_3NO_2. Nitrations were studied in CH_3NO_2, CH_3CN, and sulfolane solution. The nitrations were found to take place via a nucleophilic displacement pathway involving the *N*-nitropyridinium ions themselves and not by the free nitronium ion.

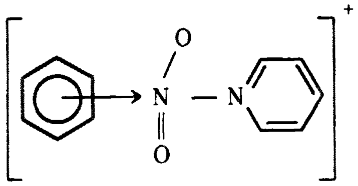
Table 6. Nitration by acetone cyanohydrin nitrate/BF_3 etherate

Compound	Yield, %	Relative yield, %		
		2-Nitro	3-Nitro	4-Nitro
Toluene	77.6	59.8	4.5	35.7
o-Xylene	75.2	0	60.3	39.7
m-Xylene	78.0	15.3	0	84.7
p-Xylene	90.0	—	—	—
Mesitylene	74.1	—	—	—
Anisole	73.1	72.4	0	27.6

Table 7. Nitration over Nafion-H catalyst with and without mercury promotion

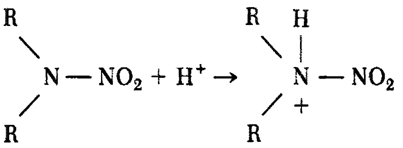
Substrate	Products	Isomer distribution, %	
		Nafion-H	Nafion-H/Hg$(NO_3)_2$
Toluene	2-Nitro	56	33
	3-Nitro	4	7
	4-Nitro	40	60
Ethylbenzene	2-Nitro	44.7*	43
	3-Nitro	2.0	6
	4-Nitro	53.3	51
o-Xylene	3-Nitro	45	33
	4-Nitro	55	67
Chlorobenzene	2-Nitro	38	37
	3-Nitro	1	2
	4-Nitro	61	61
Bromobenzene	2-Nitro	45	44
	4-Nitro	55	56
Naphthalene	1-Nitro	98	97
	2-Nitro	2	3
tert-Butylbenzene	2-Nitro	18	11
	3-Nitro	11	17
	4-Nitro	71	72

* Results of HNO_3/H_2SO_4 nitration (18).



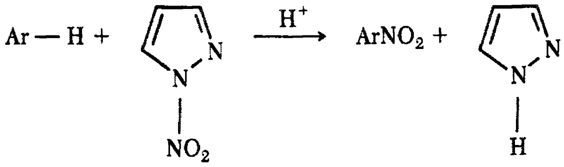
Steric factors, however, were shown to play a minor role in determining the positional selectivity of nitration. Positional and substrate selectivities were found to be independent of one another and are suggested to be determined in two separate steps (see the discussion of mechanism below).

Transfer Nitrations with *N*-Nitropyrazole. Although *N*-nitropyridinium salts used in transfer nitrations are quite stable, they require handling in a dry atmosphere because of their sensitivity to moisture. In principle, one could generate the *N*-nitrammonium salt *in situ* by protonation of a nitramine.



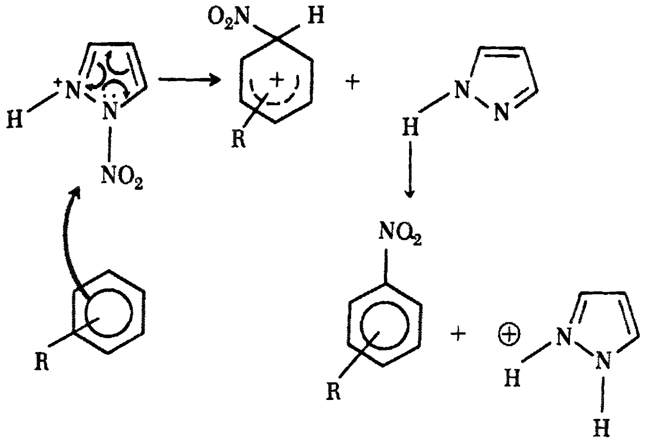
$$R_2N-NO_2 + H^+ \rightarrow R_2\overset{+}{N}H-NO_2$$

This approach was developed successfully by using *N*-nitropyrazole as a transfer nitrating agent (25).



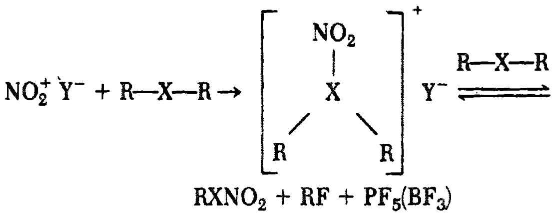
N-Nitropyrazole is a stable, crystalline compound.

Transfer nitrations with *N*-nitropyrazole can be carried out with Lewis acids (BF_3 etherate) or protic acids (CH_3SO_3H, CF_3SO_3H, etc.). *N*-Nitropyrazolonium ion or a related Lewis acid complexed species is the actual nitrating agent displaced by the aromatics.



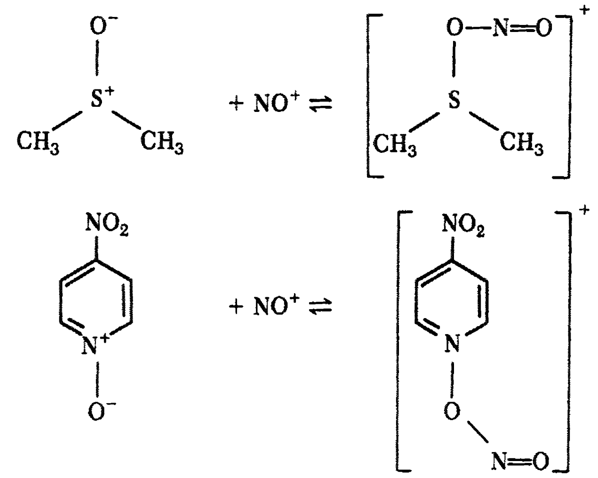
Protonation of *N*-nitropyrazole on the unsubstituted nitrogen was demonstrated by ^{13}C NMR studies. The substrate selectivities in nitration with *N*-nitropyrazole/BF_3 etherate are lower than in nitration with HNO_3/H_2SO_4 acid in sulfolane, CH_3CONO_3, CH_3NO_3/BF_3, or *N*-nitropyridinium salts but higher than in nitration with nitronium salts, thereby suggesting that the developing nitronium ion is still loosely bound to the pyrazole ring.

Transfer Nitrations with Nitro and Nitrito Onium Salts. Zollinger and co-workers (26) showed that addition of 2 equivalents of water changes the substrate reactivities observed in nitronium salt nitrations to those conventionally observed in HNO_3 solutions. A more detailed study of the competitive nitration of toluene and benzene in the presence of a series of nucleophiles was undertaken. The results, summarized in Table 8, show that the $k_{toluene}/k_{benzene}$ rate constant ratios are in the range 2–5 when 1 equivalent of alcohol, ether, or thioether is added but are 25–66 when 2 equivalents of the nucleophile are used. The relative reactivity of the nitrating agent in the presence of added nucleophiles is in the decreasing order ROH > ROR > RSR. The isomer distributions, however, are similar. The data are best interpreted in terms of the nitronium ion reacting with the n-donor nucleophile forming an *O*- or *S*-nitro onium ion intermediate, which can either reverse, or transfer nitrate, or form a covalent intermediate.

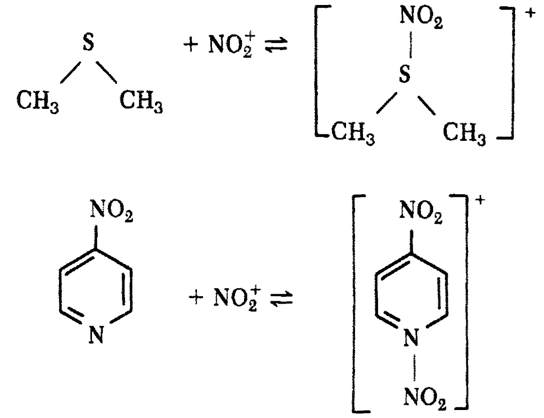


$Y = PF_6^-, BF_4^-; X = O, S; R = \text{alkyl}, H.$

In the course of our studies, we have also prepared *N*- and *S*-nitrito onium salts and found them to be electrophilic nitrating agents in their own right (27). The dimethylnitritosulfonium ion and *N*-nitrito-4-nitropyridinium ion were prepared from nitrosonium hexafluorophosphate and dimethyl sulfoxide or 4-nitropyridine *N*-oxide, respectively.



The isomeric nitro onium ions were also prepared by treating nitronium hexafluorophosphate with dimethyl sulfide and 4-nitropyridine, respectively.



The nitrito onium ions were found to possess significantly less nitrating ability than the corresponding nitro onium ions. The electrophilic nitrating ability of the nitrito compounds is somewhat surprising in view of the fact that nitrites are known to act mainly as nitrosation agents. To our knowledge, the above-mentioned onium salts are the only known examples of nitrito derivatives acting directly as nitrating agents in electrophilic aromatic nitrations (excluding nitrosative nitrations of highly activated aromatics, such as phenols and anilines).

According to Ingold (5), the reactivity of a nitrating agent, X-NO_2, is proportional to the electron affinity of X. As a consequence, it is obvious that differences in species such as

Table 8. Competitive nitration of benzene and toluene with $NO_2^+PF_6^-$ and $NO^+PF_6^-$ in the presence of alcohols, ethers, thioethers, sulfoxides, and *N*-oxides in CH_3NO_2 at 25°C

Nitrating agent	k_T/k_B	Isomer distribution, %			Ratio:
		ortho	*meta*	*para*	*o/p*
$NO_2^+PF_6^-$/methanol (1:1)	3.3	63	3	34	1.85
$NO_2^+PF_6^-$/methanol (1:2)	26.1	62	3	35	1.77
$NO_2^+PF_6^-$/neopentyl alcohol (1:1)	2.8	62	3	35	1.77
$NO_2^+PF_6^-$/neopentyl alcohol (1:2)	25.4	62	3	35	1.77
$NO_2^+PF_6^-$/methyl ether (1:1)	4.0	62	4	34	1.82
$NO_2^+PF_6^-$/methyl ether (1:2)	31.3	62	4	34	1.82
$NO_2^+PF_6^-$/ethyl ether (1:1)	3.8	62	4	34	1.82
$NO_2^+PF_6^-$/ethyl ether (1:2)	32.8	62	4	34	1.82
$NO_2^+PF_6^-$/tetrahydrofuran (1:1)	3.6	62	3	35	1.77
$NO_2^+PF_6^-$/tetrahydrofuran (1:2)	28.9	62	4	34	1.82
$NO_2^+PF_6^-$/dimethyl sulfide (1:1)*	4.6	62	3	35	1.77
$NO_2^+PF_6^-$/dimethyl sulfide (1:2)	65.7	62	3	35	1.77
$NO^+PF_6^-$/dimethyl sulfoxide (1:1)†	27.3	59	4	37	1.60
$NO^+PF_6^-$/4-nitropyridine-*N*-oxide (1:1)†	33.4	51	8	41	1.24

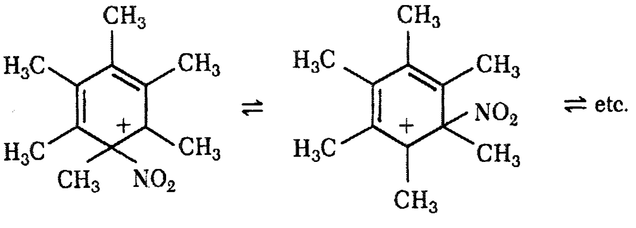
k_T/k_B, ratio of rate constant in toluene to that in benzene.
* In nitroethane at −78°C.
† At 60°C.

$R_2^+XNO_2$, R_2^+XONO, and R-X-NO_2 play an important role in these reactions. Furthermore, these studies indicated the ambident reactivity of the nitronium ion.

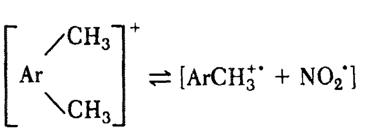
Ambident Reactivity of the Nitronium Ion. Nitronium hexafluorophosphate (tetrafluoroborate) was found to react rapidly at −78°C with diaryl, arylalkyl, and dialkyl sulfides, affording sulfoxides as the major products (28). Selenides, phosphines, arsines, and stibines react equally readily, giving the corresponding oxygenated products. In the case of diphenyl sulfide, less than 5% of competing ring C nitro products were obtained. These observations suggest that the intermediate nitrito onium ion (X^+-ONO) is in equilibrium with the related nitro onium ion (X^+-NO_2). The ambident reactivity of NO_2^- and $NO_2^\cdot$ is well known from the literature. The suggested equilibrium was confirmed by carrying out *trans*-nitrosation of *N,N*-dimethylaniline in the presence of these onium salts. ^{13}C, ^{15}N, and ^{31}P NMR studies of the onium salts showed that nitro onium salts are irreversibly transformed into nitrito onium salts either upon raising the temperature or during prolonged reaction times. The ambident nature of the nitronium ion has far-reaching implications in the industrial nitration of aromatics, in which phenolic products could be arising by attack through the oxygen of the nitronium ion.

Reversibility of Electrophilic Aromatic Nitrations. Acid-catalyzed nitration is a typical electrophilic aromatic substitution reaction. Nitration is generally considered to be an irreversible reaction, and nitroaromatics, in general, do not undergo rearrangement or isomerization under the reaction conditions; however, some isomerization of the nitroarenium ion intermediates has been observed (29). Relative reactivities and substituent effects have been extensively studied in nitration of aromatics, on the assumption that the nitro compounds formed do not revert to starting materials. Otherwise, relative reactivities calculated on the basis of product ratios would be affected and require a more rigorous treatment taking into account the reverse reaction.

Examples of acid-catalyzed migration of nitro groups have been reported (29). The mechanisms of these migrations, however, are not always fully established and, at least in some instances, may involve radical cations [as in the case of nitramine rearrangements (30)]. In the case of hexamethylnitrobenzenium ion, the intramolecular nitro group migration was directly studied by us using NMR spectroscopy, and the complex was also found capable of transfer nitration of added aromatics (31).



This degenerate rearrangement was subsequently also studied by Koptyug and co-workers (32). They showed that the rearrangement takes place through successive intramolecular 1,2-migrations of the nitro group and ruled out the possibility of an alternative pathway proceeding through the formation of a radical cation.

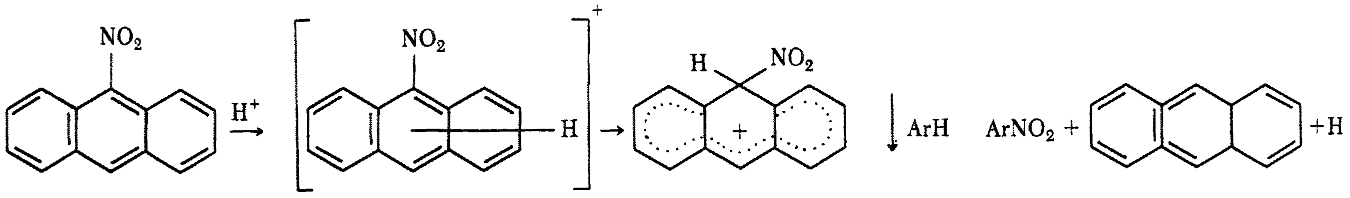


$$\left[\mathrm{Ar}\begin{matrix}CH_3\\ CH_3\end{matrix}\right]^+ \rightleftharpoons [\mathrm{ArCH_3^{+\cdot}} + \mathrm{NO_2^{\cdot}}]$$

In the course of acid-catalyzed nitration of aromatics, the reversibility of nitration was not directly established until recently. Gore (33) reported in 1957 that heating of 9-nitroanthracene with 6 M sulfuric acid in trichloroacetic acid solution for 15 min at 95°C gave a dark solution in which, after dilution with water, an 81% yield of free nitric acid was estimated. Anthracene itself could not be isolated, but a 20% yield of anthraquinone and appreciable amounts of polymer and soluble sulfonic acids were obtained. Experiments conducted in the presence of added nitrobenzene to detect cross-nitration products failed.

A strong indication for the possible reversibility of aromatic nitration was obtained by Cerfontain and Telder (34) who found a primary kinetic hydrogen isotope effect in the nitration of anthracene-9-d (compared to light anthracene), indicative of the relative slowness of the proton transfer from the σ intermediate of the reaction.

We have recently obtained unequivocal evidence for the reversibility of electrophilic aromatic nitration by observing superacid-catalyzed transfer nitration of mesitylene and toluene by 9-nitroanthracene and pentamethylnitrobenzene, respectively, and isolating the product nitromesitylene and nitrotoluenes (35). The following mechanism was proposed for the transfer nitration with 9-nitroanthracene.



The primary kinetic hydrogen isotope effect, $k_H/k_D = 2.25 \pm 0.05$, in the nitration of anthracene-d_{10} with nitronium hexafluorophosphate in CH_3NO_2 solution is thus in good accord with the reversibility of the nitration of anthracene.

MECHANISMS

Electrophilic aromatic nitration has been shown by Ingold's classical studies (5) to proceed via the formation of the nitronium ion (NO_2^+). Reaction of the electrophile with aromatic substrates results in the formation of nitroarenium ions (σ complex; Wheland intermediate) which, upon proton abstraction, yield the nitro products. There are spectroscopic indications for the σ complex and significant isotope effects in the nitration (with nitronium salts) of anthracene (34). A consequence of the two-step/one-intermediate mechanism is that substrate and positional (inter- and intramolecular) selectivity are determined in one and the same step—i.e., the formation of the σ complex. This is expressed in the Brown–Stock reactivity/selectivity relationship (36) which is based on the empirical Hammett equation. Indeed, a large body of data correlate well with the relationship. The implication of the Brown–Stock reactivity/selectivity rule is that, if substrate selectivity is lost, positional (regio-) selectivity also should be lost.

Olah *et al.* (27, 37–41) found that nitration with highly reactive nitronium salts under homogeneous conditions results in loss of substrate selectivity ($k_T/k_B \approx 1.7$ vs. ≈20 under normal acidic conditions) with maintenance of positional selectivity (*meta* substitution, < 4%). It is instructive to note that free-radical nitrations with N_2O_4, $C(NO_2)_4$, and chloropicrin result in low substrate and regio-selectivity, with close to statistical product distributions (27, 42).

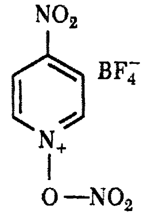
Accordingly, Olah proposed (43, 44) a three-step mechanism in which the first step determines the substrate selectivity (if rate controlling) and the second step, the positional selectivity. Thus, for a given substrate the reactivity of the nitrating agent determines which of the two transition states is of highest energy. The same applies to variations of the basicity of aromatic substrates in a given nitrating system. Schofield and co-workers (45) similarly found that, in nitric acid nitration in strong acids, substrate selectivity only may be lost, and they also formulated the formation of an intermediate prior to the σ complex.

The nature of the first intermediate has been discussed by Olah (43, 44) in terms of π-complex character. The fast nitric acid nitrations were interpreted by Schofield and co-workers (45) to be a result of microscopic diffusion control with formation of the first intermediate at the encounter rate—accordingly named "encounter pair"—in which there is no significant interaction between the reactants. Nitronium salt nitrations have been discussed in terms of macroscopic diffusion control (mixing control) (46). However, we consider this inadequate to explain many of the experimental observations. Although mixing control for very reactive species (mesitylene, durene) has been suggested (47, 48), there is no evidence for the fundamental cases of benzene and toluene. On the contrary, the fact that a reverse isotope effect was found for nitration of heavy and light benzene and toluene (49, 50) ($k_H/k_D = 0.81$) renders mixing control, if present at all, of minor importance.

Formulation of the first intermediate in terms of π-complex nature is strongly supported by the recent observation of a nitronium ion charge transfer complex, reported by Fukujumi and Kochi (51) between *m*-tolunitrile and nitronium tetrafluoroborate. In their elegant study they also suggested, for various slow electrophilic aromatic substitutions, the occurrence of a CT complex prior to σ-complex formation on the reaction pathway. It is noteworthy that the calculated diffusion barrier for encounter pair formation ($\approx$6 kcal/mol) (4) is similar in magnitude to that of CT complex formation in general ($\leq$4 kcal/mol) (52). Also, the correlation of calculated encounter rate with solvent viscosity has only been shown for HNO_3 nitration in strong H_2SO_4 and H_3PO_4 (4).

The proposal of initial one-electron transfer between the nitronium ion and the aromatic substrate, recently reemphasized by Perrin (53), resulting in a radical–radical cation pair prior to the formation of the σ complex is in fact only an extreme of the π-complex formulation. A full one-electron transfer can occur if the ionization potential and electron affinity for the reactants are compatible prior to electronic interactions, and it is named "outer sphere mechanism" in molecular complex terminology (54, 55). Although nitrations with very reactive aromatic substrates are likely to be subject to one-electron transfer, this is not the case for benzene and toluene and it seems not even for naphthalene. For an argument against the electron-transfer mechanism in the nitration of mesitylene, see ref. 56. Perrin (53) found in the "electrochemical nitration" of naphthalene, by generation of the naphthalene radical cation in the presence of $NO_2^{\cdot}$, the α/β isomer distribution of 9, similar to that of the HNO_3/H_2SO_4 nitration, 11. Our results (57) on nitration of naphthalene with various nitrating agents in different solvents, as well as other literature data (53, 58) (Table 9) show that the α/β ratio may vary between 9 and 29. Eberson *et al.* (59) examined in detail the diffusion-controlled radical cation coupling, by reaction of solid [naphthalene]$^{\cdot+}PF_6^-$ with N_2O_4, and found an α/β ratio of $\approx$40, whereas a ratio of 10–12 was found for the naphthalene NO_2^+ reaction under similar conditions. From repetition of Perrin's experiments, Eberson *et al.* (59, 60) concluded that the electrochemical nitration of naphthalene is predominantly, if not exclusively, due to the homogeneous nitration of naphthalene by dinitrogen tetroxide catalyzed by anodically generated acid.

Table 9. Nitration of naphthalene with various nitrating agents

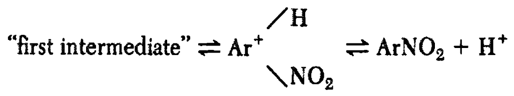
Reagent	Solvent	Temp., °C	α/β isomer ratio
NO_2BF_4	Sulfolane	25	10
NO_2BF_4	Nitromethane	25	12
HNO_3	Nitromethane	25	29
HNO_3	Acetic acid	25	21
HNO_3	Acetic acid	50	16
HNO_3	Sulfuric acid	70	22
HNO_3	Acetic anhydride	25	9
CH_3ONO_2/CH_3OSO_2F	Acetonitrile	25	13
$AgNO_3/CH_3COCl$	Acetonitrile	25	12
$AgNO_3/C_6H_5COCl$	Acetonitrile	25	12
N_2O_4	Acetonitrile	25	24
$N_2O_4/Ce(NO_3)_4{\cdot}2NH_4NO_3$	Acetonitrile	65	16
HNO_3/H_2SO_4/urea	Acetonitrile	—	11
Electrochemical oxidation + N_2O_4	Acetonitrile	—	9
$C(NO_2)_4$	Gas phase	300	1
$AgNO_3/BF_3$	Acetonitrile	25	19
	Acetonitrile	25	10

From ref. 57. Isomer ratios are accurate to ±1.

The above addresses, in fact, the question to what extent the isomer distribution (as determined in the σ-complex forming step) varies on changing the rate-determining step. Although, as discussed, positional selectivity is maintained when substrate selectivity is lost, careful scrutiny of the isomer distributions for various toluene nitrations shows (4, 27) that there are varying substitution patterns with respect to the *ortho/para* ratios but, significantly, the amount of the *meta* isomer is always $\approx$3%. Extreme *ortho/para* ratios are 2.19 and 0.50, but the main body of ratios ranges from 2.1 to 1.6 (4). Steric factors, such as the bulkiness of the effective nitrating agent, can affect the *ortho/para* isomer ratio (increasing the *para*) but are not considered to be the only reason for the observed variations. *Ipso* attack of toluene by NO_2^+, if leading to product formation, would result in *ortho* substitution and also affect the *ortho/para* isomer ratio, but only to a small extent (<4% *ipso*) (4). It is anticipated that the reactivity of the nitrating agent is reflected in the energetics of the first intermediate, affecting the nature and position of the transition state on the reaction coordinate for σ-complex formation.

Despite the debate on the nature of the first intermediate, all recent studies agree on the necessity of two separate steps in the mechanism leading to the σ complexes. The first step determines the substrate selectivity (if rate controlling) and the second step determines the positional (regio) selectivity. Proton elimination does not result in a primary hydrogen isotope effect and thus is not rate controlling. Consequently, the original Ingold scheme must be amended.

$$NO_2^+ + ArH \rightleftharpoons \text{“first intermediate”}$$



$$\text{“first intermediate”} \rightleftharpoons Ar^+\begin{matrix}/H\\ \backslash NO_2\end{matrix} \rightleftharpoons ArNO_2 + H^+$$

The nitronium ion can be obtained under protic conditions from nitric acid

$$H^+ + HNO_3 \rightleftharpoons H_2ONO_2^+$$

$$H_2ONO_2^+ \rightarrow H_2O + NO_2^+$$

or nitronium salts can be directly used under aprotic conditions or bound to a conjugate base (transfer nitration).

CONCLUSIONS AND OUTLOOK

Thirty years after Ingold's fundamental studies on the mechanism of electrophilic aromatic substitution were published, the field is undergoing a renaissance of interest and activity. The preparation and preparative use of stable nitronium salts as nitrating agents opened up new possibilities in anhydrous nitrations. A series of other more selective new nitrating agents and systems were also developed. A recent trend is the use of highly acidic solid catalysts to replace liquid acids such as H_2SO_4. Mechanistic studies resulted in realization of the necessity of an additional step in the classical Ingold mechanism between the reactive nitrating agent and aromatics, determining overall substrate reactivity (if rate controlling), prior to regioselective arenium ion (σ complex) formation. Because substrate and positional (regio) selectivities may be determined in separate steps, no simple relationship between reactivity and selectivity exists.

The ambident nature of the nitronium ion was also demonstrated and utilized in explaining nitration and oxidation reactions.

Support of our work by the U.S. Army Office of Research is gratefully acknowledged.

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