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Current approach to the problem of nitrenium ions

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ABSTRACT. This review is devoted to the chemistry of nitrenium ions, which are highly reactive species whose bivalent nitrogen atom has an incomplete (sextet) electron shell and bears a formal positive charge. All known methods for generating these ions, including a nuclear chemical method developed by the authors, their reactions, structure, and also the role of nitrenium ions in the chemistry of nitrogen-containing compounds are examined.

The bibliography includes 159 references.

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I. Introduction

The idea that it is possible to form charged species containing bivalent nitrogen (nitrenium cations) was first put forward at the beginning of this century in the studies of Stieglitz et al.[1-3]

Up to the 1970s the publications devoted to studies on these species were not only limited but also contradictory. Different schemes for the same reaction of nitrogen-containing compounds were put forward, assuming and excluding the formation of nitrenium ions as intermediates. It is sufficient to say that an unequivocal affirmation of the fact that nitrenium ions are actually formed only became possible as a result of studies during the last 20 – 25 years.

The first attempt to correlate the available information on nitrenium ions was made in 1970.[4] However, an extensive series of studies by Gassman marked the beginning in the development of the chemistry of these reactive nitrogen-containing intermediates. The results of Gassman's studies, which were published in a review article,[5] contained fundamental data that demonstrated the possibility of such cations existing as independent species. Gassman produced convincing data on the electronic structure of nitrenium ions and evidence for their possible existence both in a singlet and triplet state.

Subsequent experimental studies[6-8] and quantum-mechanical calculations[9-25] confirmed the basic conclusions of Gassman. It was shown that nitrenium ions containing alkyl groups occur mainly in a triplet ground state while those containing aryl groups occur mainly in a singlet ground state.

In the 1970s and 1980s physicochemical[26-27] and nuclear chemical[28-32] methods for generating nitrenium ions were developed. It should be noted that with nuclear chemical methods it is possible to obtain these species in a free state and to study their reactions.

During the last ten years research on nitrenium ions and their reactions has been conducted with particular intensity.[28-48] The increased interest in this problem is mainly due to the important role of these species in carcinogenetic processes. Nitrenium ions are known to constitute the active form of strong chemical carcinogens, such as arylamines, *N*-arylhydroxylamines, and arylnitroso and arylnitro compounds.[24,49-53] It has been established that the active forms of chemical carcinogens are strong electrophilic reagents that are covalently bonded with the nucleophilic forms of nucleic acids and proteins. One of the main problems is to obtain information about the macromolecularly bonded products for each carcinogen. This is important in determining the relative role of each adduct in the carcinogenetic process.[49]

Furthermore, reactions of nitrenium ions open up exceptional opportunities for direct amination and on this basis the development of novel synthetic methods for preparing nitrogen-containing compounds.[54]

II. General characteristics and electronic structure of nitrenium ions

Nitrenium ions are nitrogen-containing organic compounds in which the nitrogen atom has an incomplete (sextet) electron shell and bears a formal positive charge (+1).

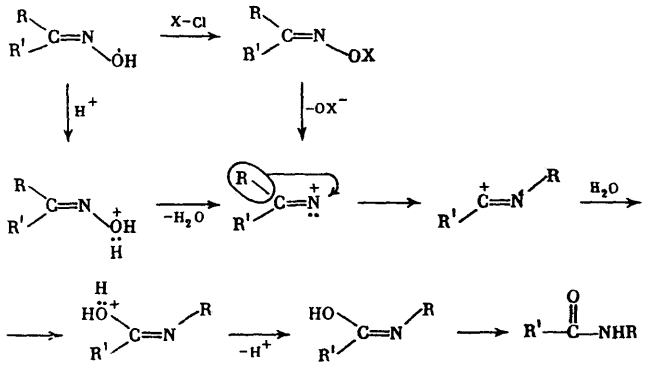
Nitrenium ions are formed as a result of the heterolytic elimination of a substituent from amines of two structural types:[55]

$$R_3N \xrightarrow[-R^-]{} R_2\overset{+}{N}: \qquad \text{(A)}$$

$$R^1R^2C{=}NX \xrightarrow[-X^-]{} R^1R^2C{=}\overset{+}{N}: \qquad \text{(B)}$$

Nitrenium ions of type (A) form the subject of our investigation.

An example of a reaction in which cations of type (B) are formed as an intermediate is provided by the Beckmann rearrangement (see the study of Donaruma and Heldt).[56] The mechanism by which this rearrangement occurs is described by Saik.[57]



X = $R''CO^-$; $R''SO_2^-$ etc.

In this case the synchronous cleavage of the N–O bond and migration of the group without formation of a nitrenium ion also cannot be excluded (possibly via a three-centred transition state), which is supported by the stereoselectivity of the reaction.

Nitrenium ions resemble carbocations in their behaviour. However, a number of significant differences in their behaviour caused by the nature of the heteroatom should be noted. Because of the presence of a positive charge on the more electronegative nitrogen atom compared to a carbon atom, the stability of nitrenium ions is expected to be lower than that of carbocations. By analogy with carbocations, nitrenium ions have a sextet of electrons and a vacant *p* orbital, but in contrast to carbocations there is a free electron pair on the nitrogen atom. The presence of the latter is responsible for several characteristics of the chemical behaviour of nitrenium ions that distinguish them from carbocations—the possibility of these species occurring in singlet (A) and triplet (B) states.[58]



(A) (B)

The singlet nitrene cation differs from triplet biradical species by virtue of its chemical behaviour and it displays a similarity to carbocations.

Quantum-chemical calculations carried out for the parent nitrenium ion $\overset{+}{N}H_2$,[9–13,16–19,23] its alkyl homologues $MeNH$,[11,14,21,23] Me_2N,[14,21,23] and others[15,23] and also for phenylnitrenium ions[24,25] demonstrated that the difference in energy between the singlet and triplet states is 20–40 kcal mol^{-1} in certain cases. For the unsubstituted $\overset{+}{N}H_2$ and the simplest alkyl homologues the ground state is the radical-like triplet state.†

Arylnitrenium ions occur preferentially in a singlet ground state.[24] Both forms (singlet and triplet) in the case of arylnitrenium ions are stabilised through transfer of electron density from the phenyl substituent to the nitrogen atom, but for the triplet form this transfer, and hence the magnitude of the stabilising effect, is less than for the singlet, since the *p* orbital in the triplet state is partly filled[24] (Fig. 1).

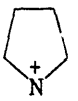
The calculated heats of formation of certain nitrenium ions (ΔH_f) and their relative stabilisation energies (ΔE) are given in Table 1.



S T

Figure 1. Mesomeric stabilisation of singlet and triplet nitrenium ions.

Table 1. Heats of formation (ΔH_f) and relative stabilisation energies (ΔE) of the singlet and triplet states of certain nitrenium ions (MNDO method).

Ion	ΔH_f, kcal mol^{-1} (Ref.24)		(S_0-T_1), kcal mol^{-1}	ΔE^*, kcal mol^{-1} (Ref.24)	
	S_0	T_1		S_0	T_1
$\overset{+}{N}H_2$	313.4	292.2	21.2	0	0
$MeNH$	277.9	271.7	6.2	-37**	-22
Me_2N	259.1	251.1	8.0	-57	-44
	240.4	250.9	-10.5	-70	-38
$PhNH$	241.5	267.6	-26.1	-106**	-59

*Values of the stabilisation energies given relative to $\overset{+}{N}H_2$.

**The corresponding stabilisation energies of $MeCH_2$ and $PhCH_2$ relative to CH_3 are −37 and −56 kcal mol^{-1}.

The data shown are in good agreement with the results of experimental studies by Japanese research workers.[45,48] In the case of the reactions between alkyl- and phenyl-nitrenium ions with different aromatic nucleophiles it is possible to establish a trend for the decrease in energy of singlet nitrenium ions:

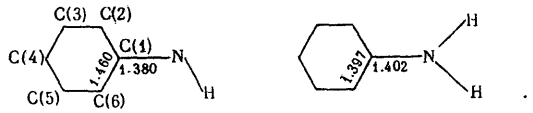
$$\overset{+}{N}H_2 > AlkNH > PhNH.$$

It can be seen from Table 1 that aromatic nitrenium ions have a higher stabilisation energy than the aliphatic ions.[5]

Quantum-chemical calculations of the energy, geometry, and electronic structure of phenylnitrenium ions were made in two studies.[24,25] Calculation of electron density by the MNDO method

† At the same time it was established[58] that solvents containing heavy atoms can catalyse spin inversion. This effect has been observed in three studies.[41,43,59]

for phenylnitrenium ions[24] assumes an optimum geometry for planarity of the cation.‡ From the calculations of Krylov[25] the following optimum geometry of the phenylnitrenium ion was established (the geometry of aniline is shown for comparison):



It should be noted that the C–N bond in phenylnitrenium ions is considerably shorter than in alkylnitrenium ions. As expected, the results of calculation of the electronic structure of phenylnitrenium ions suggest that a partial positive charge occurs on the second (0.112), sixth (0.112), and fourth (0.169) carbon atoms of the benzene ring. At the same time the charge on the carbon atom at the *para* position exceeds the positive charge on the nitrogen atom (0.123) (Table 2).

Table 2. Charges on the electrophilic sites of phenylnitrenium ions.

Atom	MNDO method (Ref.24)		CNDO/2 method (Ref.25)
	LUMO	*q* (total)	*q* (total)
N	0.444	0.001	0.123
C(1)	-0.087	-0.065	—
C(2)	-0.459	0.346	0.112
C(3)	0.043	-0.010	—
C(4)	0.590	0.384	0.169
C(5)	-0.004	-0.041	—
C(6)	-0.496	0.233	0.112

Krylov[25] concluded from the charge distribution data that there is a considerable contribution from mesomeric carbocation structures in phenylnitrenium ions.



(I) (II) (III) (IV)

The values of the LUMO coefficients§ shown in Table 2 also show that four electrophilic sites occur in phenylnitrenium ions.

‡ Similar calculations[63,64] give a nonplanar structure for aniline.

§ According to general multielectron perturbation theory, a donor-acceptor interaction may be charge-controlled (type I) or (frontier) orbital-controlled (type II). Electrophilic aromatic substitution (benzene as a mild nucleophile) is a "frontier orbital-controlled" reaction. The reaction sites of the electrophile will be atoms having the highest charge density on their lowest unoccupied molecular orbital (LUMO).[65]

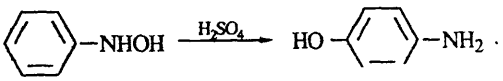
The experimental data (see Section IV) suggest that nitrenium ions with aromatic substituents do in fact behave both strictly as nitrenium ions (I) and as carbocations (II)–(IV).

III. Methods of generation

1. Bamberger and Stieglitz rearrangements

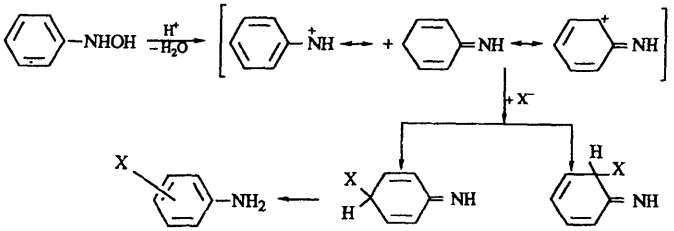
The original ideas about the existence of unstable bivalent nitrogen intermediates developed as a result of studies on the rearrangements of *N*-arylhydroxylamines — the so-called Bamberger and Stieglitz rearrangements.

The Bamberger rearrangements takes place on treatment of *N*-phenylhydroxylamine with aqueous mineral acid, resulting in the formation of *p*-aminophenol.[66–68]



Bamberger assumed that arylhydroxylamines are dehydrated to nitrenes, which react with nucleophilic reagents to give rearrangement products.

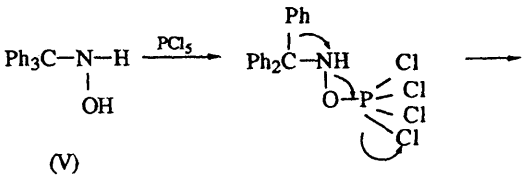
Subsequent studies of this reaction[69–72] demonstrated that a nitrenium ion is formed at an intermediate stage. In an investigation of the acid catalyst trifluoromethanesulphonic acid (TFMSA), *ortho*- and *para*-substituted anilines were obtained.[72]



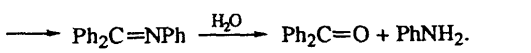
X = HO, PhO, MeO, Cl, Ph etc.

It could be assumed from kinetic studies that the nitrenium ion is formed in a slow stage and then rapidly adds a nucleophile molecule.[73]

Stieglitz et al.[1,2] initially studied the rearrangement of *N*-monoalkylhydroxylamines in which the carbon atom adjacent to the nitrogen was fully substituted, such as in tritylhydroxylamine (V).



(V)

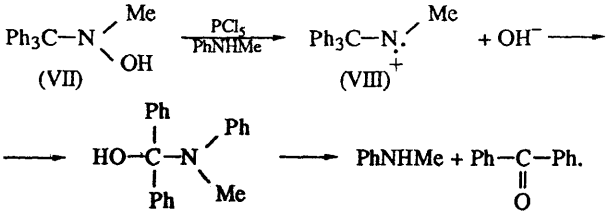


(VI)

Treatment of (V) with phosphorus pentachloride causes one of the phenyl groups to migrate to the nitrogen atom with the formation of the imine (VI), and after hydrolysis benzophenone and aniline are formed. At the same time migration was thought to be an

intramolecular process. Stieglitz et al. put forward the suggestion that species with a univalent nitrogen atom (nitrene as interpreted at the present time) were formed as an intermediate.

This interpretation of substituted hydroxylamines as originally proposed by Stieglitz encounters difficulties when attempts are made to distinguish between nitrenium ions and nitrenes in *N*-monosubstituted hydroxylamines. In order to exclude the formation of nitrene, Stieglitz et al.[3] studied the rearrangement of a dialkyl-substituted hydroxylamine, namely, triphenylmethyl-*N*-methylhydroxylamine (VII) under similar conditions (with PCl_5), as a result of which only triphenylchloromethane was formed. However, when the reaction was carried out in the presence of small quantities of *N*-methylaniline, the rearrangement products—benzophenone and *N*-methylaniline—were isolated in low yield together with triphenylchloromethane. In this case it is impossible to depict the formation of nitrene, and the authors put forward another reaction scheme, which actually features the nitrenium ion (VIII):



Later studies[5] supported the conclusion of Stieglitz, by demonstrating that under certain conditions the rearrangement of disubstituted hydroxylamines actually occurs via the formation of a nitrenium ion.

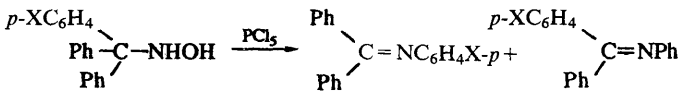
Research on the rearrangements of Stieglitz and Bamberger assisted in the development of different methods for the synthesis of nitrenium ions. For a long time the most widely studied of the reactions that occur via intermediate nitrenium ions were the reactions of hydroxylamine and *N*-haloamine derivatives.

Other methods of generating nitrenium ions are reactions involving organic azides and hydrazine derivatives and the photolysis and thermolysis of pyridinium and sulphonium salts and other salts. At the present time nitrenium ions may also be obtained by physicochemical and nuclear chemical methods. Let us examine these methods in greater detail.

2. Generation of nitrenium ions at intermediate stages of organic reactions

a) Reactions of hydroxylamines. It was possible to conclude from an examination of the rearrangements of Stieglitz and Bamberger that the formation of nitrenium ions is affected both by the nature of the actual nitrogen-containing organic compounds (sources of nitrenium ions) and by the medium in which these reactions occur.

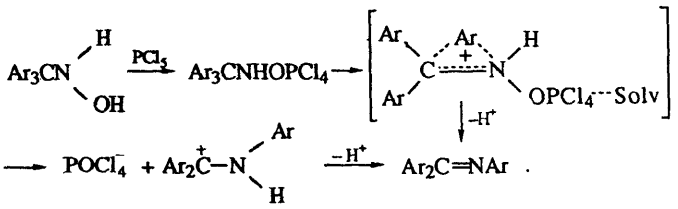
Studies by Newman and Hay[74] also provide evidence for the formation of nitrenium ions in the Stieglitz rearrangement. In a study of the effect of substituents in the aromatic ring on the migrating ability of the ring in the rearrangement of triarylhydroxylamines on treatment with PCl_5



X = OMe, Cl, NO_2 ,

it was established that a decrease in the electron-donating properties of the substituents leads to a reduction in the migrating ability of the corresponding group: 9.10 (C_6H_4OMe), 0.55 (C_6H_4Cl), and 0.38–0.18 ($C_6H_4NO_2$). The authors concluded that, by analogy with the pinacol rearrangement (a typically ionic process), the Stieglitz rearrangement is also accompanied by the formation of ionic species.

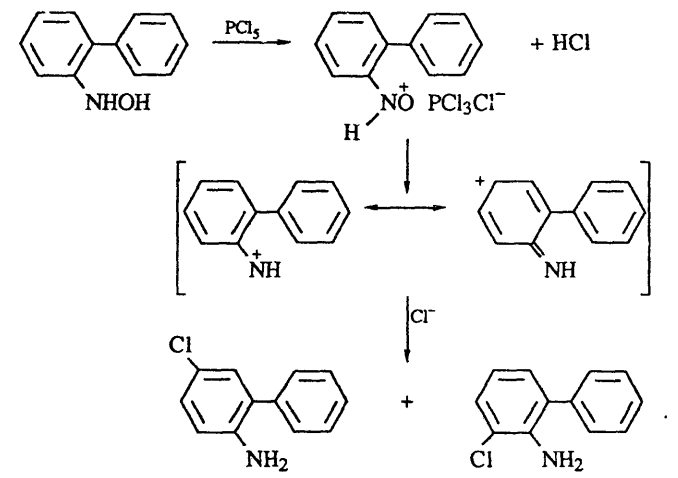
We should not that this rearrangement is interpreted by Krylov[25] as the synchronised cleavage of the N–O bond and migration of a group to the nitrogen atom



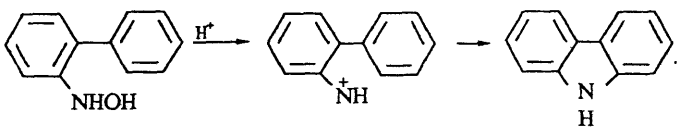
However, the possibility of nitrenium ions being formed in very polar media (in polyphosphoric acid, for example) cannot be excluded.

It should be noted that the mechanism of the Stieglitz rearrangement by treatment with various Lewis acids[75–77] depends on the electrophilicity of the reagent used. The probability of a nitrenium ion being formed increases with an increase in the electrophilicity of the reagent and is reduced to zero in the case of weak electrophiles (*o*-isopropyl methylphosphonochloridate, for example).[78]

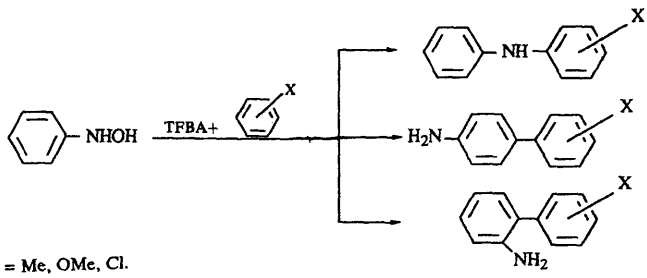
For the rearrangement of 2-hydroxylamino-1,1′-biphenyl, which takes place on treatment with PCl_5, a scheme involving the formation of an intermediate nitrenium ion was proposed by Potts et al.[79]



A similar process, but one that occurs on treatment with strong proton acids, gives carbazole which is formed from a nitrenium ion.[80]



Considerable attention has been given recently to intermolecular reactions involving the introduction of aminophenyl groups into an aromatic ring. On treatment of phenylhydroxylamine with tetrafluoroboroic acid (TFBA) in aromatic hydrocabons, the arylamination products were isolated in 20–50% yield:[81]

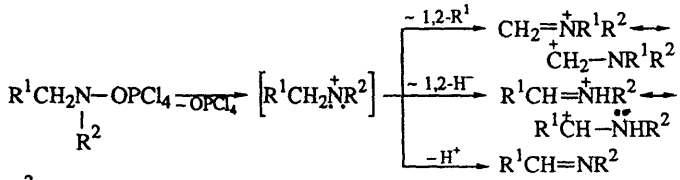


X = Me, OMe, Cl.

It was assumed in this case that initially a phenylnitrenium ion is formed, which subsequently reacts with an aromatic ring.

Further studies in this area showed that other acids, such as acetic acid (AA),[33,34,36] trifluoroacetic acid (TFAA),[35,37,40,41,43] and trifluoromethanesulphonic acid (TFMSA)[39,43,72,82] can act as catalysts of arylamination occurring via the formation of a nitrenium ion. It was found, moreover, that the nature of the acid has an effect on the ratio of the final products.

Four studies by Krylov et al.[6–8,25] investigated the rearrangements of *N*-alkyl- and *N,N*-dialkylhydroxylamines and also their salts with phosphorus pentachloride involving migration of hydrogen and alkyl groups:



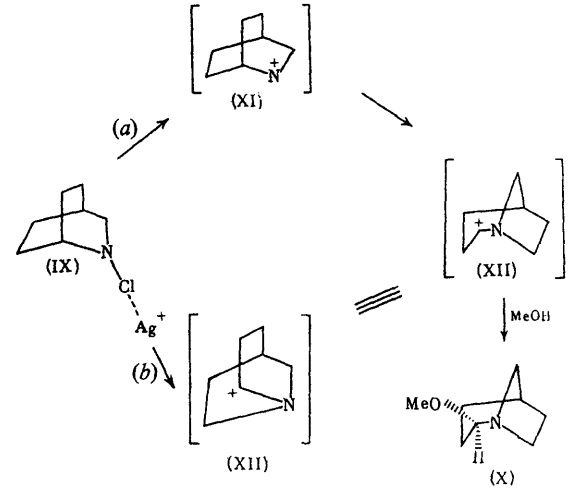
R^2 = H, CH_2R.

The authors assumed that the primary and secondary amines were formed as a result of the rearrangement of nitrenium ions, accompanying migration of a group to the electron-deficient nitrogen atom.

b) Reactions of *N*-haloamines. The first, rather contradictory, studies on the preparation of nitrenium ions as a result of the cleavage of the N–Hal bond in *N*-haloamines were published in the mid-1960s.[83–85] Because of the large number of studies in this area, it has been shown at the present time that many of the compounds that contain an N–Hal bond are very convenient substrates for the preparation of nitrenium ions.[5,59,86–108] Such compounds include azabicyclic compounds, haloamines with cyclic groups (cyclopropane and cyclobutane) and aromatic groups (anilines), etc.

Scheme 1 illustrates the formation of nitrenium ions by solvolysis of *N*-chloroisoquinuclidine (IX) in a methanol solution of silver nitrate.[5]

Scheme 1

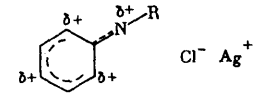


The conversion of (IX) to (X) can occur by two routes: route (*a*)—the heterolytic cleavage of a chloride anion resulting in the formation of nitrenium ion (XI): route (*b*)—simultaneous loss of a chloride anion and migration of an alkyl group with its pair of bonding electrons, giving product (XII). Regardless of which of the two routes is followed in this rearrangement, the species (XI) with a deficiency of electrons on the nitrogen atom participates in this process.

In studying the reaction depicted in Scheme 1, Gassman and Cryberg[59] conducted an experiment on the conversion of nitrenium ions from a singlet to a triplet state. By using solvents containing heavy atoms, it was possible to control the conversion of singlet to triplet states according to a previously established method.[109–110] The authors[59] believe that this constitutes evidence for the existence of nitrenium ions.

A series of studies[90,94,97,101,102,105] is concerned with the formation of nitrenium ions in nucleophilic aromatic substitution in anilines. Thus, on solvolysis of *N*-chloroanilines, products that were similar to those of the Bamberger rearrangement[72] were isolated, as illustrated by Scheme 2. It is clear from Scheme 2 that, at the initial stage of the reaction, ionisation of (XIII) occurs with the formation of arylnitrenium ions with various resonance structures [(XIVa) ⟷ (XIVb) ⟷ (XIVc)].

Even though an excess of silver ions is present in the reaction mixture, chloro derivatives are formed. Gassman et al.[101] attribute this phenomenon to the formation of an intimate ion pair at an intermediate stage of the reaction.



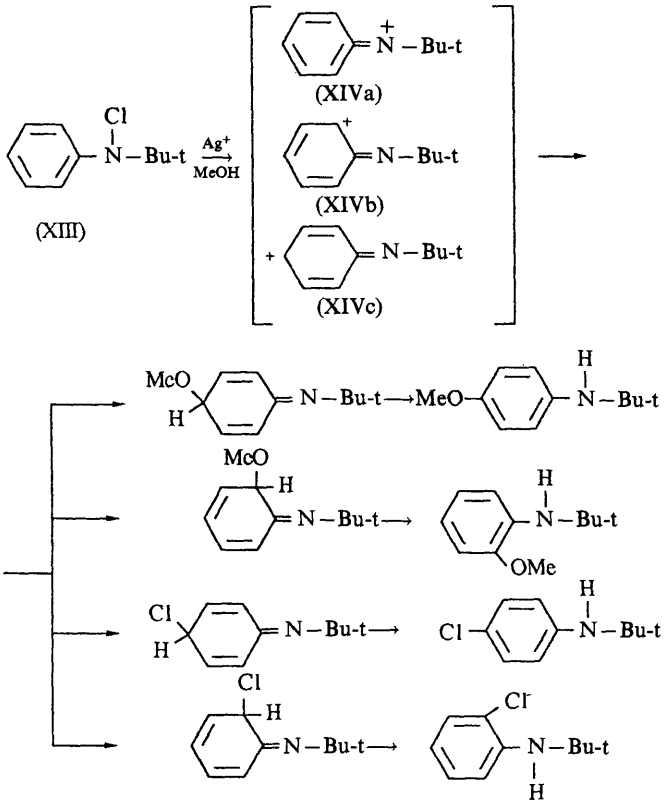
Similar results were obtained from the thermal rearrangement of *N*-chloroanilines.[102]

The formation of nitrenium ions as intermediate species was also detected in the solvolysis of *N*-chloroamines containing a multiple bond.[89,96,111–115] It should be noted that in the solvolysis of *N*-haloamines, cleavage of the N–Hal bond can take place both heterolytically and homolytically, depending on the structure of the

initial compound and the reaction conditions. The presence of rearrangement products in the reaction mixture may be regarded as an important argument in favour of heterolytic cleavage of the bond.

It has been shown in a number of studies[116–123] that the rearrangements of *N*-haloamines on treatment with Lewis acids also occur via the formation of nitrenium ions.

Scheme 2



c) Reactions of organic azides. It was shown in studies in the 1950s and then particularly in research carried out in the 1980s that organic azides represent convenient sources of nitrenium ions. The majority of organic azides are unstable compounds. They readily decompose with the elimination of molecular nitrogen on exposure to heat, light, and various chemical reagents. Reactions involving the acid-catalysed decomposition of azides and their possible conversions through reaction of the latter with carbocations (Schmidt reaction) are of interest in relation to the problem of nitrenium ions

$$RNN_2 + X^+ \longrightarrow \left[R-\underset{\displaystyle X}{\underset{|}{N}}-N_2\right]^+ \longrightarrow R-\overset{+}{\underset{\cdot\cdot}{N}}-X + N_2$$

X = H, R etc.

Despite the considerable quantity of experimental data, the question as to whether nitrenium ions are formed during acid-catalysed decomposition of azides and in the Schmidt rearrangement remains open. In a number of studies[124–129] the concept of the intermediate formation of nitrenium ions was introduced to explain the acid-catalysed rearrangement of azides. However, the alternative possibility of synchronous migration of a group to the nitrogen atom and the elimination of a nitrogen molecule generally cannot be excluded. In three review articles devoted to the rearrangement of azides[130–132] it is noted that despite the concept of nitrenium ions being introduced to explain a number of azide reactions, it has not been possible to date to provide significant evidence for their formation at an intermediate stage of the reaction.

It was shown in four studies[133–136] that rearrangements similar to the Schmidt reaction occur by interaction of azides with a nitrosonium cation. Doyle et al.[134] assumed that nitrosonitrenium ions are formed at an intermediate stage of the reaction. However, in two subsequent studies[135,136] another reaction scheme was put forward:

$$Ph_2CH-N_3 + NO_2^+ \longrightarrow Ph_2CH^+ + N_2 + N_2O,$$

$$Ph_2CH-N_3 + Ph_2CH^+ \longrightarrow Ph_2CHN(N_2^+)CHPh_2 \xrightarrow{-N_2} PhCH=\overset{+}{N}(Ph)CHPh_2 \xrightarrow{-Ph^-} Ph_2CH-\overset{+}{N}-CHPh_2 \xrightarrow{H_2O} PhCHO + PhNHCHPh_2 .$$

The constant ratio of unsubstituted to substituted benzaldehydes for reactions of phenylarylazidomethanes with nitrosonium tetrafluoroborate or $PhAr\overset{+}{C}H\ BF_4^-$ whatever the reagent used was regarded[135,136] as evidence for the participation of dialkylnitrenium ions in these reactions.

A group of Japanese scientists directed by H Takeuchi[33–48] studied the photolysis and thermolysis of azides, pyridinium and sulphonium salts, and other products in the presence of proton acids, which result in the formation of nitrenium ions. They generate nitrenium ions with various structures: $\overset{+}{N}H_2$ and its alkyl homologues,[45,46,48] ethoxycarbonylnitrenium ions,[33,35,40] unsubstituted phenylnitrenium ions,[34,37,39,41,46] and phenyl-substituted[42–44,46] and naphthyl-substituted[39] nitrenium ions with different substituents.

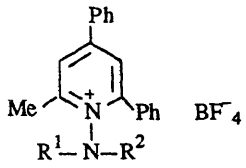
It was found that in proton acids such as acetic acid, trifluoroacetic acid (TFAA), and trifluoromethanesulphonic acid (TFMSA), phenyl azide completely decomposes after a few minutes at 25 °C,[43] whereas in aromatic solvents azides decompose at temperatures above 130 °C.[43] Furthermore, Takeuchi et al. studied the decomposition of azides in a mixture of an aromatic solvent and a proton acid. For example, in a mixture of benzene (70%) and trifluoroacetic acid (30%) at 25 °C, phenyl azides decompose over a period of 10 h. In the opinion of Takeuchi et al.[43] photolysis (thermolysis) of azides yields a nitrene, which is protonated by the acid to form its conjugate base and a nitrenium ion.

For example, in the thermolysis of ethyl azidoformate in acetic acid, nitrene (XV) is first formed, then the ion pair (XVI) is formed:[33,34]

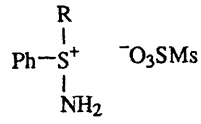
Scheme 3

$$N_3CO_2Et \xrightarrow{h\nu \text{ or } \Delta T} :\ddot{N}CO_2Et \xrightarrow{MeCOOH} [MeCOO^- \ ^+NH_2CO_2Et].$$
(XV) (XVI)

d) Photolysis (thermolysis) of pyridinium and sulphonium salts. In addition to azides, Takeuchi et al.[45,47,48] proposed the use of sulphonium and pyridinium salts as sources of nitrenium ions. The photolysis or thermolysis of pyridinium tetrafluoroborate (XVII) or *S*-aminosulphonium salts (XVIII) in the presence of TFAA



(XVII)



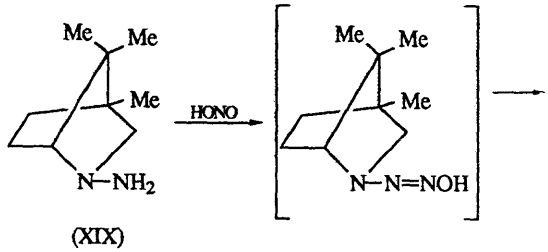
(XVIII)

$R^1 = R^2 = H$; $R^1 = H$, $R^2 = Ph$;
$R^1 = R^2 = Alk$.

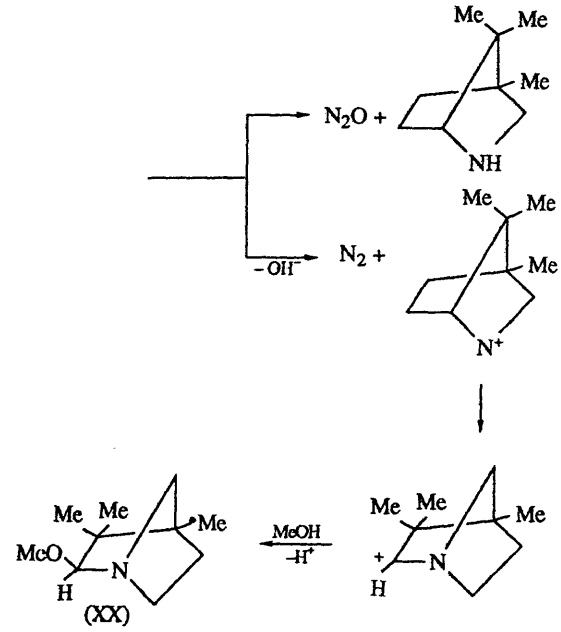
generates nitrenium ions in both singlet and triplet states. These studies are of particular interest because quantum-chemical calculations showed that for the simplest nitrenium ion and its alkyl homologues the ground state is triplet (see Section II).

e) Other reactions that occur via the formation of nitrenium ions. Together with the previously studied solvolysis reactions of *N*-haloamines, where the formation of intermediate nitrenium ions was established, reactions of hydrazines with a similar structure were also studied.[98] On nitrosation of the hydrazine (XIX) with isoamyl nitrite, the product (XX) was isolated (21% yield), derived from a hypothetical rearranged nitrenium ion (Scheme 4). Unfortunately, in this study there was no analysis of the gaseous products that was necessary to establish the actual pathway for formation of the secondary amine.

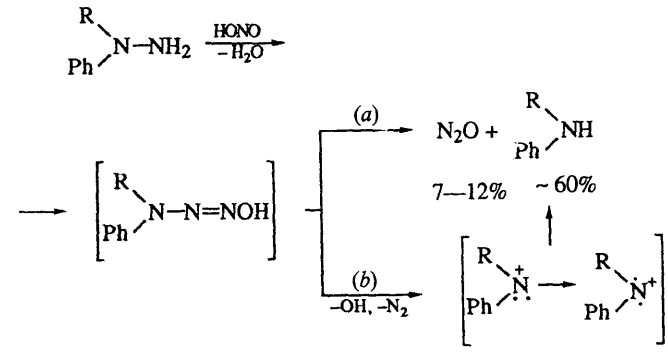
Scheme 4



(XIX)



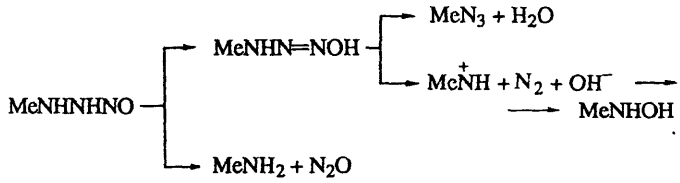
The reactions of 1,1-alkylarylhydrazines with nitrosating agents were studied in greater detail by De Rosa,[137] who put forward the following reaction scheme:



Analysis of the products showed that the yield of secondary amine was much higher than that of nitrous oxide. This phenomenon, in the opinion of De Rosa,[137] demonstrates the possibility that the secondary amine is formed via the conversion of a nitrenium ion from a singlet to a triplet state [route (*b*)].

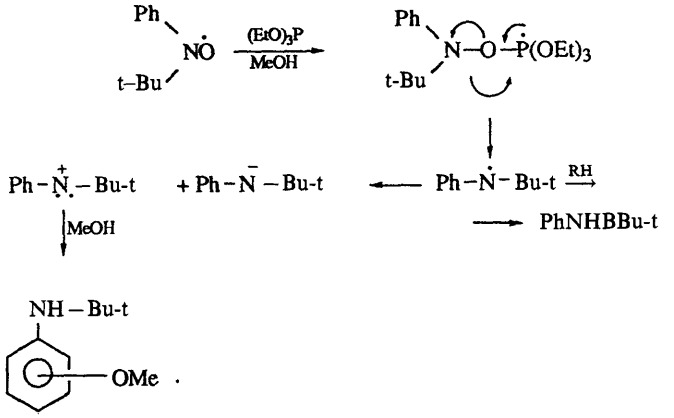
The possible formation of monosubstituted alkylnitrenium ions was also noted by Perrott et al.[138] A study of the kinetics of the nitrosation of hydrazines suggested the possibility of this reaction occurring by two routes (Scheme 5)

Scheme 5

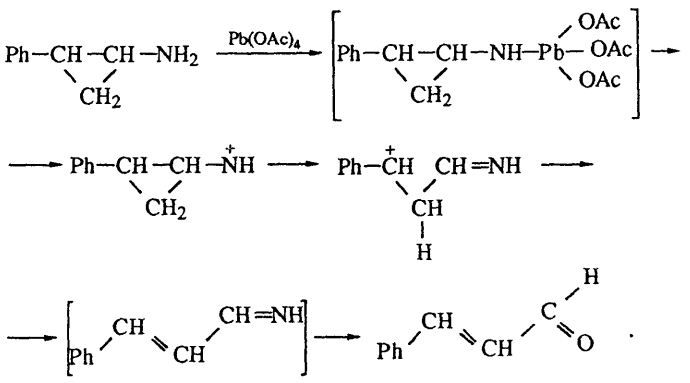


It is clear from Scheme 5 that nitrosation on the unsubstituted atom can result in the formation of a nitrenium ion.

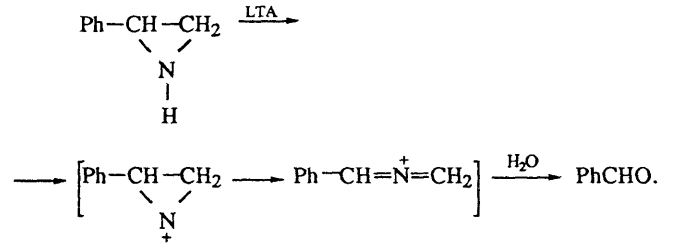
A further route for the generation of nitrenium ions was investigated by Cadogan and Rowley:[139]



It is assumed that the oxidation of the *trans*- and *cis*-isomers of 2-phenylcyclopropylamine with lead tetraacetate (LTA) to the *trans*-isomer of cinnamaldehyde also occurs via the formation of an intermediate nitrenium ion.[140]

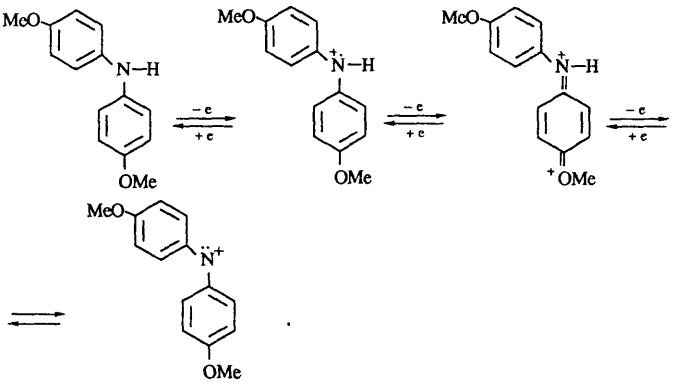


Isomerisation of an intermediate nitrenium ion to an azaallyl ion also occurs on oxidation of aziridines with ring opening:[140]



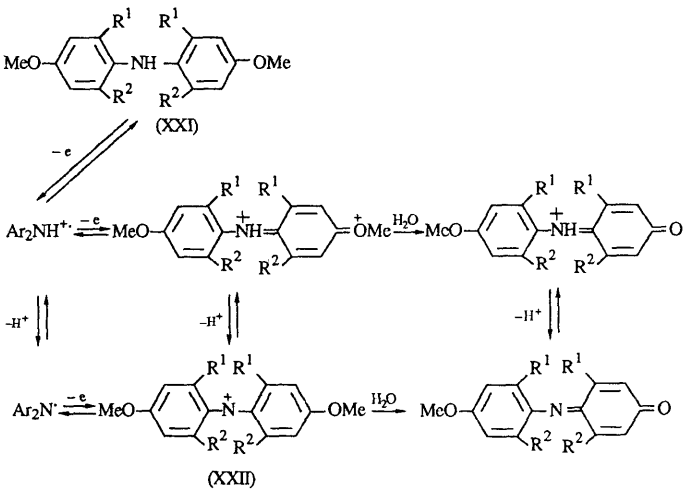
3. Physicochemical methods of generating nitrenium ions.

Electrochemical methods have been used to generate and study the behaviour of nitrenium ions.[26,27,141,142] It was through the use of electrochemical research methods such as polarography and different forms of voltammetry that the first direct evidence for the existence of nitrenium ions was obtained.[26] Cyclic voltammetry was used to study the oxidation of dianisylamine and to establish the lifetime of the dication formed by two-electron oxidation of dianisylamine (~1 s). In acetonitrile the equilibrium is probably shifted towards the unprotonated form—a nitrenium ion.



Similar studies were carried out for a number of other diarylamines:[141]

Scheme 6



$R^1 = R^2 = OMe$(a); $R^1 = OMe$, $R^2 = H$ (b); $R^1 = R^2 = H$ (c).

Table 3. Half-wave potentials for oxidation of diphenylamines (XXI) in MeCN and absorption spectra of amines (XXI) and nitrenium ions (XXII).[141]

Amine	$E^{ox}_{1/2}$, V	λ_{max} of (XXI), nm; (lg ε), neutr. MeCN	λ_{max} of (XXII), nm; (lg ε), MeCN with 2,6-lutidine
(a)	0.035; 0.570	345(4.19); 373(4.02); 796(4,23)	364 (4.36); 535 (3.43); 723(4.39)
(b)	0.180; 0.725	259(3.66); 377(4.34); 798(4,46)	378(4.27); 675(4.58)
(c)	0.295; 0.850	294(3.98); 360(4.23); 762(4,50)	660

* Values of $E_{1/2}$ given relative to Ag/10^{-2} M Ag^+.

Solutions of nitrenium ions (XXII) were obtained by controlled-potential electrolysis of amines (XXI). Values of λ_{max} for amines (XXI) and for cations (XXII) are given in Table 3. The spectra of the initial amine and radical cation differ considerably from the values given for the nitrenium ion.

Electrolysis was also employed subsequently in the oxidation of different substituted pyrroles[142] and the UV spectra of the corresponding nitrenium ions were obtained.

It has been reported[143] that nitrenium ions are also formed by electron bombardment of a mixtures of methane and ammonia, but the reactions investigated only apply to the gas phase.

$$CD_3^+ + NH_3 \longrightarrow [CD_3NH_3^+]^* \begin{cases} \xrightarrow{70\%} (CD_2{=}NH_2^+)^* + HD \\ \xrightarrow{30\%} CD_3{-}NH^+ + H_2 \end{cases}$$

4. Nuclear chemical method for generating nitrenium ions

The nuclear chemical method of obtaining reactive species is based on the chemical consequences of the β^--decay of atoms forming part of the different molecules.[28,144,145]

β^--Decay is known to be the spontaneous conversion of the nuclei that accompanies the emission of a nuclear electron and antineutrino. At the same time changes occur in the nucleus in accordance with the following scheme:

$$^0_1n \rightarrow {}^1_1p + e^- + \tilde{\nu},$$

where n and p are nuclear particles (neutron and proton); e^- and $\tilde{\nu}$ are an electron and antineutrino. Such a conversion signifies the formation of the nucleus of an atom of a new element that lies one square to the right relative to the mother (initial) element in the Periodic Table. This process occurs within about $10^{-22}-10^{-21}$ s. The electron formed in the nucleus leaves the atom after about 10^{-18} s.

Since the process of β^--decay is accompanied by an increase in the number of protons (nuclear charge) by one and the electron shell is inherited from the mother atom, there is a deficit of electrons in the latter in relation to the new (daughter) nucleus. Thus, the charge state of the daughter atom increases by one. If the decaying atom forms part of a molecule, the composition and charge state of the new chemical structure—the primary molecular ion (PMI)—is given by the general scheme

$$[^A_ZXY]^q \xrightarrow{\beta^-} [^A_{Z+1}XY]^{q+1},$$

where ^A_ZX is the atom undergoing β^--decay and Y is the normal state of the molecular system. For example,

$$^{14}CH_4 \xrightarrow{\beta^-} [^{14}NH_4]^+,$$

$$NH_2{}^3H \xrightarrow{\beta^-} [NH_2He]^+ \rightarrow NH_2^+ + He.$$

It is quite clear that there is continuity between the electronic structure of the initial molecule and the primary molecular ion formed as a result of β^--conversion of one of the atoms. The number and nature of the ligands also remains unchanged. Thus, the initial and final molecular forms are isoelectronic, isostructural, and have the same number of ligands.

Furthermore, there is a definite correlation between the free energy in the initial molecule and in the primary molecular ion. Will the PMI be stable? In the examples shown the resulting NH_4^+ ion is the familiar stable ammonium ion while NH_2He^+ is an unstable ion which fragments to form a nitrenium ion and helium.

Theoretical calculations and numerous experimental results suggest that in the vast majority of cases β^--decay of the atoms in molecules results in the formation of stable PMIs in high yield.[28]¶ Only in the β^--conversions of tritium (and the lightest halogens) does the formation of unstable ions occur.[145]

The instability of helium-containing organic primary molecular ions is primarily due to the migration of positive charge from the helium atom to the organic group:

$$[RHe^+] \rightarrow [R^+He].$$

This redistribution of charge occurs because the ionisation potential of the helium atom is higher than that of the organic groups. At the next stage the species $[R^+He]$ decomposes to form positively charged ions (carbenium, nitrenium, etc.) and helium atoms (the energy of the C–He bond is close to zero):[146,147]

$$[R^+He] \rightarrow R^+ + He.$$

The time required for such processes to occur is 10^{-13} s, which is considerably less than the time between collisions of two interacting particles. Therefore, the resulting reactive species will interact with molecules of the surrounding medium as free particles.

The nuclear chemical method of obtaining intermediate reactive species has a number of advantages over known methods, in particular classical methods. It follows from the above description that the nuclear chemical method provides the possibility of obtaining reactive charged species in a free state (without counterions or solvent cage),† with a strictly defined structure and a given initial charge localisation.

The rate of generation of reactive species using the nuclear chemical method is determined solely by the rate of radioactive decay of tritium [$T_{1/2}(^3H)$ = 12.2 years] and does not depend on external conditions (temperature, pressure, state of aggregation, composition of reaction mixture, etc.).

The number of molecular ions (N_{R^+}) formed after a given time t from N_{R-^3H} mother molecules can be calculated from the equation

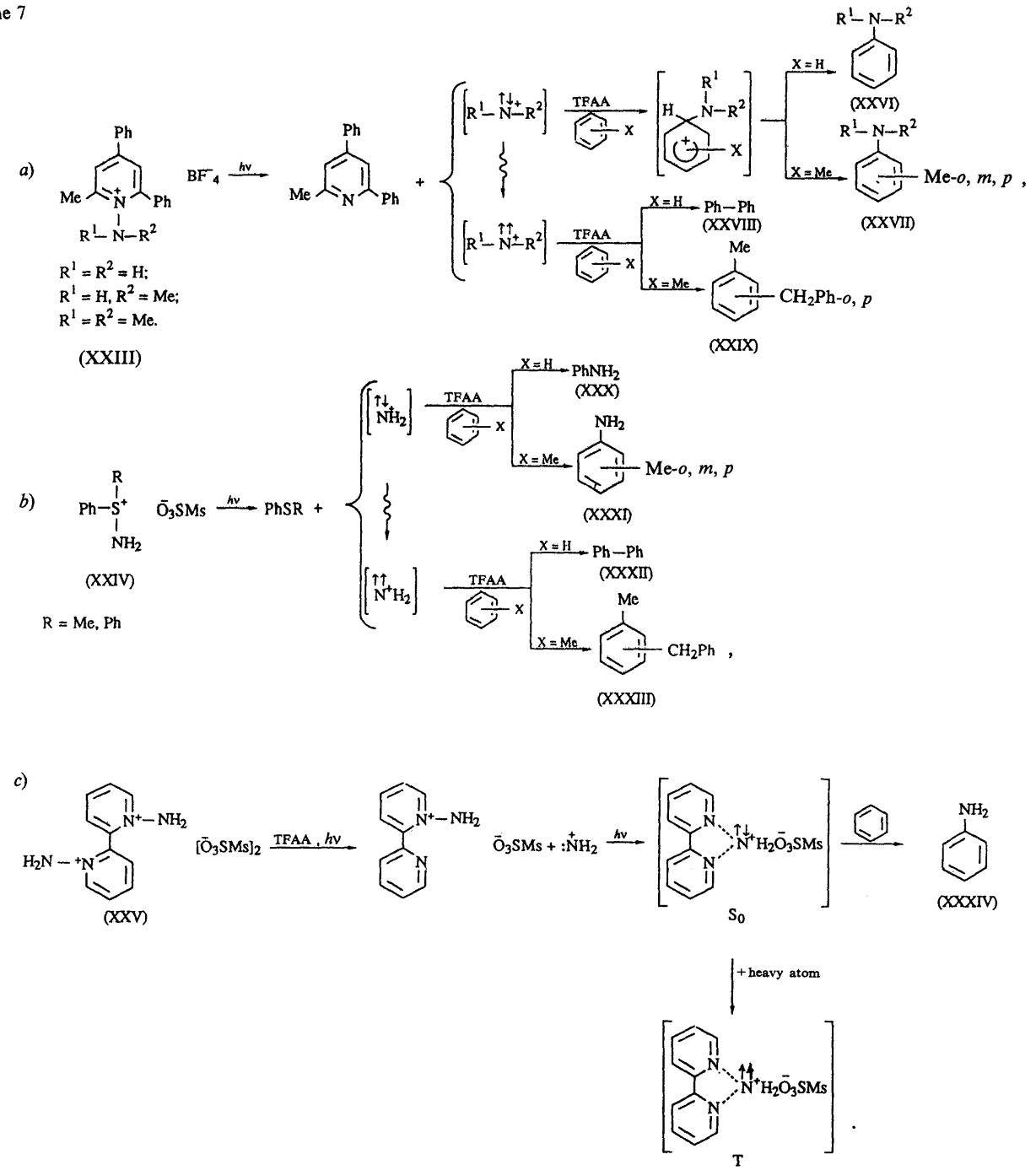
$$N_{R^+} = kN_{R-^3H}\cdot(1-e^{-\lambda t}) \approx k\lambda N_{R-^3H}t \text{ when } t \ll T_{1/2},$$

where N_{R-^3H} is the number of molecules of hydrocarbon labelled with tritium; λ is the radioactive decay constant of tritium; k is the coefficient of probability of particle formation; $k = ng$ (n is the number of tritium atoms in the mother molecule; g is the proportion of β^--emissions resulting in the formation of unexcited primary molecular ions).

¶ We have deliberately not considered processes involving the excitation and ionisation of the electron shells of daughter atoms which result in decomposition of PMIs, since the proportion of such β^--conversions does not exceed 30%.

† The β^--particle (nuclear electron) emitted in the process of decay cannot serve as a counterion since it escapes to a distance at which the interaction energy between the ion and the nuclear electron is very low.

Scheme 7



Let us consider the decay of tritium in PhN^3H_2 as an example. If the activity of aniline in this series is 3.7×10^{10} Bq, the total number of nitrenium ions formed in 24 hours is 4.8×10^5.

An undoubted merit of the nuclear chemical method is its potential for studying the reactions of free reactive species with pure compounds and their mixtures in the gas, liquid, and solid states. Considerable experience in the generation of carbocations[28,144,145,148–151] and silicenium[152] ions using the nuclear chemical method has been gained to data. This method has also been used during the last ten years to generate nitrenium ions. The nuclear chemical method has been successfully used by Nefedov et al.[29–32] for the synthesis of free phenylnitrenium ions and to study their reactions with aromatic hydrocarbons.

The formation of phenylnitrenium ions occurs as a result of the β^--decay of tritium in aniline that has doubly tritiated amino group according to the following scheme

$$PhN^3H_2 \xrightarrow{\beta^-} [PhN^3HHe]^+ \rightarrow [PhN^3H^+He] \rightarrow PhN^3H^+ + He.$$

IV. Reactions of nitrenium ions

As indicated above, nitrenium ions are reactive species having a positive charge and free *p* orbital. With these characteristics they can be classified as species with well-defined electrophilic properties. The large heats of formation[23] (for example, for phenylnitrenium ions in singlet and triplet states these are 241.5 and 267.5 kcal mol^{-1} respectively)[24] and the presence of a charge and free orbital govern not only the reactivity but also the strictly controlled interaction pathway of these species. These species interact with residues with high electron density in substrate molecules. These reaction characteristics of nitrenium ions also govern the nature of the resulting intermediate complexes and reaction products.

1. Reaction of alkylnitrenium ions

The simplest nitrenium ion $:\overset{+}{N}H_2$ and its alkyl homologues have a triplet ground state[23] and are not capable of causing direct aromatic amination.[48]

Takeuchi et al.[48] carried out the direct amination of benzenes in arene–TFAA (30%) mixtures with singlet alkylnitrenium ions generated by photolysis of pyridinium (XXIII), sulphonium (XXIV), and bipyridinium (XXV) salts (Scheme 7) containing an amino substitutent on the nitrogen or sulphur atoms. The reactions depicted in Scheme 7 indicate that the products (XXVI), (XXVII), (XXX), (XXXI), and (XXXIV) are typical examples of the aromatic substitution of hydrogen in benzene or toluene by a singlet nitrenium ion. Products (XXVIII), (XXIX), (XXXII), and (XXXIII) are characteristic of the reaction of triplet nitrenium ions. It was noted that S → T conversion is more favourable in toluene. Takeuchi et al. established the following pattern of change in energy of the singlet state on going from an unsubstituted to an aliphatic and aryl nitrenium ion:

$$\overset{+}{N}H_2 > Alk\overset{+}{N}H > Ph\overset{+}{N}H,$$

which is supported by the fact that aromatic amination with singlet alkylnitrenium ions, in contrast to aryl ions, has both low substrate and positional selectivity.[40,42,46,48]

It was established[48] that the reactivity of the simplest nitrenium ion generated from *N*-aminopyridinium salt (XXIII) is governed by the nature of the substituent in the pyridine ring of salt (XXIII) and by the nature of the counterion. An electron-withdrawing group (for example, CN) in the pyridine ring and a counterion capable of forming an H-bond with the nitrenium ion increase the selectivity factor. It is assumed that the unsubstituted nitrenium ion which is generated at the first stage is not free but interacts with both the unshared electron pair of the pyridine and with the counterion (Fig. 2).

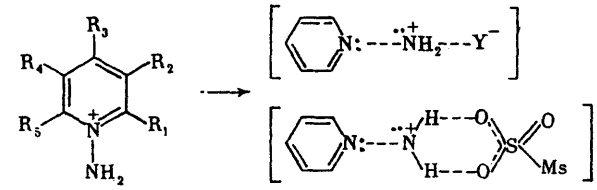
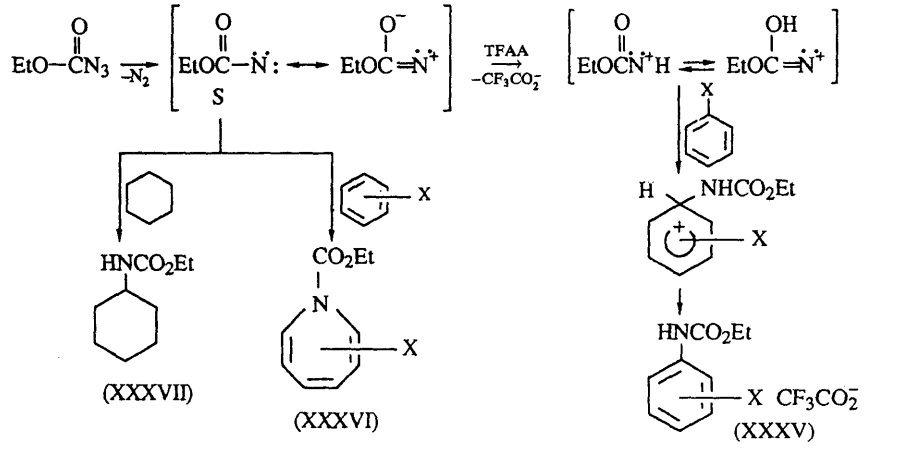


Figure 2. Interaction of an unsubstituted nitrenium ion with an electron pair and hydrogen bonding.[48]

This type of interaction assumes a favourable singlet reaction. A similar interaction of the unshared electron pairs of heteroatoms was predicted in the chemistry of nitrenes.[153–155]

By comparing pyridinium (XXIII) and sulphonium (XXIV) salts (Scheme 7) as sources of nitrenium ions, Takeuchi et al.[48] established that for (XXIII) for nitrenim ions were predominantly in the singlet state while for (XXIV) they were mainly in the triplet state. The explanation for this is that the electron pair of sulphur interacts with the nitrenium more weakly than the electron pair of nitrogen in pyridine, since sulphides are less electrophilic then pyridine. Thus, it may be concluded that interaction of nitrenium ions with a free electron pair plays an important part in stabilisation of the singlet

Scheme 8



X = H (a), Me (b).

X = H (a), *o*-Me (b), *p*-Me (c) *o*-NO_2 (d), *m*-NO_2 (e).

state. A weakening of this interaction assists a more rapid S → T triplet conversion.

In the photolysis of pyridinium or sulphonium salts in solvents containing heavy atoms (for example, dichloromethane, dibromomethane, an oxygen molecule, etc.), the yields of singlet products are considerably reduced.

Stabilisation of the singlet state through hydrogen bonding between the nitrenium ion and counterion is currently being investigated.[48]

Takeuchi et al.[33,35,40] studied the electrophilic substitution reaction between the ethoxycarbonylnitrenium ion generated from the corresponding azide and certain aromatic compounds (benzene, toluene, nitrobenzene) in different media that affect the nature of the intermediate (Scheme 8).

Product (XXXV) in Scheme 8 results from the reaction of ethoxycarbonylnitrenium ion with substituted benzenes. In the absence of TFAA, products (XXXVI) and (XXXVII) are obtained, resulting from the reaction between the intermediate nitrene in a singlet state and benzene (toluene) or cyclohexane. The subsequent addition of TFAA to (XXXVI) and (XXXVII) gives products (XXXVa)–(XXXVc).

The reactions of ethoxycarbonylnitrenium ions with aromatic substrates having electron-donating and electron-withdrawing substituents, as shown in Scheme 8, suggest that this nitrenium ion has low substrate selectivity and high positional selectivity. The latter relates to the selective attack at the *ortho* and *para* positions in toluene and the *ortho* and *meta* positions in nitrobenzene. This phenomenon is in good agreement with the assumption that the transition state with the highest energy, which governs substrate selectivity, depends on the nature of the π-complex, and the resulting σ-complex governs the positional selectivity.[156,157] The activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for thermolysis of azide do not differ in TFAA and benzene. This demonstrates that thermolysis of the azide in TFASA does not occur via the azide–acid conjugate but via a nitrene. Thus, the keto and enol forms of the nitrenium ion occur on transfer of a proton from TFAA to nitrene.

This review of the above classical studies on the reactions of alkylnitrenium ions indicates that a considerable number of factors influence the chemical behaviour of these species. These are primarily the methods and conditions of their generation, the nature of the source of nitrenium ions, the nature and concentration of the components of the media in which these reactions occur, etc. This introduces certain difficulties in the interpretation of the chemical nature of these reactive species.

2. Reactions of phenylnitrenium ions

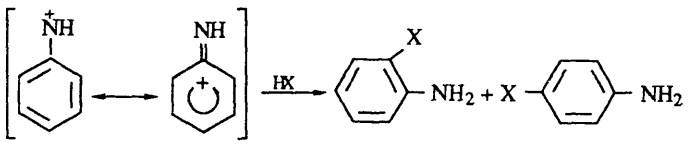
As indicated above, arylnitrenium ions are reactive metabolites of carcinogenic amines and act as intermediates in many organic syntheses. This accounts for the fact that the greatest number of studies have been devoted to the reactions of these species.

The qualitative composition of the products of the ion-molecule reactions between phenylnitrenium ions and different nucleophilic reagents can be predicted from the structural characteristics of these species. The occurrence of four mesomeric structures of the phenylnitrenium ion with an almost equal contribution from each to the actual hybrid structure (see Section II) suggests that these cation sites interact with nucleophilic reagents and that various aminophenylation products of the latter are formed.

Despite the results of quantum-chemical calculations[24,25] which indicate the preference for attack on the carbon atoms of the benzene ring in the phenylnitrenium ion, the experimental data, with a few exceptions,[81] suggest that reactions on the nitrogen cation site of arylnitrenium ions are preferred.

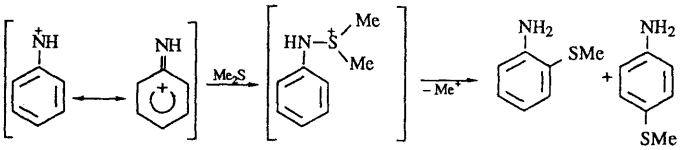
It is shown in a number of studies[37,39,41,43,46,72,81,124–126] that arylnitrenium ions are usually formed at the intermediate stages of reactions in strong proton acids. The chemical behaviour of phenylnitrenium ions usually does not depend on their source of generation (phenyl azides or phenylhydroxylamines) but is dependent on the specific nature of the media in which this ion is formed.

a) Interaction of phenylnitrenium ions with the unshared electron pair of a nucleophile. When nucleophiles containing atoms with an unshared electron pair (alcohols, phenols, acids, water) are treated with phenylnitrenium ions generated from phenylhydroxylamine in the presence of TFMSA, *ortho*- and *para*-substituted anilines are formed in significant yield.[72,124–126]



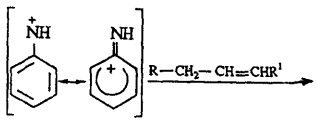
X = OH, PhO, MeO, Cl.

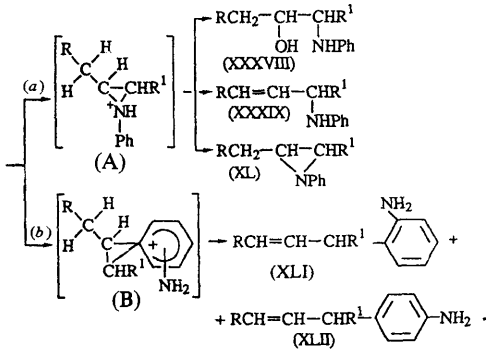
The reaction of phenylnitrenium ions with dimethyl sulphide results in the formation of similar products.[47]



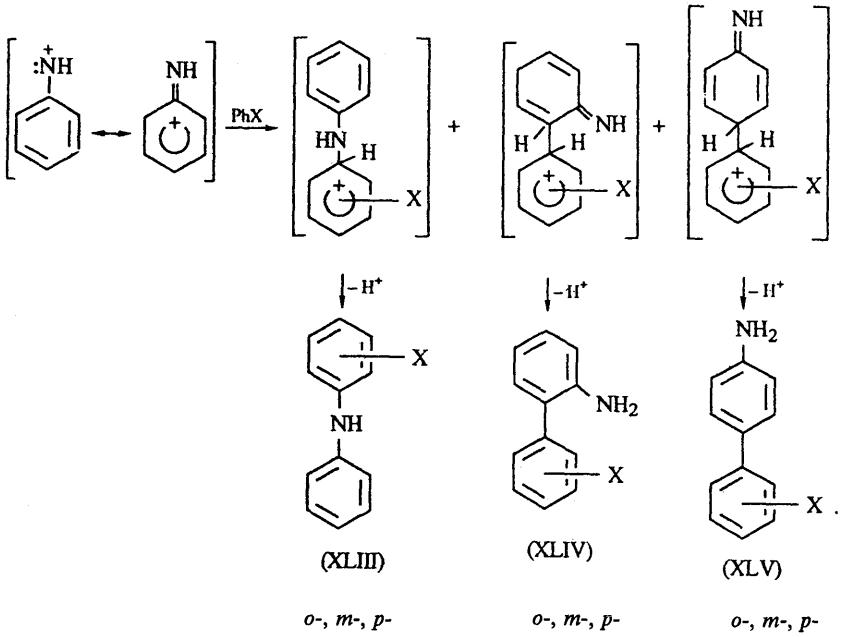
b) Reactions of phenylnitrenium ions with olefins. The reaction of phenylnitrenium ions obtained from azides in the presence of TFAA with aliphatic and cyclic olefins on their double bond results in the formation of addition products both on the N-cation [route (a)] and C-cation [route (b)] sites of the phenylnitrenium ions according to Scheme 9.[41]

Scheme 9





Scheme 10



In the absence of steric hindrance a mixture of products (XXXVIII)–(XLII) is always formed through reaction of the phenylnitrenium ion with aliphatic olefins as shown above. Only their ratio varies according to the reaction conditions. The reaction of a phenylnitrenium ion by route (*a*) occurs via the substituted aziridine cation (A) as an intermediate. The yields of reaction products depend on both the structure of the olefins and the concentration of TFAA. The main reaction product is the *N*-phenyl-β-hydroxylamine (XXXVIII). As the concentration of TFAA is increased, the yield of main product usually decreases, which is due to a side reaction involving polymerisation of the initial alkene.

With cyclohexene the reaction is stereospecific and the *trans* isomer is formed. The unsaturated compounds (XXXIX), (XLI), and (XLII) are isolated as by-products in the reaction with cyclohexene. Product (XXXIX) results from the addition of phenylnitrenium ion to the nitrogen site, while products (XLI) and (XLII) are formed as a result of the reaction of phenylnitrenium ion on a carbon site of the benzene ring. In the latter case the reaction occurs via the cation complex (B).

Products of C-substitution are not formed in the reaction of *cis*- and *trans*-4-methyl-2-pentene with the phenylnitrenium ion. Takeuchi et al.[41] assume that intermediate complex (B) is not formed because of steric hindrance.

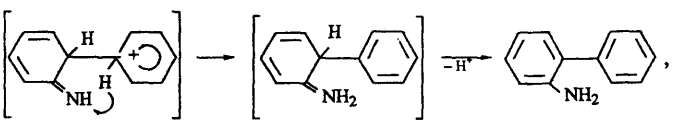
In the reaction of the phenylnitrenium ion with *cis*-4-methyl-2-pentene not only product (XXXIX) but also (XL) is isolated, which corroborates the mechanism put forward by the authors.

The by-product (XXXIX) is not formed at all with methyl acrylate.

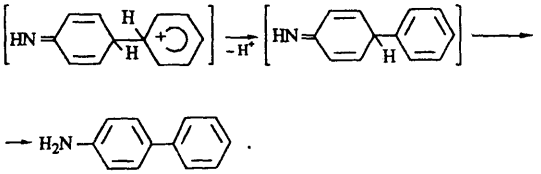
c) Reactions of phenylnitrenium ions with aromatic hydrocarbons. The reactions of phenylnitrenium ions with aromatic compounds have been studied in the greatest detail. These are reactions involving the electrophilic substitution of hydrogen in a benzene ring (S_E) which are complicated by the presence of four cation sites in phenylnitrenium ions.

Reaction of the latter with benzene, depending on the nature of the medium, leads either exclusively to N-substitution products[47,158] or to preferential attack on the carbon atoms of the phenylnitrenium ion,[81] and more frequently to both products with preferential substitution on nitrogen.[37,39,72,159] In this case the *ortho*- and *para*-isomers of aminobiphenyls (C-substitution products) are formed in almost equal proportion.

It is interesting to compare the results of the reactions of benzene and phenylnitrenium ions obtained by classical methods with the reactions of free phenylnitrenium ions generated by the nuclear chemical method.[30] In the absence of specific media that are capable of suppressing the nitrogen or carbon cation sites of the phenylnitrenium ions, the free nitrenium ion on reacting with benzene behaves to an almost equal extent as a nitrenium ion (55%) and a carbocation (45%). At the same time the ratio of *ortho*- to *para*-isomers—the C-substitution products (XLIV) and (XLV) in Scheme 10—was 8 : 1, which is probably due to a difference in the rate of proton transfer in the intermediate σ-complexes. In the case of the *ortho*-isomers this is a rapid direct intramolecular process



while for the *para*-isomer intermolcular deprotonation occurs:



In the reaction of phenylnitrenium ions with toluene, the formation of six products (XLIII, *o*, *p*-), (XLIV, *o*, *p*-), and (XLV, *o*-, *p*-) is possible, according to the classical orientation rules (see Scheme 10). However, Takeuchi et al.[37,39,47] detected only the N-substitution products (XLIII, *o*-, *p*-) and the ratio of *ortho*- to *para*-isomers varied in relation to the method of generating the phenylnitrenium ion (from pyridinium salts or azides) in TFAA. On conducting this reaction, Parish and Whiting[81] isolated all six isomers with a twofold or greater excess of C-substitution products. Differences in the reaction conditions may account for these findings.

In the reaction of toluene with free phenylnitrenium ion generated by the nuclear chemical method, the sole product was 4-methyldiphenylamine (XLIII, *p*-) (Scheme 10).[31] The results of other studies[82] also show that the reaction mainly occurs on nitrogen.

In the reactions of nitrenium ions with other substituted benzenes (RPh, where R = Pr, Cl, Ph) and with naphthalene there is a tendency for preferential substitution on the nitrogen atom to occur.[37,39] Only when special media are used, as demonstrated by Parish and Whiting,[81] is there a marked increase in the yields of C-substitution products.

On reaction of phenylnitrenium ions in TFMSA with a substrate having an electron-withdrawing substituent (for example, nitrobenzene), products of the aminophenylation of nitrobenzene were not detected.[39]

The reactions of *para*-substituted phenylnitrenium ions (p-$RC_6H_4\overset{+}{N}H$, where R = Me, OMe, CN, NO_2) with benzene and toluene have been studied by Takeuchi et al.[43] It was established that the phenylnitrenium ions with electron-withdrawing groups (CN, NO_2) solely undergo aromatic N-substitution. On the other hand, the positive charge of phenylnitrenium ions with electron-donating groups is preferentially delocalised on the carbon atoms of the ring as a result of the positive mesomeric effect of the substituent. Prolongation of the lifetime in this type of resonance effect can lead to the coexistence of both the triplet and singlet states, which results in an increase in the yields of products of hydrogen removal.

Studies were carried out by Takeuchi et al.[39] on the reactions of naphthylnitrenium ions obtained from 1-azidonaphthalenes in the presence of TFMSA with benzene. 1-Amino-4-phenylnaphthalene—a C-substitution product—is formed as a result of this reaction. No N-substitution products were detected. This results from the preferential localisation of positive charge in the naphthylnitrenium ion at the *para* position of the ring rather than on the nitrogen atom.

Thus it may be concluded from the above information that in the organic reactions of nitrogen-containing compounds monitoring the behaviour of nitrenium ions meets with certain difficulties. The fact that these species are formed at intermediate stages has usually been established from the final reaction products. However, the ratio of final products depends on the nature of the specific media in which these reactions are occurring.

It is evident that the most reliable data on the chemical nature and properties of the intermediate species may be obtained when there is the possibility of generating them in a free state and studying their reactions in the absence of extraneous substances (counterions, catalysts, etc.). The nuclear chemical method of generating nitrenium ions opens up considerable possibilities in this respect. This non-traditional approach to the study of reactive intermediate species can assist in the interpretation of the mechanisms of classical organic reactions.

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The review of studies on the properties and reactions of nitrenium ions presented here indicates the increased interest shown in these species by scientists from different countries. This is mainly because a study of these reactive intermediate species is closely related to the development of general theoretical problems in organic chemistry. In particular, a study of the properties and reactions of nitrenium ions is necessary for an understanding of the reaction mechanisms and development of synthetic methods for organonitrogen compounds. In this respect the new methods for obtaining and studying the reactions of free nitrenium ions that have been developed during the last ten years are of particular significance.

It follows from several original publications[49–53] that an important part is played by these species in carcinogenetic and mutagenetic processes. Therefore, a study of nitrenium ions is of paramount importance in finding a solution to specific problems in oncology, genetics, and ecology.

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