Nitrenium Ions

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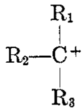
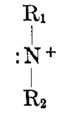
The role of carbonium ion reactions in modern organic chemistry is widely accepted. Trivalent electron-deficient carbon species (**1**) have been studied under an expansive variety of conditions, in various states of solvation, and in all degrees of association with appropriate counterions.



$R_2-\overset{R_1}{\underset{R_3}{C^+}}$

1

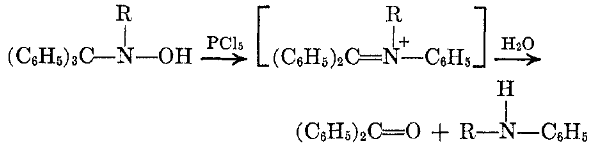


$:\overset{R_1}{\underset{R_2}{N^+}}$

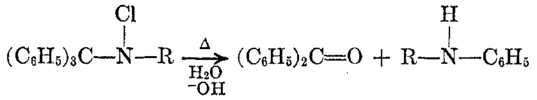
2

In view of the extensive information available on carbonium ions, we were somewhat amazed that, at the beginning of our investigations in 1962, very little was known about the nitrogen analog. We felt that a nitrogen species should exist which has six electrons in its valence shell and which bears a positive charge on nitrogen. We speculated that this species should resemble a carbonium ion in its chemical behavior, but that it should be much more reactive. Our predictions on relative stability were based on the known electronegativities of carbon and nitrogen which indicate that nitrogen, with an additional proton in its nucleus, should be less stable than carbon, when both have the same number of valence electrons and both are positively charged. In discussing the existence and chemistry of divalent electron-deficient nitrogen species (**2**) we shall refer to them as "nitrenium ions."[1]

The basis for nitrenium ion chemistry, although unrecognized as such, is quite old. During 1913–1916 Stieglitz and coworkers published an elegant series of papers on the rearrangement of substituted hydroxylamines and N-chloramines.[4] The findings of this group were that tritylhydroxylamines and trityl-N-chloramines rearranged readily to give (after hydrolysis) benzophenone and aniline, but that disubstituted hydroxylamines and disubstituted N-chloramines either did not rearrange or they rearranged only under extremely forcing conditions. Whereas reactions 1 and 2 were reported to be facile when R was hydrogen, it was noted that reaction 2 failed to occur when R was methyl.[4] Thus Stieglitz concluded that the rearrangement was occurring *via* the intermediacy of a monovalent nitrogen (nitrene) species.[5,6] In view of more recent data[6] it is likely that the rearrangements observed by Stieglitz actually involved a divalent electron-deficient nitrogen intermediate (nitrenium ion) rather than a univalent nitrogen species (nitrene).[7]



$$(C_6H_5)_3C-\overset{R}{\overset{|}{N}}-OH \xrightarrow{PCl_5} \left[(C_6H_5)_2C=\overset{R}{\overset{|+}{N}}-C_6H_5\right] \xrightarrow{H_2O} (C_6H_5)_2C=O + R-\overset{H}{\overset{|}{N}}-C_6H_5 \tag{1}$$



$$(C_6H_5)_3C-\overset{Cl}{\overset{|}{N}}-R \xrightarrow[H_2O,\ ^{-}OH]{\Delta} (C_6H_5)_2C=O + R-\overset{H}{\overset{|}{N}}-C_6H_5 \tag{2}$$

Stieglitz's original interpretation illustrates the pitfalls involved in trying to distinguish between nitrenium ions and nitrenes when there is a hydrogen on the nitrogen. Thus, several types of reactions, such as the acid-catalyzed decomposition of alkyl azides and certain reactions of protonated monosubstituted hydrazines, have been postulated to occur *via* nitrenium ions where one of the substituents on nitrogen is hydrogen.[3] However, since protons are easily transferred it is difficult to ascertain whether the actual reactive intermediate in many of these reactions is a nitrene or nitrenium ion (protonated nitrene).

At the inception of our work on nitrenium ions priority was given to establishing that alkyl migration could occur to a divalent electron-deficient nitrogen species where both substituents on nitrogen were alkyl groups.[7] This approach was dictated by the tendency of alkyl groups to migrate to cationic centers and not to radical centers, in contrast to the behavior of aryl groups and

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(1) Divalent electron-deficient nitrogen has been referred to as both a "nitrenium ion"[2] and as an "imidonium ion."[3] Utilizing the latter type of nomenclature requires that a nitrene (monovalent, neutral nitrogen) be called an imidogen.[3] We feel that the term nitrenium ion (*i.e.*, a nitrene which has shared one of its electrons with a second substituent) is the more descriptive name and, hence, the name we choose to use.

(2) O. E. Edwards, D. Vocelle, J. W. ApSimon, and F. Haque, *J. Am. Chem. Soc.*, **87**, 678 (1965).

(3) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).

(4) J. Stieglitz and P. N. Leech, *Ber.*, **46**, 2147 (1913); J. Stieglitz and P. N. Leech, *J. Am. Chem. Soc.*, **36**, 272 (1914); J. Stieglitz and B. A. Stagner, *ibid.*, **38**, 2046 (1916), and following papers.

(5) For additional comments and references see P. A. S. Smith in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 479–483.

(6) R. T. Conley and H. Brandman have recently found that the rearrangement shown in reaction 2 does occur when R is methyl if suitable reaction conditions are used. This finding removes the major argument for postulating that the rearrangement of tritylhydroxylamines and trityl-N-chloramines occurs *via* formation of univalent nitrogen. We wish to thank Professor Conley for informing us of his results prior to publication.

(7) It now appears that Stieglitz was the first to generate dialkyl-substituted nitrenium ions. Qualitative support for this premise was provided by Newman and Hay through their study of migratory aptitudes of aryl groups in the rearrangement of tritylhydroxylamines.[8] More recent examples of reactions which probably occurred *via* the formation of dialkyl-substituted nitrenium ions are the rearrangement of protonated oxazirines,[9] transannular bond formation to nitrogen in medium-sized rings,[2] and certain intramolecular C–N bond formations.[10]

(8) M. S. Newman and P. M. Hay, *J. Am. Chem. Soc.*, **75**, 2322 (1953).

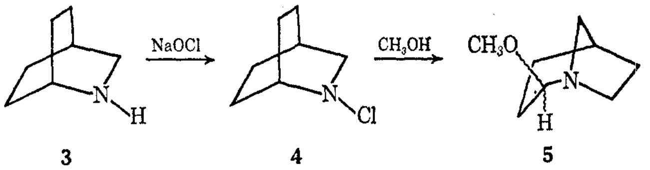
(9) W. D. Emmons, *ibid.*, **79**, 5739 (1957).

(10) G. Adam and K. Schreiber, *Angew. Chem.*, **76**, 752 (1964).

hydrogen which are known to migrate to both cationic and radical centers. Thus the migration of an alkyl group from carbon to divalent nitrogen would indicate that the nitrogen was significantly electron deficient.

A Product Study Approach to Establishing the Existence of Nitrenium Ions

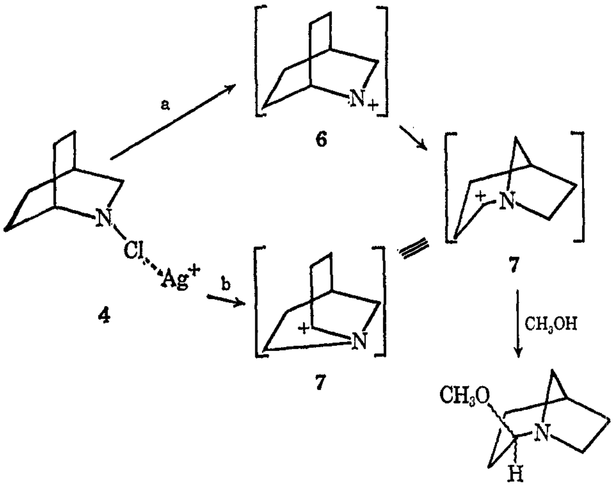
Studies of terpenes and related bicyclics have provided ample evidence for the ease of rearrangement of bridged bicyclic skeletons *via* carbonium ion mechanisms. The facile nature of the rearrangement of these carbocyclic systems indicated that the corresponding azabicyclics would be ideal systems for establishing the existence of alkyl migration to divalent electron-deficient nitrogen. It was with this concept in mind that we converted isoquinuclidine (**3**) into N-chloroisoquinuclidine (**4**) and investigated its solvolytic behavior.[11,12]



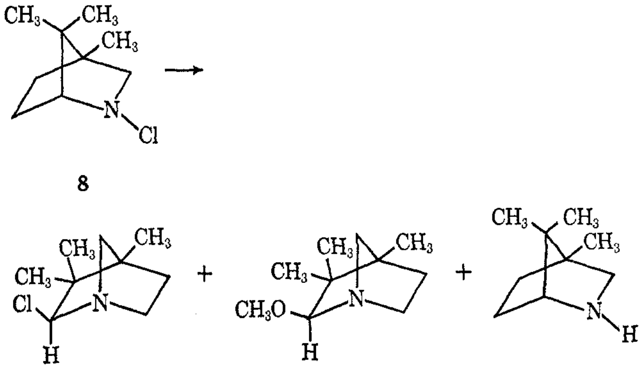
3 4 5

Refluxing **4** in a methanolic solution of silver nitrate gave a 60% yield of 2-methoxy-1-azabicyclo[3.2.1]octane (**5**).[13] The skeletal rearrangement from a 2-azabicyclo[2.2.2]octane system to a 1-azabicyclo[3.2.1]octane derivative clearly requires the migration of an alkyl group with its pair of electrons from carbon to nitrogen. As shown in Chart I the formation of **5** from **4** can occur by either of two routes. Path a involves the removal of chlorine anion by cationic silver to yield the nitrenium ion **6** as a discrete intermediate, which *via* alkyl migration would produce **7**. Nucleophilic addition of solvent to the resulting carbonium ion, **7**, would give **5**.[14] An alternate route (path b) would involve a concerted loss of chlorine and migration of the alkyl group with its pair of bonding electrons to give **7** directly. On the basis of the rearrangement of **4** to give **5** one cannot establish whether or not a discrete intermediate with unit positive charge on nitrogen was formed. However, regardless of whether path a or path b was followed, the alkyl group must have migrated with its electron pair. Thus an electron-deficient nitrogen species must have been involved. This observation provided the foundation for a general theory of the existence and reactions of divalent electron-deficient nitrogen.

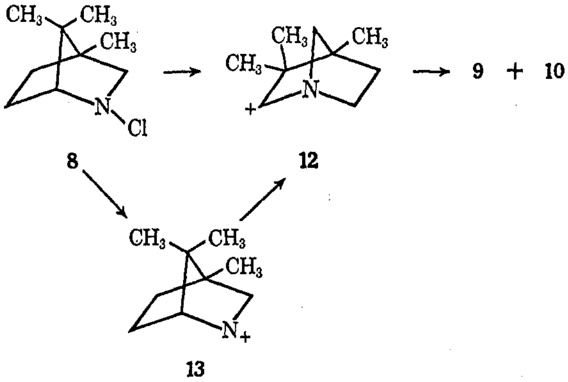
Chart I



Several additional examples demonstrated that alkyl migration to divalent nitrogen species, with either a partial or unit positive charge on nitrogen, was a general phenomenon. The solvolysis of 4,7,7-trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane (**8**) in methanol is one of the more dramatic examples of this rearrangement.[15]



In refluxing methanol **8** gave **9**, **10**, and **11** in 59, 20, and 7% yields, respectively. As in the case of the methanolysis of **4**, the formation of **9** and **10** requires the migration of the alkyl group with its pair of electrons. The resulting carbonium ion, **12**, could then partition



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(11) P. G. Gassman and B. L. Fox, *Chem. Commun.*, 153 (1966); P. G. Gassman and B. L. Fox, *J. Am. Chem. Soc.*, **89**, 338 (1967).

(12) The conversion of secondary amines into the corresponding N-chloramines is best accomplished by vigorously stirring the amine with aqueous hypochlorite at ice-bath temperatures. In the case of very reactive N-chloramines which are unstable under aqueous conditions, the conversion can be accomplished utilizing *t*-butyl hypochlorite in hydrocarbon solvents.

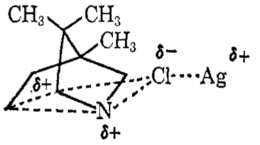
(13) In addition small amounts of **3** are formed from **4** under the reaction conditions.

(14) By analogy with other systems where the stereochemistry of the methoxyl function is rigorously known (*vide infra*) the methoxyl group of **5** was tentatively assigned the *exo* stereochemistry.

(15) P. G. Gassman and R. L. Cryberg, *J. Am. Chem. Soc.*, **90**, 1355 (1968); P. G. Gassman and R. L. Cryberg, *ibid.*, **91**, 2047 (1969).

itself between the methanolic solvent and the chloride ion formed in the heterolysis of the N–Cl bond, to produce **10** and **9**. Again the products of the reaction did not permit a distinction to be made between the presence of **13** as a discrete intermediate and the presence of **13** only as a convenient concept used to predict the formation of **9** and **10** from **8**.[16]

The silver ion catalyzed methanolysis of **8** demonstrated the dramatic effect of silver ion on the reaction rate. When **8** was added to *ca.* 2 equiv of a 0.1 *M* methanolic solution of silver perchlorate at room temperature, the conversion of **8** to **9**, **10**, and **11** occurred with a half-life of less than 1 min. This constitutes a rate acceleration of greater than 2 × 10^3 due to silver ion catalysis. In view of the significant role played by silver ion relative to the kinetics of the reaction, it was anticipated that the amount of **9** would decrease and that **10** would be obtained in much higher yield. Instead the yield of **9** increased from 59 to 77% and the yields of **10** and **11** decreased to 8 and 4%, respectively. The increase in chlorine-containing product in the presence of silver ion was somewhat surprising. It indicated that the silver ion catalyzed rearrangement of **8** involved either a very tight ion pair or a highly concerted transition state as illustrated by **14**. The dramatic rate increase in the presence of silver ion was consistent with decreased need for solvation in the transition state. In addition we have the added steric effect of the silver ion on the side of the molecule from which methanol would have to add in order to form **10**. Thus, the increased internal return of chlorine in the silver ion catalyzed reaction of **8** is not without a satisfactory rationale.



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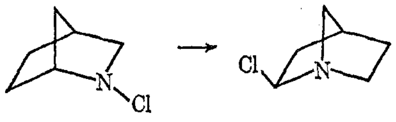
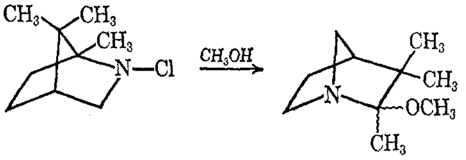
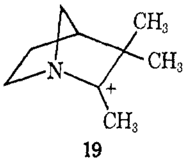
Additional examples of the silver ion catalyzed rearrangement of derivatives of 2-azabicyclo[2.2.1]heptane to derivatives of 1-azabicyclo[2.2.1]heptane are the conversion of **15** into **16** in 75% yield[15,17] and the transformation of **17** into **18** in 74% yield.[17] The complete loss of chlorine in the formation of **18** from **17** is consistent with a heterolytic cleavage of the N–Cl bond. The carbonium ion resulting from the ionization–rearrangement of **17** would be the reasonably stable tertiary carbonium ion **19**. Thus the complete removal of chloride from **17** by silver ion and the addition of solvent to **19** to give **18** is consistent with expectations based on nitrenium ion concepts.



15 **16**

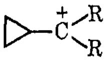


17 **18**



19

All the rearrangements discussed in the preceding portion of this Account have involved bicyclic systems. A nonbicyclic system which appeared to be very attractive was the nitrogen analog of the cyclopropylcarbinyl cation **20**,[18] since the cyclopropylnitrenium ion structure **21** would be expected to undergo ring expansion.



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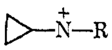
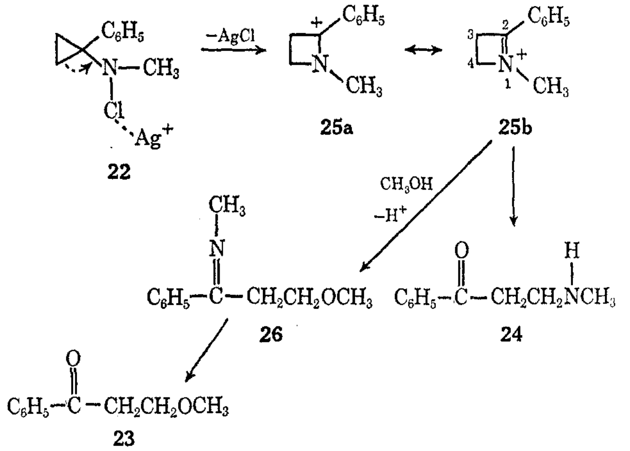


21

When **22** was solvolyzed in methanol containing silver trifluoroacetate a mixture of **23** (85%) and **24** (7%) was obtained.[19] The formation of **24** is best explained in terms of an alkyl migration from carbon to nitrogen to give **25**. Hydrolysis of **25** would then yield **24**. The production of **23** can be explained in a variety of ways. One attractive mechanism involves direct attack of



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[16] In the early stages of our investigation of nitrenium ion chemistry the formation of **11** from **8** (and of **3** from **4**) seemed anomalous. However, it was just this transformation which was the key factor in establishing the discrete existence of nitrenium ions (*vide infra*).

[17] P. G. Gassman and R. L. Cryberg, unpublished work.

[18] For a discussion of cyclopropylcarbinyl cations see D. Bethel and V. Gold, "Carbonium Ions," Academic Press, New York, N. Y., 1967, pp 266–271. See also R. Breslow in ref 5, pp 259–276.

[19] P. G. Gassman and A. Carrasquillo, *Chem. Commun.*, 495 (1969).

methanol at C-4 of **25** to give **26**, which on hydrolysis would give **23** and methylamine. The methylamine was isolated in 80% yield.[19]

The rearrangements of **4**, **8**, **15**, **17**, and **22** discussed above all provide convincing evidence for the migration of alkyl groups from carbon to nitrogen. Since the end products involve the addition of nucleophiles to carbonium ions, the alkyl groups must have migrated with their electron pairs. These migrations could only occur to electron-deficient centers. Thus the reactions studied must have involved heterolytic cleavage of the N–Cl bond to cationic nitrogen species and chloride anion.

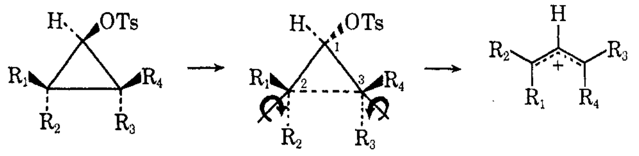
Kinetic Evidence for the Heterolytic Cleavage of the N–Cl Bond

The kinetic data for the methanolysis of **8**, **15**, and **17** are listed in Table I. In general the thermodynamic parameters observed for these solvolyses are typical of what might be expected for a process involving separation of charged ions. The kinetic measurements were made spectrophotometrically by following the disappearance of the N–Cl absorption in the ultraviolet region of the spectrum.[20]

Table I
Methanolysis of Derivatives of 2-Chloro-2-azabicyclo[2.2.1]heptane

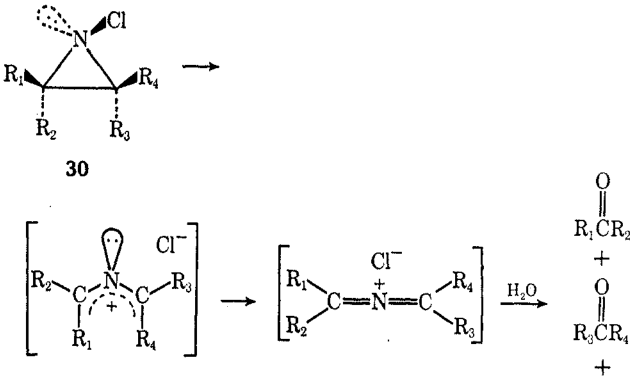
Compound	Temp, °C	k, sec^{-1}	k_{rel} (50°)	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
15	80.0 ± 0.1	1.98×10^{-4}	1	22.3	−12.7
	70.0 ± 0.1	8.60×10^{-5}			
	60.0 ± 0.1	2.79×10^{-5}			
8	70.0 ± 0.1	1.53×10^{-4}	1.7	23.8	−6.7
	60.0 ± 0.1	5.82×10^{-5}			
	50.0 ± 0.1	1.66×10^{-5}			
17	50.0 ± 0.1	2.26×10^{-4}	23	22.6	−5.4
	40.0 ± 0.1	8.17×10^{-5}			
	30.0 ± 0.1	2.09×10^{-5}			

More definitive kinetic evidence for the heterolytic cleavage of the N–Cl bond under solvolytic conditions was provided by a study of the kinetics of N-chloroaziridine ionization in polar solvents. The basis for these studies can be found in the elegant molecular orbital symmetry considerations of Woodward and Hoffmann,[21] which have been applied with great success to the solvolytic ring opening of derivatives of cyclopropyl tosylates and chlorides.[22,23] Studies of the concerted electrocyclic ring opening of cyclopropyl cations to allylic cations have shown that when the R groups of **27** are hydrogen or methyl a consideration of electronic and steric interaction coupled with molecular orbital symmetry arguments permits predictions of rates and products which are in complete agreement with experimental findings.[22,23] Thus **27** ionizes with concerted cleavage of the C_2–C_3 bond, as illustrated by **28**, in a disrotatory process with outward rotation of the groups *trans* to the leaving group to give **29**.



27 **28** **29**

As shown by Brois, N-chloroaziridines (**30**) are stereochemically stable since inversion at nitrogen is a relatively slow process.[24] Utilizing this stereochemical stability of N-chloroaziridines we have studied the solvolysis of the derivatives of **30** in which the R groups are either methyl or hydrogen.[25] Concerted ionization–ring cleavage of **30** would be expected to give an intermediate such as **31** which under the solvolytic conditions would be expected to hydrolyze to give 2 moles of carbonyl compound and amonium chloride. Table II shows the six N-chloroaziridines studied, their relative rates of solvolysis, and the reaction products.



30 **31**

In general the rates and products were all consistent with a concerted ionization–ring cleavage as anticipated on the basis of a disrotatory ring opening. In progressing from transition state **33** to **35** two effects are involved. In **33** the partial positive charge is distributed between two incipient primary carbonium ions, whereas in **35** the distribution is between a primary and a secondary center. This increased stability of the carbonium ion portion of **35** is probably partially balanced by the inward rotation of the methyl group which should result in a steric retardation of the concerted ionization. This is demonstrated better by a comparison of **35** and **37** where the stability of the carbonium ions is the same but where the required rotation in **37** is one which would decrease the interaction between the methyl

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(20) P. G. Gassman and R. L. Cryberg, unpublished work.

(21) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965). See also H. C. Longuet-Higgins and E. W. Abrahamson, *ibid.*, **87**, 2045 (1965).

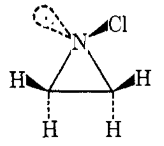
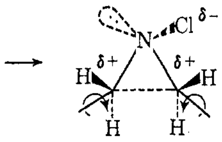
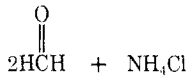
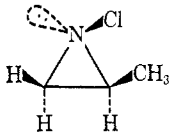
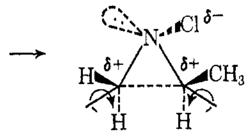
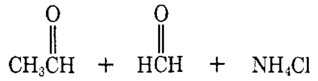
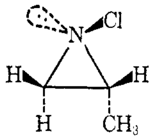
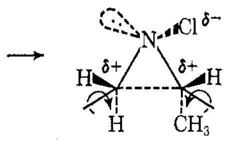
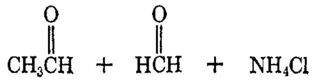
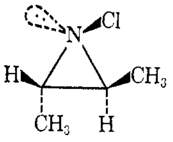
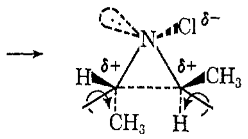
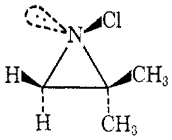
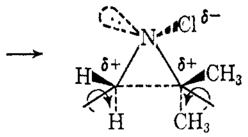
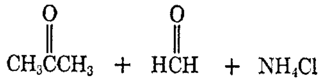
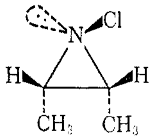
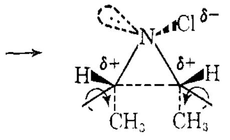
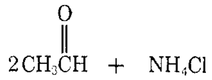
(22) C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiedemann, *ibid.*, **87**, 4006 (1965).

(23) P. von R. Schleyer, G. W. Van Dine, U. Schöllkopf, and J. Paust, *ibid.*, **88**, 2868 (1966); U. Schöllkopf, F. Fellenberger, M. Patsch, P. von R. Schleyer, T. Su, and G. W. van Dine, *Tetrahedron Letters*, 3639 (1967); P. von R. Schleyer, T. M. Su, M. Saunders, and J. C. Rosenfield, *J. Am. Chem. Soc.*, **91**, 5174 (1969).

(24) S. J. Brois, *J. Am. Chem. Soc.*, **90**, 506, 508 (1968).

(25) P. G. Gassman and D. K. Dygos, *ibid.*, **91**, 1543 (1969); P. G. Gassman and J. E. Trent, unpublished work.

Table II

N-Chloroaziridine	Mode of ring opening	k_{rel}	Products
 **32**	 **33**	1	 $2\,\mathrm{H}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{H} + \mathrm{NH_4Cl}$
 **34**	 **35**	15	 $\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{H} + \mathrm{H}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{H} + \mathrm{NH_4Cl}$
 **36**	 **37**	210	 $\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{H} + \mathrm{H}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{H} + \mathrm{NH_4Cl}$
 **38**	 **39**	1490	 $2\,\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{H} + \mathrm{NH_4Cl}$
 **40**	 **41**	1860	 $\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{CH_3} + \mathrm{H}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{H} + \mathrm{NH_4Cl}$
 **42**	 **43**	155,000	 $2\,\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\Vert}{\mathrm{C}}}\mathrm{H} + \mathrm{NH_4Cl}$

group and the hydrogen. This decrease *vs.* increase in methyl–hydrogen interaction accounts for a rate factor of 12. The solvolysis of **39** is significantly faster than **37** because both incipient carbonium ion centers are secondary. Steric interactions in **39** are balanced because in the disrotatory process one methyl–hydrogen interaction is decreasing while the other methyl–hydrogen interaction is increasing.

In comparing **41** with **39** we see that a primary and a tertiary center next to nitrogen are slightly better than two secondary centers. In **42** we find a dramatic increase in rate relative to both **38** and **40**. Although both **39** and **43** involve development of partial positive charge on two incipient secondary centers, the steric interactions in **39** and **43** resulting from a disrotatory ring opening are very different. In **43** there is a relief of a methyl–methyl interaction due to the outward rotation of the methyl groups, as required by the molecular orbital symmetry considerations for a process involving heterolytic cleavage of the N–Cl bond. The dramatic overall effect of the two methyl groups was illustrated by the difference of 155,000 in the rates of solvolysis of **32** and **42**.

Additional evidence for the polar nature of the transition state in N-chloramine solvolyses was provided by the increased rate of reaction in water as compared to methanol. For instance **38** ionized 76 times faster in water than in methanol, as might be anticipated due to the more polar nature of the aqueous solution.

The Discrete Existence of Nitrenium Ions

The combination of product studies and kinetic data listed above leaves little doubt but that the cleavage of the N–Cl bond under solvolytic conditions is a heterolytic process which produces a chloride anion and an electron-deficient nitrogen species. Unfortunately, the observations discussed thus far did not permit a distinction to be made between a divalent nitrogen species with a unit positive charge and a slightly electron-deficient nitrogen species which represents only a transitory

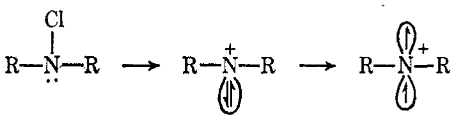
Table III
Products from the Solvolysis of 8

Solvents[a,b]	% yield 9	10	11	Total % yield	% yield of singlet products	Singlet product/ triplet product
CH$_3$OH-C$_6$H$_{12}$	56	10	8	74	66	8.2
CH$_3$OH-p-Br$_2$C$_6$H$_4$	33	10	25	68	43	1.7
CH$_3$OH-CCl$_4$	13	<1	59	73	13	0.22
CH$_3$OH-CHCl$_3$	4	<1	63	67	4	0.06
CH$_3$OH-CHBr$_3$	~1	≪1	45	46	1	0.02
CH$_3$OH-CH$_3$OH	59	20	7	86	79	11.3

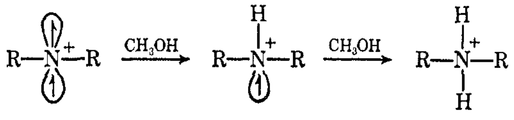
[a] With the exception of the CH$_3$OH-p-Br$_2$C$_6$H$_4$ solvent mixture, which was made up on a 1 ml of CH$_3$OH to 1 g of p-Br$_2$C$_6$H$_4$ basis, all of the solvent mixtures were 1:1 by volume. [b] To a first approximation the table is arranged in order of increasing solvent polarity.

point on the reaction pathway. It occurred to us that the nitrenium ion, if it existed as a discrete intermediate with a unit positive charge, might have one property which would permit its detection.

The nitrenium ion is unusual in that it has both a positive charge and a nonbonding pair of electrons. Of necessity the mode of generation of nitrenium ions would require that **44** ionize to give **45** with the electron spins paired. If this singlet had a sufficient lifetime and if spin inversion would decrease the energy of the system, **45** could convert to **46**. The singlet, **45**, would be expected to exhibit carbonium ion like behavior while the triplet, **46**, would be expected to resemble a nitrogen cation radical in its chemical reactivity. For instance **46** should be an excellent hydrogen abstractor. In the presence of a hydrogen source such as methanol **46** should be converted into the cation radical **47**, which is known to be a strong hydrogen abstractor[26] and would react with methanol to give **48**.

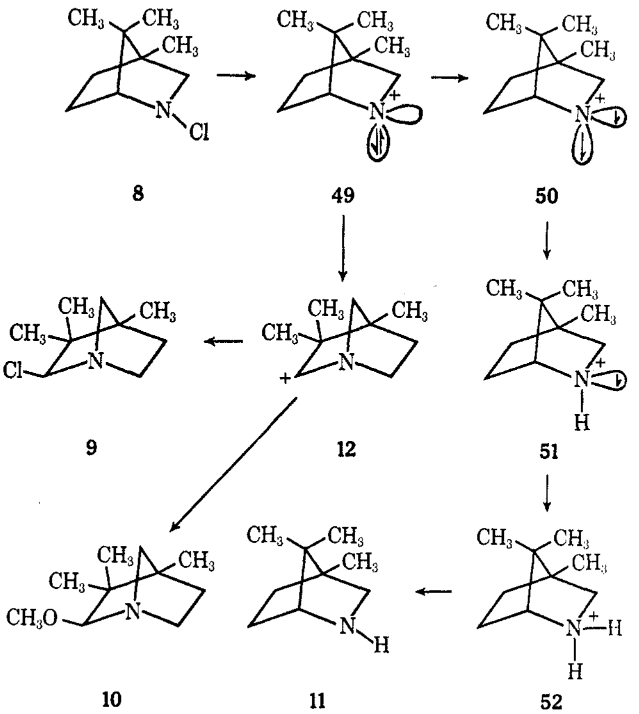


44 **45 singlet** **46 triplet**



46 **47** **48**

Chart II



As noted above the solvolyses of the bicyclic N-chloramines often produce small amounts of the starting secondary amine from which the N-chloramine was derived. As outlined in Chart II, a rationale for the formation of **11** from **8** would involve the initial formation of **49** as a discrete entity. This singlet species could either rearrange and add nucleophile to give **9** and **10** or spin invert to produce **50**. The reaction of **50** with methanol would give **52** *via* the intermediate formation of **51**. Neutralization of **52** would give **11**. If the conversion of **49** to **50** could be controlled, then it could be demonstrated that the hypothetical scheme shown in Chart II resembled the actual mechanistic pathway. Fortunately, it has been established that heavy atom solvents can catalyze spin inversion.[27] Table III shows the results of our studies on the effect of heavy atom solvents on the product ratio observed in the solvolysis of **8**.[28]

It is obvious from Table III that halogenated solvents have a dramatic effect on the product ratio observed in the solvolysis of **8**. For instance, a 500-fold change in product ratio occurred when bromoform was added to the methanol. The close similarity of the least polar media, methanol–hexane, with the most polar solvent system, pure methanol, demonstrates that the solvent effect is not due to solvent polarity. This same com-

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(26) The nitrogen cation radical is the proposed intermediate in the Hofmann-Löffler-Freytag reaction. For a review see M. Wolff, *Chem. Rev.*, **63**, 55 (1963).

(27) (a) A. G. Anastassiou, *J. Am. Chem. Soc.*, **88**, 2322 (1966); (b) C. D. Dijkgraaf and G. J. Hoijtink, *Tetrahedron Suppl.*, **2**, 179 (1963). See also J. N. Murrell, "The Theory of the Electronic Spectra of Organic Molecules," John Wiley & Sons, Inc., New York, N. Y., 1963, pp 294–300.

(28) P. G. Gassman and R. L. Cryberg, *J. Am. Chem. Soc.*, **91**, 5176 (1969).

parison shows that the observed phenomenon is not due to a dilution effect.[29,30]

Before considering the results listed in Table III in terms of a solvent heavy atom effect, it seems best to discuss alternate explanations. A casual evaluation of our data might tempt one to suggest that our findings could be explained by a homolytic cleavage of the N–Cl bond of **8** to give a nitrogen radical and a chlorine radical. In the presence of chloroform or bromoform, the nitrogen radical could abstract a hydrogen atom to give **11**, and a radical chain reaction could then ensue. However, we observe the same qualitative results in carbon tetrachloride which cannot serve as a hydrogen source. Also, *p*-dibromobenzene is slightly more effective than bromoform on a per bromine basis. This would appear to rule out any explanation based on initial homolytic cleavage of the N–Cl bond of **8**.

Another explanation would involve initial homolytic cleavage of the heavy atom solvent followed by abstraction of the chlorine from **8**. Since it is inconceivable that *p*-dibromobenzene could undergo such spontaneous cleavage under the reaction conditions, this possibility seems highly improbable.

The possibility that the heavy atom solvents are catalyzing the heterolytic cleavage of the N–Cl bond of **8** to give an amide anion and positive chlorine also merits consideration. However, it is not obvious how a molecule such as dibromobenzene could effect a reversal of the heterolytic process.

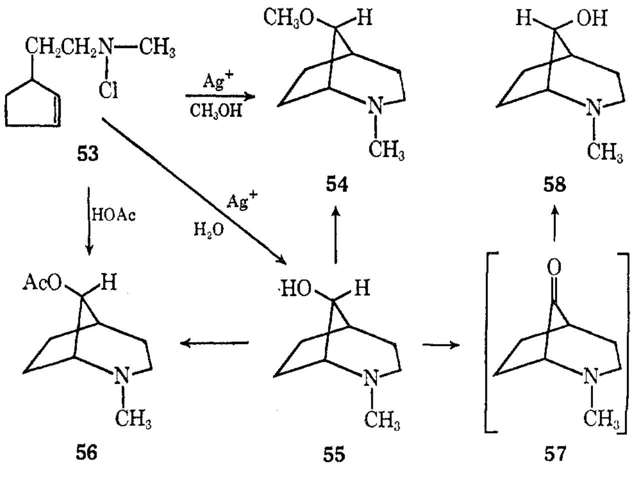
As a result of the considerations discussed above it appears that the results listed in Table III are best rationalized in terms of the heavy atom effect of the halogenated solvents. In order for a catalyzed spin inversion to occur, **49** must have existed as a discrete entity with unit positive charge on nitrogen. Not only does this set of experiments offer substantial evidence for the existence of nitrenium ion singlets, it also provides a convenient entry to the preparation of nitrenium ion triplets.

Since the relative magnitudes of the heavy atom effects observed in our work differ considerably from those observed in certain spectroscopic studies,[27b,31] a short speculative discussion is merited in order to avoid confusion. It should be remembered that our studies involve a solvolytically generated ground-state intermediate, not a photolytically produced excited-state intermediate. In generating such a nitrenium ion solvolytically, the ionizing N–Cl bond becomes highly dependent on the stabilizing ability of the polar solvent shell. In the examples in Table III this shell consists of methanol molecules. However, the coupling of spin and orbital angular momenta necessary for spin inversion requires a collision between the halogenated solvent and the singlet. The ability of a halogenated solvent molecule to penetrate the solvating shell of methanol will depend on both the size and polarity of the specific approaching halogen-containing molecule. The larger the halogenated molecule the less effective it should be as a catalyst for spin inversion. The more polar the halogenated species the more effective it should be. These properties will be balanced against the natural tendency of bromine to be much more effective than chlorine as a spin inversion catalyst. Thus the relative effects observed in our study are consistent with what might be expected of heavy atom effects on a solvolytically generated singlet species.

Application of Nitrenium Ion Theory to Synthetic Problems

Having established a firm basis for nitrenium ion theory we turned our attention to the synthetic application of nitrenium ions. Of particular interest to us was whether nitrenium ions could be *intramolecularly* added to double bonds in a "π route" to nitrogen-containing heterocyclics. An initial study involved the solvolytic behavior of **53**. As shown in Chart III the silver ion catalyzed cyclization of **53** in methanol gave **54** in 43% yield.[32,33] The corresponding silver ion catalyzed reaction in water gave **55** in 60% yield.[34] The correlation of **55** with **54** was readily accomplished by the sequential reaction of **55** with sodium hydride and methyl iodide. Similarly solvolysis in acetic acid gave **56** which could also be obtained by acetylation of **55**. The π route was a stereospecific reaction giving only the one isomer at C-7. The epimeric series could be obtained by oxidation of **55** to **57** and reduction of **57** with potassium borohydride to give predominantly **58**.[34]

Chart III



Cyclization of **59** gave **60** and **61** as the major bicyclic

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(29) For examples of dilution effects see S. Lwowski and J. S. McConaghy, Jr., *J. Am. Chem. Soc.*, **87**, 5490 (1965); E. Ciganek, *ibid.*, **88**, 1979 (1966); M. Jones, Jr., and K. R. Rettig, *ibid.*, **87**, 4103 (1965).

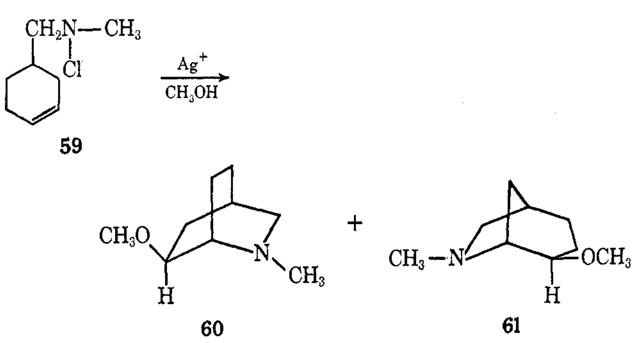
(30) The very slight difference in product ratio between pure methanol and methanol–hexane indicates that a very small dilution effect could be operative but that this dilution effect would be much too small to explain the changes observed in the presence of halogenated solvents.

(31) S. P. McGlynn, T. Azumi, and M. Kasha, *J. Chem. Phys.*, **40**, 507 (1964); A. R. Horrocks, T. Medinger, and F. Wilkinson, *Photochem. Photobiol.*, **6**, 21 (1967); T. Medinger and F. Wilkinson, *Trans. Faraday Soc.*, **61**, 620 (1965).

(32) P. G. Gassman, F. Hoyda, and J. Dygos, *J. Am. Chem. Soc.*, **90**, 2716 (1968).

(33) The stereochemistry of the methoxyl function was not rigorously proven, but was assigned by analogy to cyclizations in the cyclohexenyl system (*vide infra*).

(34) P. G. Gassman and J. Dygos, unpublished work.



products.[34] The independent synthesis of **60** rigorously established the stereochemistry of the methoxyl function in **60**. Thus it was established that the nucleophile added *trans* to the attacking nitrenium ion. The stereochemistry of the methoxyl functions of **54** and **61** was assigned on this basis.

Summary

Nitrenium ions have been rigorously established as useful intermediates in a variety of synthetic applications. The chemistry of nitrenium ion singlets has been explored in relation to molecular rearrangements and new routes for forming carbon–nitrogen bonds. It has been chemically demonstrated that nitrenium ion singlets may be converted to nitrenium ion triplets. Since it is evident that nitrenium ions (both singlet and triplet forms) are potentially very important species for the synthesis of a wide variety of nitrogen-containing compounds, we are continuing our efforts to develop new and useful applications of nitrenium ion chemistry.

I wish to thank the National Cancer Institute, Public Health Service, for Grant CA-07110 which supported this work, and the Alfred P. Sloan Foundation for a fellowship. I also wish to acknowledge the impressive efforts of my collaborators mentioned in the references, who have contributed much to the knowledge of nitrenium ions.

Determination of the Chemical Structure of Organic Compounds at the Microgram Level by Gas Chromatography

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Chemists, especially those dealing with natural products, are frequently confronted with the problem of identifying substances they have isolated in insufficient amount. Frustrations of this kind are probably more common today than in the past because of the remarkable success and ease with which the chemist can separate microgram and lesser amounts of a pure compound from complex mixtures by means of gas and other forms of chromatography.

At the U. S. Department of Agriculture we are plagued with this problem of identification in our efforts to elucidate the chemical structure of insect sex attractants, which we need to combat insect pests. Attractants of this kind are used to bait traps that are deployed around our ports of entry to detect incipient infestations of imported insect pests. Should one of the target insects be found, the infestation can be eradicated before it can spread. One such operation saved the U. S. Department of Agriculture more than nine million dollars in potential eradication costs.

One of the biggest handicaps in our efforts to determine the structure of insect sex attractants is the enormous number of insects needed to obtain a minute amount of pure attractant; the chemical does have to be pure before its structure can be determined. Since these insect collections are costly, structure determinations must be carried out on a limited amount of material. This is not a specialized need because, regardless of a chemist's interest, being able to make identifications with less material is bound to accelerate progress in virtually all fields, but especially in the life sciences. Spectral probes, such as ir, uv, nmr, and mass spectrometry, are invaluable and are a first resort, but more and better techniques are needed to cope with problems of this kind.

Several of the techniques to be described were devised to fill this need. Most of these combine a chemical reaction with gas chromatography and can be used with 1 to a few micrograms of substance for identification or for some other analytical advantage.

As anyone who has had to deal with minute amounts of substance soon learns, the value of manipulative skills and techniques is most important, and apparatus that allows those less than generously endowed with such skills to perform difficult analyses is certainly needed. The emphasis on means of getting a job done is therefore an important part of the quest to do more with less.

Carbon-Skeleton Chromatography

Carbon-skeleton chromatography[3a] strips off all func-

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(1) Recipient of the 1969 American Chemical Society Award in Chromatography and Electrophoresis, sponsored by Lab-Line Instruments, Inc.

(2) Presented in part at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., on April 15, 1969; award address.

(3) (a) M. Beroza, *Anal. Chem.*, **34**, 1801 (1962); (b) M. Beroza and F. Acree, Jr., *J. Ass. Offic. Agr. Chem.*, **47**, 1 (1964).