

For analysis of monodisperse molecules of biological interest the cross-linked dextrans have enjoyed a great success across the entire molecular weight range. Commercial and laboratory applications are too numerous to mention.⁷³⁻⁷⁶ As stated before, partition behavior has been observed, with compounds eluting with $V_r > V_t$. Porous glass packings are becoming more popular, and may be used in aqueous solutions up to pH 9 without ill effects. Deactivation is achieved using poly(ethylene oxide) surface treatment, and sometimes this polymer is also added to the eluent.⁷⁷⁻⁷⁹

(72) M. Duval, B. Bloch, and S. Kohn, *J. Appl. Polym. Sci.*, **16**, 1585 (1972).

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(74) L. Fisher in "Laboratory Techniques in Biochemistry and Molecular Biology," T. S. Work and E. Work, Ed., North-Holland, Amsterdam, 1969.

(75) J. M. Curling, *Exp. Physiol. Biochem.*, **3**, 417 (1970).

(76) "Saphadex-Gel Filtration in Theory and Practice," available from Pharmacia Fine Chemicals.

(77) H. H. Geschwinder, W. Haller, and P. H. Hofschneider, *Biochim. Biophys. Acta*, **190**, 460 (1969).

Conclusion

GPC is entering its "second generation" of sophistication with the development of more advanced chromatographic theory and improved instrumentation and column packings. Already it is the most widely employed analytical technique for the laboratory MWD characterization of synthetic polymers and analysis and purification of many biological materials. The future can only bring proliferation of commercial and scientific uses of GPC in the fields of quality control, preparative-scale operation, and analytical separations.

Complete understanding of the separation mechanism and definition of differences between packing material behavior remain elusive. In this respect, GPC is one of the most fertile research fields in chromatography.

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Nitrosamine Photochemistry: Reactions of Aminium Radicals

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The extensive current interest in photochemical excitation of organic compounds stems largely from the synthetic utility of the reactions that ensue. The introduction of powerful techniques that permit the identification of the reactive intermediate involved in photolyses has also provided stimulus to photochemists.¹ It was such a combination that drew us to investigate the photochemical reactions of *N*-nitrosamines (1).

In the early 1960's, systematic studies by several groups, particularly Barton's, revealed the scope and synthetic utility of photolyses of nitrite esters.² Irradiation of these esters in neutral solutions causes homolytic dissociation to nitric oxide (NO) and alkoxy radicals; stereospecific intramolecular hydrogen atom abstractions of the latter have been utilized elegantly in syntheses of otherwise inaccessible compounds.² Insofar as the primary photochemical process is concerned, the behavior of nitrosamides³ as

well as *C*-nitroso compounds^{4,5} parallels that of nitrite esters. The photolysis generates amido and alkyl radicals, respectively, together with NO as the counter radical. In contrast to the photolability of these nitroso compounds, dialkyl nitrosamines (1) (except *N*-nitrosodibenzylamine) are stable toward uv irradiation in neutral solution.^{6,7}

In 1964 we discovered that, in the presence of a dilute acid, *N*-nitrosamines rapidly undergo various photoreactions.⁶ In the ensuing years, we have investigated the scope and synthetic utility of this interesting photolysis. We have employed the flash excitation technique to establish that the primary photoprocess involves generation of NO and aminium radicals ($R_2NH^{\cdot+}$).

(1) For general discussions of organic photochemistry reference is made to the monograph by N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965.

(2) For a review of this reaction, see M. Akhtar, *Advan. Photochem.*, **2**, 263 (1964), and R. H. Hesse, *Advan. Free Radical Chem.*, **3**, 83 (1969).

(3) Y. L. Chow and J. N. S. Tam, *J. Chem. Soc. C*, 1138 (1970), and references cited therein.

(4) (a) H. A. Morrison in "The Chemistry of the Nitro and Nitroso Groups," H. Feuer, Ed., Interscience, New York, N. Y., 1969, p 165; (b) J. A. Maassen, Ph.D. Dissertation, University of Amsterdam, Amsterdam, 1972.

(5) Y. L. Chow, J. N. S. Tam, and K. S. Pillay, *Can. J. Chem.*, in press.

(6) Y. L. Chow, *Tetrahedron Lett.*, 2333 (1964); *Can. J. Chem.*, **45**, 53 (1967).

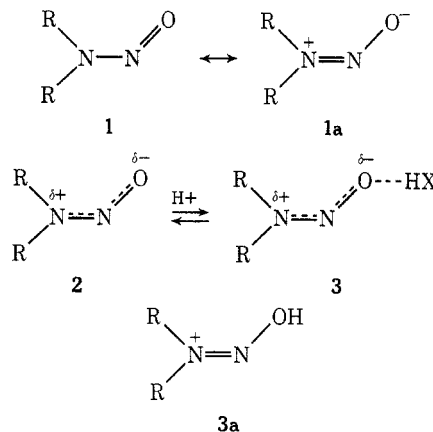
(7) E. M. Burgess and J. M. Lavanish, *Tetrahedron Lett.*, 1227 (1964).

Y. L. (Joe) Chow received his undergraduate education in National Taiwan University, Taipei, Taiwan, and obtained his Ph.D., under H. Hary Szmant, at Duquesne University. Subsequently he studied as a postdoctoral fellow with M. L. Bender, H. Erdtman, and D. H. R. Barton, during which time he developed research interests in solution photochemistry. The nitrosamine photochemical studies were inaugurated in 1963 at the University of Alberta, Edmonton. During recent years his research interests have extended to the chemistry of "onium" radicals. He has been Professor of Chemistry at Simon Fraser University since 1969.

The latter, rather unusual, cationic radical⁸ has previously been proposed as the reactive intermediate in photolyses and metal ion (Fe^{2+} , Ti^{3+} , Cu^+ , etc.) catalyzed redox reactions of *N*-chloramines in strong acids.⁹ In recent years, these processes have been recognized as selective and convenient chlorination and amination techniques.⁹⁻¹¹ Because of the high acidity (20% or higher H_2SO_4 in AcOH) required in the *N*-chloramine decompositions, the corresponding aminium radicals behave somewhat differently from those generated in dilute acids by nitrosamine photolyses. Indeed, the mild conditions used in the nitrosamine route make the process more versatile in synthesis.

It is reasonable to suspect that the dilute acid promoted photolability of nitrosamines is associated with their dipolar character. The ground-state electronic configuration of *N*-nitrosamines (2) has been assessed by SCF calculations¹² to possess a 48% contribution of polar resonance form 1a. Considerable evidence indicating partial N-N double bond character and location of the negative pole at the nitroso oxygen (in 2) has been gathered by physical measurements.¹³⁻¹⁵ Inevitably a proton (or a Lewis acid) would seek the nitroso oxygen as the coordination site. This has been shown to be the case for a few known nitrosamine-metal complexes.¹⁶ Ultraviolet spectroscopic studies of nitrosamines in aqueous sulfuric acid have demonstrated that at low concentrations of acid (pH >1) association through hydrogen bonding (3) is the primary mode of interaction. At higher concentrations of acid (>2 M H_2SO_4) nitrosamines are protonated on the nitroso oxygen¹⁷ (3a). It is the former (3), but not the latter (3a), that is photolabile, since in the presence of 4 M H_2SO_4 (or in solutions of higher acidity) nitrosamines do not undergo photoreaction.¹⁸

Interest in the photochemical behavior of nitrosamines is heightened by the observation that they are generally carcinogenic to animals.¹⁹ As nitrosamines are quite readily formed by electrophilic attack of a potential nitrosyl ion (NO^+) on a secondary amine under a wide variety of conditions, their bio-



logical hazard can be far-reaching. Doubtless, the facility of their formation is determined by the nucleophilicity of the amine and the nitrosyl donating power of the nitrosation reagent. In the laboratory, nitrosamines are conveniently prepared by treatment of the corresponding ammonium salts with NaNO_2 or an alkyl nitrite; other variants include reaction of the amine with a nitrosating reagent such as NOCl , N_2O_4 , or NOBF_4 .¹¹

Kinetic Profile of Aminium Radicals

When an acidic aqueous solution (pH 2) of *N*-nitrosopiperidine (NNP), degassed or saturated with oxygen, was studied by flash photolysis a transient was observed; it exhibited an absorption curve identical with that generated from *N*-chloropiperidine under comparable conditions.⁸ Since the decay kinetics of both transients are, within experimental error, identical, they must be the piperidinium radical 5 which has recently been established as the intermediate in photolysis of *N*-chloropiperidine²⁰ in H_2SO_4 in acetic acid.

In nitrosamine flash photolysis⁸ the kinetic behavior of piperidinium radical 5 is the same whether generated by $n-\pi^*$ or $\pi-\pi^*$ band excitation and whether in the presence or absence of oxygen. In an acidic aqueous solution, 5 decays with first-order kinetics with a rate constant (k) of $1.85 \times 10^4 \text{ sec}^{-1}$ (lifetime, $\tau = 1/k = 54 \pm 2 \mu\text{sec}$). In aqueous methanol (pH 2), the transient decays with pseudo-first-order kinetics from which the bimolecular rate constant of H-atom transfer from methanol to 5 is computed²¹ to be $4.8 \times 10^8 \text{ M}^{-1}$. In a similar manner it has been shown that 5 adds to cyclohexene in methanol-water (2:1) with rate constant $2.4 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}$. Since the observed zero-time absorbances of the transient at the several monitoring wavelengths remain virtually constant, the precursor(s) of 5 is obviously not reacting with methanol or cyclohexene; that is, piperidinium radical 5 is the common intermediate involved in the various photoreactions. It can be calculated that 5 adds to cyclohexene (photoaddition) 5000 times faster than it abstracts a hydrogen atom from methanol (photoreduction);

(8) M. P. Lau, A. J. Cessna, Y. L. Chow, and R. W. Yip, *J. Amer. Chem. Soc.*, **93**, 3808 (1971), and unpublished data.

(9) (a) R. S. Neale, *Synthesis*, **3**, 1 (1971); (b) N. C. Deno, *Methods Free Radical Chem.*, **3**, 135 (1972); (c) F. Minisci, *Synthesis*, **5**, 1 (1973); (d) P. Kovacic, M. K. Lowery, and K. W. Field, *Chem. Rev.*, **70**, 639 (1970).

(10) The intramolecular hydrogen-chlorine atom exchange reactions in *N*-chloroamine decompositions have been known as the Hofmann-Löffler reaction; for the definitive study of the reaction see E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.* **82**, 1657 (1960).

(11) For the ground-state chemistry of nitrosamines see the recent reviews: (a) P. A. S. Smith, "Open-chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, Chapter 15; (b) A. L. Fridman, F. M. Mukhametshin, and S. S. Novikov, *Russ. Chem. Rev.*, **40**, 34 (1971).

(12) Y. Tanaka, *J. Chem. Soc. Jap.*, **78**, 1647 (1957).

(13) C. E. Looney, W. D. Phillip, and E. L. Reiley, *J. Amer. Chem. Soc.*, **79**, 6136 (1957); G. J. Karabatsos and R. A. Taller, *ibid.*, **86**, 4373 (1964).

(14) Y. L. Chow and C. J. Colon, *Can. J. Chem.*, **46**, 2827 (1968).

(15) S. J. Kuhn and J. S. McIntyre, *Can. J. Chem.*, **44**, 105 (1966).

(16) U. Klement and A. Schmidpeter, *Angew. Chem.*, **80**, 444 (1968); R. D. Brown and G. E. Coates, *J. Chem. Soc.*, 4723 (1962).

(17) W. S. Layne, H. H. Jaffe, and H. Zimmer, *J. Amer. Chem. Soc.*, **85**, 435, 1815 (1963).

(18) M. P. Lau, Ph.D. Dissertation, Simon Fraser University, 1970.

(19) J. H. Weisburger and E. K. Weisburger, *Chem. Eng. News*, **43**, 124 (Feb 7, 1966).

(20) J. Spanswick and K. U. Ingold, *Can. J. Chem.*, **48**, 546, 544 (1969).

(21) In the studies of *N*-chloropiperidine photodecomposition by Spanswick and Ingold,²⁰ the rate of hydrogen atom transfer from decanoic acid to a piperidinium radical is determined, by rotating sector technique, to be $7 \times 10^3 \sim 10^4 \text{ M}^{-1} \text{ sec}^{-1}$.

consequently the photoaddition can be conducted in methanol solution without appreciable complication from photoreduction. The dimethylammonium radical generated by flash photolysis of *N*-nitrosodimethylamine (NND) exhibits comparable reaction rate constants.¹⁸

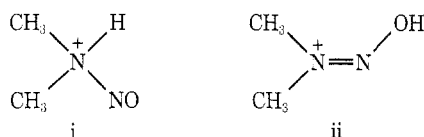
Photochemical Processes

Following photoexcitation of a nitrosamine molecule, there must exist either a triplet or a singlet pathway to the aminium radical in competition with other decay processes. However, in the absence of any observed luminescence of NNP, we can only estimate the energy levels of its excited states by indirect means. Thus NNP does quench naphthalene and 2,2'-binaphthyl triplets generated by flash photolysis in acidic media; the quenching rate constants allow us to calculate the lowest triplet energy, E_T , of NNP to be 59 kcal/mol, assuming operation of reversible energy transfer.⁸ Although NNP efficiently quenches triplet transients of various aromatic ketones of higher E_T , photosensitization of NNP by these ketones does not lead to photoreaction; the lowest triplet state of NNP is therefore not photoreactive. The energy level of the lowest singlet state (E_S) of NNP is approximated by the absorption peak at longest wavelength (366 nm) to be 78 kcal/mol. In agreement, naphthalene fluorescence is quenched by NNP (concentration $<10^{-4}$ M) at the diffusion-controlled rate. Successful naphthalene-sensitized photoreactions of NNP in acidic media indicate that the lowest singlet excited state of the NNP-acid complex undergoes dissociation to give piperidinium radical and NO. The lifetime of the singlet excited-state complex is estimated from the rising time of the transient signal to be $<10^{-7}$ sec. This, together with the failure of oxygen (10^{-3} M) to quench the photochemical processes, confirms that the reactions involve a singlet state of the NNP-acid complex.

The nitrosamino moiety of the ground-state nitrosamine-acid complex has a nearly planar configuration, as shown in 3, due to resonance interaction.¹⁴ The $n-\pi^*$ absorption of a nitrosamine has been assigned to a local symmetry-allowed but overlap-forbidden transition;²² the excitation is expected to induce sp^2 to sp^3 rehybridization of the amine nitrogen with localization of the electron pair. This electron reorganization in the nitrosamine-acid complex conceivably triggers proton migration to the electron-rich amine nitrogen to form an *N*-nitrosoammonium ion, such as 4, which decomposes, perhaps with the aid of residual vibrational energy, to an aminium radical 5. The recombination of NO with an aminium radical is probably not favored since 4 is a high-energy species.²³

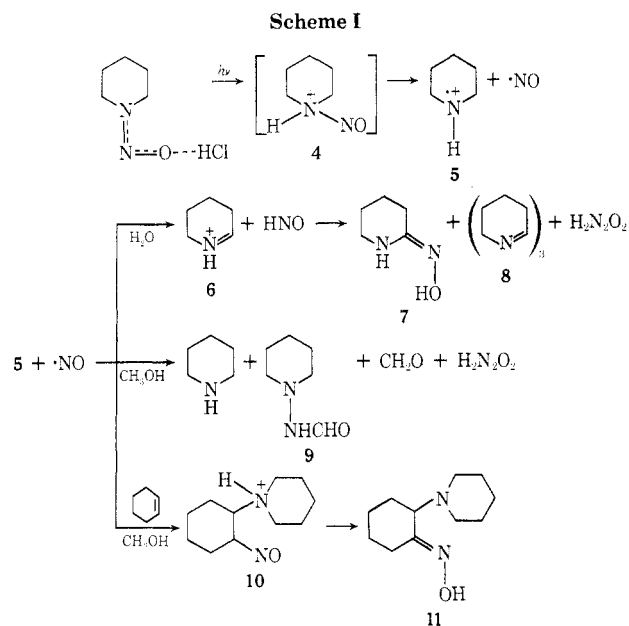
(22) (a) M. Kasha, *Discuss. Faraday Soc.*, 9, 14 (1950); (b) J. W. Sidman, *Chem. Rev.*, 58, 684 (1958).

(23) A closed-shell INDO calculation of energy levels shows that the *N*-nitrosodimethylammonium ion (i) is 16 kcal/mol less stable than the O-protonated form (ii) (T. Mojelsky, unpublished results).



Types and Scope of Photoreactions

As shown above, nitrosamine photoreactions are essentially the chemistry of an aminium radical in the presence of NO. Typical photoreactions^{6,24} of NNP in the presence of 0.1–0.001 N hydrochloric acid are summarized²⁵ in Scheme I. In an aqueous solution radical disproportionation occurs to form HNO and tetrahydropyridine 6; nucleophilic attack of HNO on 6 gives rearranged product, 2-piperidone oxime (7) (*photoelimination*). The intermediates 6 and HNO also polymerize to relatively stable isotri-piperidine (8) and $\text{H}_2\text{N}_2\text{O}_2$. In acidic methanol solution 5 abstracts a hydrogen atom from methanol, leading to redox products, including *N*-piperidinoformamide (9); methanol is concomitantly oxidized to the formyl group in 9 and to formaldehyde (*photoreduction*). In the presence of cyclohexene, the piperidinium and NO radicals add across the double bond readily, to give 1-piperidino-2-nitrosocyclohexane (10), which is usually isolated as the tautomeric oxime 11 under the photolysis conditions (*photoaddition*).



The fate of an aminium radical is determined by the rate of various competing processes, as demonstrated by kinetic studies on the piperidinium radical. The product patterns are, however, usually more complicated due to the concurrence of secondary thermal or photolytic reactions, for example, of *C*-nitroso compounds (*vide infra*). To avoid these secondary reactions, it is often essential to control the temperature (20° to *ca.* -70°) and energy sources (Pyrex, Nonex, and other filters).²⁶

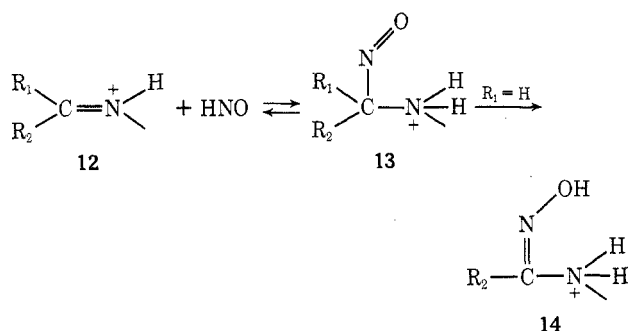
Photoelimination. In poor H-atom donating solvents, such as water or acetic acid, elimination is favored since photoreduction is suppressed. Using deu-

(24) Y. L. Chow, M. P. Lau, R. A. Perry, and J. N. S. Tam, *Can. J. Chem.*, 50, 1044 (1972).

(25) In these acidic conditions, it is understood that the basic products are present as the conjugate acids in the photolysate; usually free bases are written as the product except where a conjugate acid has to be considered.

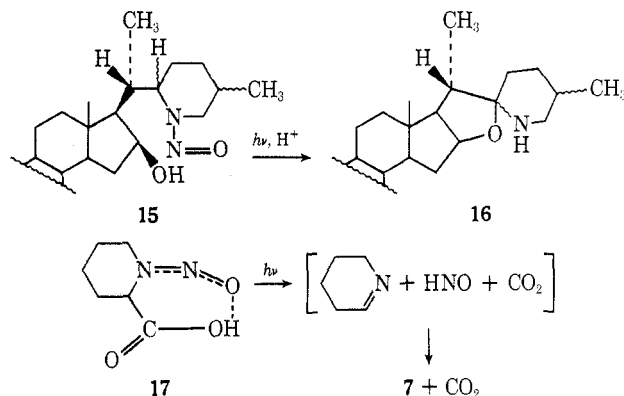
(26) Y. L. Chow, S. C. Chen, and D. W. L. Chang, *Can. J. Chem.*, 48 157 (1970).

terium- and ^{15}N -labeled *N*-nitrosodibenzylamines, Axenrod and Milne²⁷ have shown that there is extensive crossover of labels in the final product, *N*-benzylbenzamidoxime; this experiment supports the proposed stepwise elimination-recombination pathway and also proves the absence of a "cage effect" operating with intermediates HNO and immonium ion 12. When tautomerization of the *C*-nitroso product 13 ($\text{R}_1, \text{R}_2 = \text{alkyl}$) to oxime 14 is blocked by the absence of an α hydrogen atom, the reverse elimination, probably photolytic in nature, operates efficiently to regenerate immonium ion⁶ 12. Acid-catalyzed hydrolysis of the immonium product to carbonyl and amine compounds is frequently encountered in photoelimination of acyclic dialkylnitrosamines.



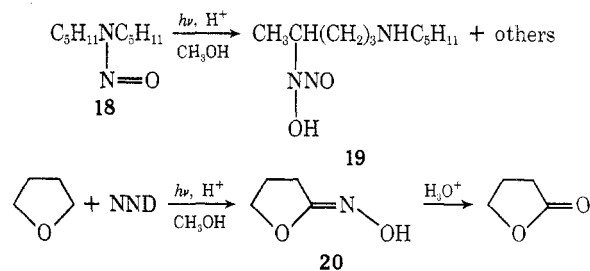
Elimination of an α hydrogen atom is probably assisted by NO in a radical pair since the decay rate of the piperidinium radical is slightly but reproducibly dependent on the nature of the counter radical.²⁸ The elimination of an α hydrogen atom in an unsymmetrically substituted dialkylaminium radical apparently proceeds in the direction which forms the most stable immonium ion 12. For example, photolyses of the *N*-nitroso derivatives of methylcyclohexylamine, methylbenzylamine,²⁹ and tetrahydroisoquinoline^{30,31} result in the elimination of the *tertiary* or the *benzylic* hydrogen atoms much faster than the alternative choices and form more substituted or conjugated C=N double bonds. Photoeliminations of the *N*-nitroso derivatives of dicyclohexylamine, diisopropylamine, and dibenzylamine are so facile that no other reaction is observed, even in methanol solution containing styrene²⁹⁻³¹ (*vide infra*).

An excellent application³² of photoelimination can be seen in photolysis of the stereoisomeric derivatives of *N*-nitroso-22,26-iminocholestane-3 β ,16 β -diol (15) which gives the corresponding immonium intermediates; they in turn undergo facile intramolecular ring closure to afford good yields of spirosolane alkaloids 16. A variation is the photolysis of *N*-nitrosopipicolinic acid (17) in neutral solution,³³ during which HNO and CO₂ are eliminated simultaneously and 2-piperidone oxime (7) is formed as the final product.



This oxidative elimination process is a very efficient and general reaction of nitroso derivatives of α -amino acids. It is noteworthy that the necessary proton is provided by the 2-carboxyl group. In contrast, neither *N*-nitrosopipicolinic acid in ethanol nor NNP in the presence of several mole equivalents of AcOH undergoes photoreaction. Obviously facile intramolecular hydrogen bonding between the 2-carboxyl and the nitroso groups is essential for the success of this photolysis. This photoprocess may prove to be a realistic pathway of oxidative decarboxylation of α -amino acids in biological systems, the occurrence of which has been frequently proposed in alkaloid biosynthesis.³⁴

Photoreduction. The H-atom abstraction of an aminium radical, when it occurs intramolecularly, is similar to Hofmann-Löffler reaction,¹⁰ the Barton reaction,² and the photolysis of nitrosamides.³ *N*-Nitrosodipentylamine (18), having a suitably located δ hydrogen, undergoes 1,5 H-atom nitroso group exchange (20%),²⁴ in competition with the intermolecular process and photoelimination, to give δ -nitroso derivatives 19.



When H-atom transfer occurs intermolecularly, various subsequent free-radical reactions may follow depending on their activation energies and the reaction conditions. Photolysis of NND in tetrahydrofuran yields γ -butyrolactone *via* oxime 20 which is formed by an intermolecular H-atom nitroso group exchange reaction.³⁵ In methanol, photolyses of NNP and NND probably involve chain processes (*via* 21 and 22) as shown in Scheme II; ketonization of 22 leads to the final product, *N*-formamidodialkylamine. In ethanol, acetaldehyde and *N*-acetamidodialkylamine have been isolated. In poor H-atom donating solvents, such as water or acetic acid, photore-

(27) T. Axenrod and G. W. A. Milne, *Tetrahedron*, **24**, 5775 (1968).

(28) Piperidinium radical generated from flash photolysis of *N*-chloropiperidine in acidic aqueous solution decays with a slower rate of $1 \times 10^4 \text{ sec}^{-1}$.

(29) T. Mojelsky, unpublished results.

(30) R. A. Perry, unpublished results.

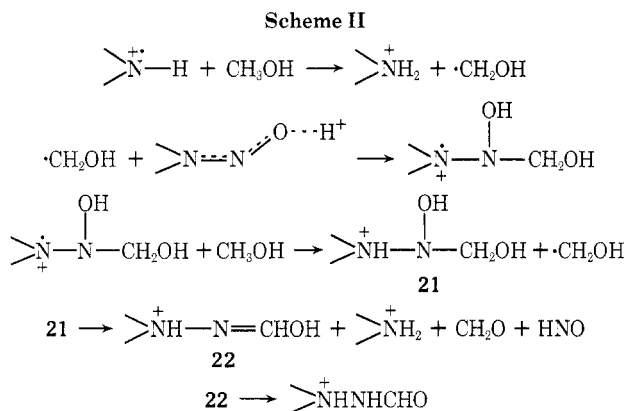
(31) Y. L. Chow and C. J. Colón, *Can. J. Chem.*, **45**, 2559 (1967).

(32) G. Adam and K. Schreiber, *Tetrahedron*, **22**, 3591 (1966).

(33) Y. L. Chow, *Tetrahedron Lett.*, 2473 (1965).

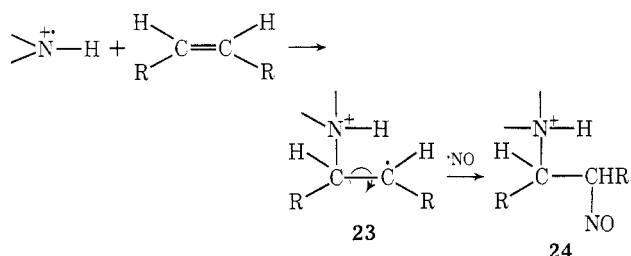
(34) T. A. Geissman and D. H. G. Crout, "Organic Chemistry of Secondary Plant Metabolism," Freeman, Cooper & Co., San Francisco, Calif., 1969.

(35) S. C. Chen, Ph.D. Dissertation, Simon Fraser University, 1970, and unpublished results.



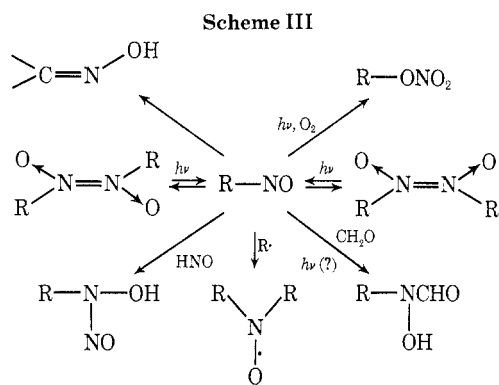
duction is curtailed in comparison to other aminium radical processes. Thus solvent choice determines the propensity of photoelimination or photoaddition (*vide infra*) of nitrosamines. Photoelimination of *N*-nitrosodibenzylamine and *N*-nitrosotetrahydroisoquinoline in methanol solution is so facile that only in the presence of a powerful H-atom donating agent such as hydroquinone and tri-*n*-butyltin hydride can photoreduction occur.¹⁸

Photoaddition. Nitrosamine photoaddition is one of the most efficient of all the known radical addition processes.³⁶ It gives the 1:1 adduct cleanly and is a powerful method for the preparation of various types of nitrogen compounds from olefins. An aminium radical, owing to its positive charge, seeks an electron-rich center but has to react as a radical, since electrophilic attack at a π bond will create an electronically impossible species. The attack is certainly subject to steric hindrance since even the smallest dimethylaminium radical is equivalent in size to the isopropyl radical. Mechanistically, nitrosamine photoaddition consists of (i) electrophilic radical attack of an aminium radical at a π bond, (ii) reaction of the C radical 23 with NO or its progenitor, and (iii)

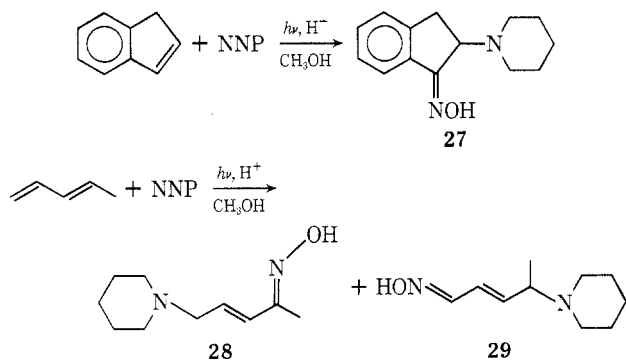
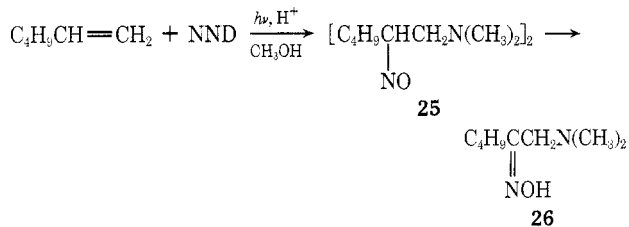


various thermal or photolytic secondary reactions (as yet not extensively investigated) of the resulting *C*-nitroso compounds (Scheme III). If there is an α -hydrogen in a *C*-nitroso compound, irreversible tautomerization is generally the dominant process under the photolysis conditions, although in certain instances other processes can compete successfully.²⁶ Accumulated evidence allows us to draw the following conclusions that agree in general with other radical characteristics.³⁶

Photoaddition of nitrosamines to simple olefins is highly regiospecific in that attack by an aminium radical always leads to a more stable radical inter-



mediate, as determined by electronic and steric controls. For example, NND photoaddition to 1-hexene gives **25** and **26**, while NNP photoaddition to indene gives **27**; in neither case are products with the alternative orientation isolated.³⁷ Operation of steric hindrance during attack of an aminium radical affects the reactivities of substituted olefins considerably. The efficiency of NNP photoaddition to various olefins can be arranged in the decreasing order: $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2 > \text{RCH}=\text{CH}_2 > \text{cis-RCH}=\text{CHR} > (\text{CH}_3)_2\text{C}=\text{C}(\text{CH}_3)_2 > \text{trans-RCH}=\text{CHR}$ in which R is an alkyl. A conjugated diene such as 1,3-pentadiene, being more reactive, photolytically adds NNP with slightly less regiospecificity to give the 1,4-adducts³⁸ **28** (60%) and **29** (4%).



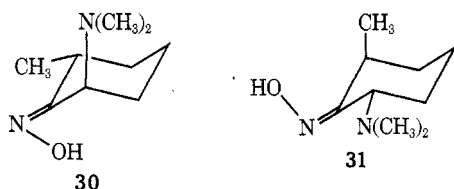
The electrophilic nature of the radical addition is demonstrated by competitive photoaddition of NNP to substituted styrenes. Addition²⁹ is facilitated by electron-releasing substituents, with $\rho = -1.29$. Obviously an aminium radical adds sluggishly to an electron-poor π bond. This is also shown by failures of NNP photoaddition to phenyl vinyl sulfone and methyl acrylate.²⁹

(37) Y. L. Chow, C. J. Colón, and S. C. Chen, *J. Org. Chem.*, **32**, 2109 (1967).

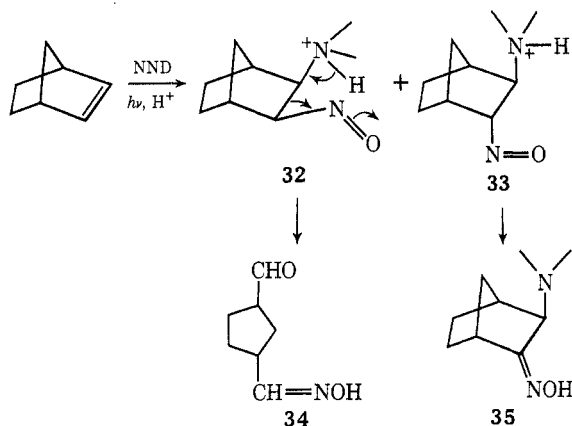
(38) Y. L. Chow, C. J. Colón, and D. W. L. Chang, *Can. J. Chem.*, **48**, 1664 (1970); Y. L. Chow, C. J. Colón, H. H. Quon, and T. Mojelsky, *ibid.*, **50**, 1065 (1972).

(36) Excellent reviews on the chemistry of representative radicals can be found in the series by E. S. Huyser, *Methods Free-Radical Chem.*, **1**, 2 (1969).

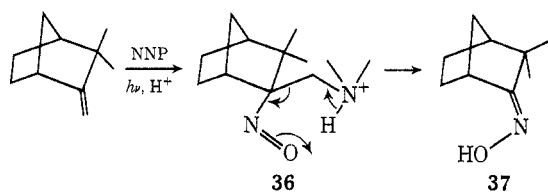
The stereoelectronic factor requires that an aminium radical approach the π bond along the p-orbital axis during which operation of subtle steric controls is evidenced in photoaddition to cyclic olefins. Photoaddition of NND to 4-*tert*-butylcyclohexene³⁹ gives four cyclohexanone anti oximes (*cis*- and *trans*-2-dimethylamino-5-*tert*-butyl and *trans*- and *cis*-2-dimethylamino-4-*tert*-butyl) in a ratio of 9:3:5:1; axial approach predominates over equatorial, and the selectivity is better than that of thiyl radical addition.³⁶ Similar photoaddition of 3-methylcyclohexene³⁹ gives a pair of conformationally frozen geometric isomers of oximes **30** and **31**, that are derived from the exclusive axial approach of dimethylaminium radical at C-1. Equatorial approach at C-1 and either approach at C-2 clearly involve steric compression from the C-3 methyl group that raises the activation energy for these pathways.



Norbornene undergoes the NND photoaddition³⁵ to give *exo-cis*-**32** and *trans*-**33** C-nitroso compounds in which the aminium radical has approached exclusively from the *exo* face of norbornene. In *exo-cis*-**32** the dimethylaminium and nitroso groups are ideally oriented for intramolecular proton transfer which triggers a cleavage reaction, yielding **34** as a



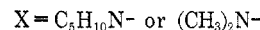
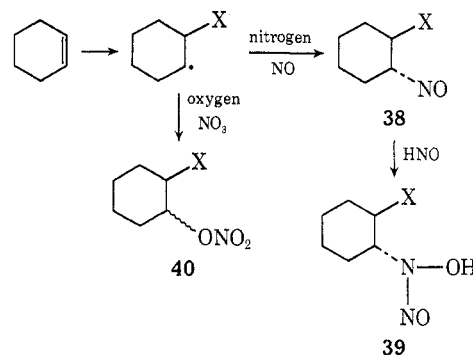
final product; no doubt relief of the bicyclic strain serves as the driving force in this case.²⁹ When a 1-nitroso-2-ammonioalkane has a relatively long lifetime due to retarded tautomerization or other reasons, the cleavage reaction occurs with particular ease; for example, camphene is degraded to give 82% of camphenilone oxime⁴⁰ (**36** \rightarrow **37**).



(39) Y. L. Chow, S. C. Chen, K. S. Pillay, and R. A. Perry, *Can. J. Chem.*, **50**, 1057 (1972).

(40) Y. Lm Chow, *J. Amer. Chem. Soc.*, **87**, 4642 (1965).

The overall stereochemistry of nitrosamine photoaddition is determined by the radical combination step (**23** \rightarrow **24**); this step is expected to be extremely rapid, as indicated by the lack of telomer formation during photoaddition to styrene.³⁷ In order to preserve the stereochemistry of the initial C-nitroso adduct **24**, the conditions must be adjusted so that **24** is diverted to final products such as a dimer and/or a *N*-nitrosohydroxylamine (Scheme III). Depending on the conditions, NND photoaddition to cyclohexene⁴¹ affords the anti dimer of *trans*-1-nitroso-2-dimethylaminocyclohexane (**38**) or *trans*-1-(*N*-nitrosohydroxylamino)-2-dimethylaminocyclohexane (**39**). Exclusive formation of the *trans* isomers indicates that stereochemically the reaction is *trans* addition.



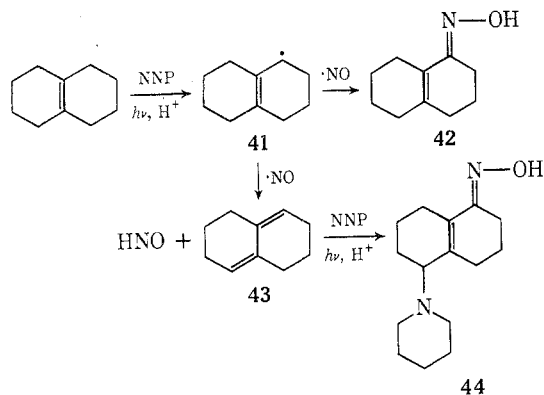
In the case of *cis*- and *trans*-2-butene,⁴¹ we have demonstrated that the intermediate C radical **23** (R = CH₃) possesses an activation energy of rotation about the C₂-C₃ bond comparable to that of the radical combination step (**23** \rightarrow **24**); in both cases NND photoaddition gives mixtures of the erythro and threo isomers of the C-nitroso compound **24** (R = CH₃) with small stereoselectivity. The photoaddition initiated with a high-energy light source (Corex filter) rapidly equilibrated intermediate **23** (R = CH₃) and led to a 4:6 thermodynamically controlled product ratio of *erythro*-**24**:*threo*-**24** from either *cis*- or *trans*-2-butene.

As shown above, intermolecularly an aminium radical undergoes addition to the exclusion of H-atom abstraction from an olefin. However, in the course of photoaddition of NNP or NND to hindered olefins, such as 3,3-dimethyl-1-butene, a certain amount of photoreduction takes place.²⁶ Attempted photoaddition of NND to the sterically hindered π bond of $\Delta^9(10)$ -octalin results in photoreduction;³⁹ the major reaction is allylic H-atom abstraction by the dimethylaminium radical to give intermediate **41**. While **41** may scavenge NO to give oxime **42**, a small fraction is dehydrogenated to give diene **43** *in situ*; oxime **44** is formed by 1,4 addition of NNP to diene³⁸ **43**.

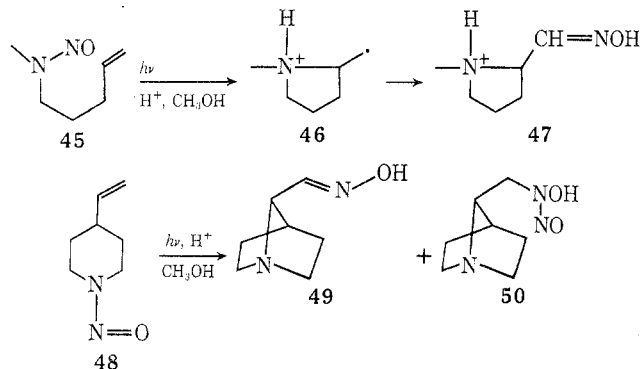
Intramolecular photoaddition of a nitrosamine group to a suitably located π bond such as **45** favors formation of a five-membered azacycle as with other radicals,⁴² even if the intermediate C radical **46** is

(41) Y. L. Chow, S. C. Chen, and D. W. L. Chang, *Can. J. Chem.*, **49**, 3069 (1971); D. W. L. Chang, M.Sc. Dissertation, Simon Fraser University, 1970.

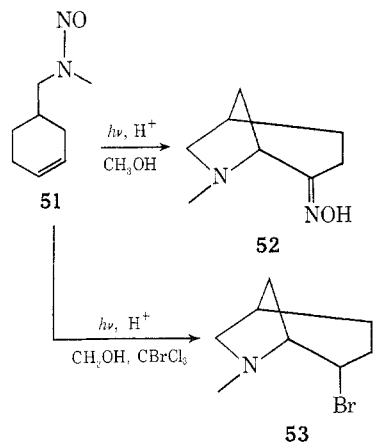
(42) A. L. J. Beckwith, *Chem. Soc., Special Publ.*, No. 24, 239 (1970).



less stable than the alternative six-membered species; a quantitative yield of a mixture of syn and anti oximes 47 has been obtained.⁴³ Cyclization of the aminium radical derived from 48 has to overcome the ring strain and, accordingly, gives a lower yield (46%) of 49 and 50; photoelimination and pho-



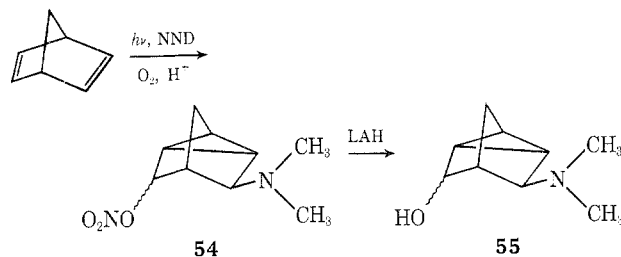
to-reduction also take place extensively during photolysis.⁴³ That intramolecularly the energy barrier for aminium radical addition is much lower than for the corresponding H-atom abstraction is demonstrated by photolysis⁴³ of nitrosamine 51: the syn and anti isomers of azabicyclic oximes 52 are obtained in excellent yield. The allylic H-atom-nitroso



(43) Y. L. Chow, R. A. Perry, B. C. Menon, and S. C. Chen, *Tetrahedron Lett.*, 1545 (1971); Y. L. Chow, R. A. Perry, and B. C. Menon, *ibid.*, 1569 (1971).

group exchange reaction may have taken place, but only to an extent of not more than 2%.

The stepwise radical reaction of nitrosamine photoaddition is further confirmed by two synthetically useful variations of the process. As exemplified by the NNP photoaddition to cyclohexene in an acidic methanol solution under oxygen, NO is intercepted by oxygen to form⁴⁴ NO₃, which combines with the C radical intermediate to form *cis*- and *trans*-1-piperidino-2-nitratocyclohexane (40) in 60% yield.⁴⁵ A stereoisomeric mixture of tricyclic amino alcohols 55 has been prepared in 52% yield by the oxidative photoaddition of NND to norbornadiene followed by LiAlH₄ reduction.⁴⁶



In the presence of excess CBrCl₃, photolysis of nitrosamine 51 gives⁴⁷ *endo*-6-bromo-2-azabicyclo[3.2.1]octane (53) instead of oximes 52. The corresponding *exo* bromo isomer, if formed, may undergo rapid intramolecular displacement, leading to as yet unidentified products.

Concluding Remarks

Because *N*-nitrosamines are photolabile in dilute acidic solutions, we have been able to investigate the chemical behavior of aminium radicals under conditions that are significantly different than when they are generated from *N*-chloramines. While aminium radicals from both routes generally exhibit similar reactivities, their reactions with aromatic substrates differ. The aminium radicals generated from *N*-nitrosamines fail to yield substitution products with aromatic compounds⁴⁷ such as anisole, whereas those generated from *N*-chloramine undergo facile aromatic amination.⁹ This leads us to suspect that the latter may have less propensity to undergo elimination by itself and, therefore, have a longer lifetime than the former. It is of obvious interest to investigate the effect of acidity on the behavior of aminium radicals.

I express sincere gratitude to my coworkers whose names appear in the references for their experimental efforts and their lively discussions that have culminated in this account. Financial support from the National Research Council of Canada, Ottawa, is gratefully acknowledged.

(44) J. Hecklen and N. Cohn, *Advan. Photochem.*, 5, 157 (1968).

(45) Y. L. Chow, J. N. S. Tam, C. J. Colón, and K. S. Pillay, *Can. J. Chem.*, in press.

(46) K. S. Pillay, unpublished results.

(47) R. A. Perry, unpublished results.