Electronic and Steric Effects in Thermal Denitrosation of *N*-Nitrosoamides

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N-Alkyl-*N*-nitrosoamides undergo competitive reactions whose rates are dependent upon the interplay of a number of factors. There already exists a significant body of work delineating the effects of pH on the partitioning of the nitrosoamides along their deaminative ($-N_2$) and denitrosative ($-$"NO^+") pathways. In this paper, the issue of pH dependence is discussed with particular attention to nitrosoamide decompositions in nonaqueous media. The role of the acidity of the medium in the partitioning of the nitrosoamide between deamination and denitrosation and in the choice of deaminative pathways is revisited. In nonaqueous media under near-neutral conditions, the partitioning's pH dependence is evidently accompanied by a sensitivity to structural features in the nitrosoamide. Thus, diminution of steric crowding around the *N*-nitroso moiety as well as the presence of strongly electron-withdrawing acyl units (i.e., those derived from strong acids, e.g., tosyl and trifyl) increase the relative yield of amides by encouraging the denitrosative pathway. A mechanism for thermal denitrosation of nitrosoamides under near-neutral conditions is proposed in which rapid protonation at the acyl O rather than slow protonation at the amidic N is the first step in the reaction profile. A rate-limiting, bimolecular reaction between the O-conjugate acid and adventitious nucleophiles at the nitrosyl group then occurs followed by rapid tautomerization to amide.

Introduction

The issue of the competing modes of decompositions of *N*-nitrosoamides (**1**) has been debated for decades.[1−5] Impressive and convincing work by White,[1] Moss,[2] Challis,[3] Williams,[4] and many others[5] has led to the current beliefs that nitrosoamides decompose principally along deaminative ($-N_2$) and denitrosative (-"NO^+") pathways that depend on pH[3,4] and temperature.[1,2]

In aqueous acidic systems, protonation of the nitrosoamides is believed to occur rapidly at the acyl or nitrosyl O's (both reactions producing the same hydrogen-bonded O-conjugate acid, **2a**; Scheme 1, path a), and slowly at the amidic N.[3,4] Deamination then proceeds via species **2a** formed in a rapid preequilibrium step (Scheme 1, path a) and is believed to be the major pathway at low acidity.[3,4] In contrast, the rate-limiting N-protonation derives the N-conjugate acid, **2b**, that rapidly decays into a nitrous acid equivalent and the corresponding amide (Scheme 1, path b). This pathway predominates at higher acidity. [3,4]

The relative rates of the N- vs O-protonations are readily interpreted in terms of resonance interactions among the lone pair of electrons on the amidic N and the acyl and nitrosyl groups attached to the latter. Such mesomerism then would enhance the basicities of the acyl and nitrosyl O's but diminish that of the amidic N. The same argument is invoked to account for the pH profiles of these aqueous reactions. Thus, the electronically activated nitrosyl and acyl O's are protonated more easily (i.e., at lower acidities) than the amidic N, which because its electron pair is dispersed among the nitrosyl and acyl groups is poorly basic and becomes protonated only at lower pH values.

Under basic conditions, nitrosoamides may decompose via attack at the acyl group to form *trans*-diazotic acids and eventually diazoalkanes (Scheme 1, path c).[6a] Basic attack on nitrosoamides at the nitrosyl group to form the amide and nitrite appears feasible, but no reference to this reaction has been found (Scheme 1, path d).[6b]

Thermal decay of *N*-nitrosoamides has been extensively studied[1,2,7] and is believed to involve rate-limiting rearrangement possibly via a charge-separated, oxadiazetyl entity[7a] to the *trans*-diazotate ester followed by

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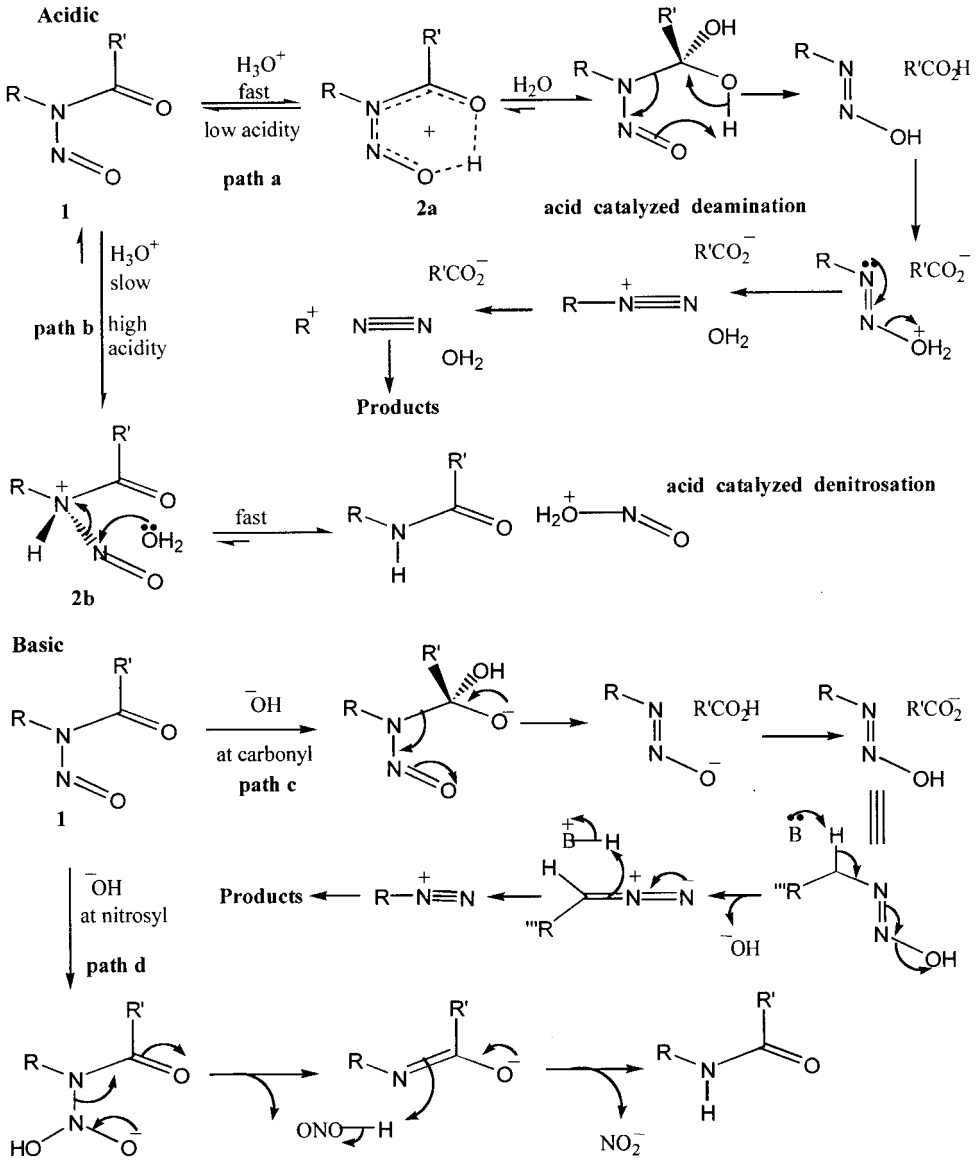
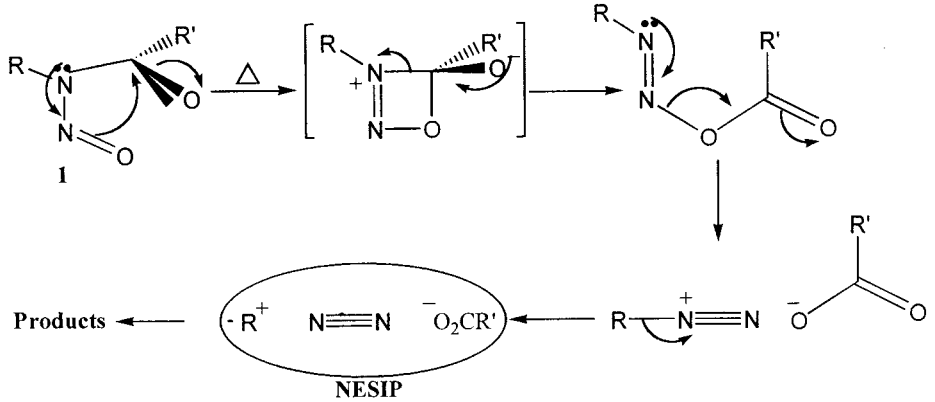
Scheme 1. pH-Dependent Decomposition Modes of *N*-Alkyl-*N*-nitrosoamides



Scheme 2. Mechanism of Thermal Deamination of N−Alkyl-N−Nitrosoamides[7a]



fragmentation to a tight ion-pair containing a diazonium ion and its nascent counterion (Scheme 2). Eventually, dediazoniation of the diazonium ion (if R is capable of forming an inductively or resonance-stabilized carbenium ion)[5b] generates the nitrogenous entity-separated ion pair (NESIP; Scheme 2),[1,2,5a] where the nitrogenous entity = N_2. The alkyl diazonium ion may effect alkylations if the alkyl cation is inaccessible (e.g., methyl, unstabilized primary, etc).[5b]

Acid-Catalyzed versus Thermal Deamination. The requirements for acid-catalyzed deamination in aqueous systems involve rapid protonation of either the acyl or nitrosyl O followed by nucleophilic attack by water at the activated carbonyl C (or sulfonyl S). Subsequent frag-

mentation into the carboxylic (or sulfonic) acid and the diazotic acid occurs. The latter after protonation then dediazoniates via a uni- or bimolecular path depending upon the nature of the alkyl group. The formation of the "hydrogen-bridged" O-conjugate acid is an inherent step in acid-catalyzed deamination and would require coplanarity of the acyl group, the amidic N, the nitrosyl group, and the H involved in hydrogen bridging (Scheme 1, path a). Thus, the stereoelectronic requirement for these deaminations would "lock" the nitrosyl and acyl groups in the same plane through hydrogen bonding.

In contrast, the stereoelectronic requirement for the thermal rearrangement is met only after a ~90° rotation about the N−N bond (from the planarity necessary for acidic deamination) bringing the nitrosyl group perpendicular to the carbonyl group (Scheme 2). This spatial arrangement is possible at relatively low acidity and elevated temperatures so hydrogen bonding does not keep the molecule in the planar geometry. Further, since thermal deaminations are encouraged by steric crowding of the *N*-nitroso amide moiety[1d,5h] (which is relieved on formation of the *trans*-diazotate ester),[7a] the studies done in aqueous acid on *N*-*n*-butyl-*N*-nitrosoacetamide at 25 °C, for example,[3] are strongly favored to undergo the acidic deamination. This would be so since the thermal process is inhibited by the low temperature and the lack of steric bulk in both the methyl and *n*-butyl groups around the O═N−N−C═O unit, as well as the high acidity that encourages the "hydrogen bridging" of the nitrosyl and acyl units.

Acid-Catalyzed Denitrosation. Acid-catalyzed denitrosation requires the slow protonation of the amidic N followed by rapid attack by nucleophilic water on the inductively activated nitrosyl N (Scheme 1, path b).[3,4] Clearly, this pathway is favored by strongly acidic aqueous conditions that could force protonation of the weakly basic amidic N and that could supply a large concentration of the only modestly nucleophilic water molecules.

To date, the only documented factors affecting the partitioning of the nitrosoamides along the deaminative/denitrosative pathways have been external (pH and temperature).[1−5] Further, the issue of thermal denitrosation has never been addressed. This work examines thermal denitrosations and the effects of intramolecular factors on this phenomenon. In particular, the classical roles of steric and electronic factors are examined.

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Table 1. Effects of Base[a] and Acyl Group on Denitrosation of *N*-Benzyl-*N*-nitrosoamides at 80 °C

acid moiety in nitrosoamide	equiv[b] of base[a]	relative yield of amide[c]
acetic	0	8.2
	2	1.5
propanoic	0	4.2
	2	0.7
dimethylacetic	0	0.5
trimethylacetic	0	0.0
	2	0.0
p-toluenesulfonic	0	24.8
	2	4.8
trifluoromethanesulfonic	0	40.0
	2	15.0

[a] For carboxamides, base = Py; for sulfonamides, base = 2,6-di-*tert*-butyl-4-methylpyridine (DBMP). [b] Equivalents. [c] Yields measured by ^{1}H NMR spectroscopy; standard deviation ~0.6.

Results and Discussion

Thermal Denitrosation of *N*-Nitrosoamides under Near-Neutral Conditions. A series of *N*-benzyl-*N*-nitrosocarboxamides and *N*-benzyl-*N*-nitrososulfonamides were thermally decomposed in chloroform-*d* at 80 °C. The product distribution was determined by ^{1}H NMR spectroscopy. The *N*-benzyl-*N*-nitrosoamides were employed in the present study because their formation of NESIPs containing benzyl carbocations through thermolysis has been well documented and is well understood.[1a,7] The thermolyses were performed under near-neutral conditions in chloroform (vide infra) so as to minimize competition from the acid-catalyzed pathways that require aqueous acid to provide both a proton source for N-protonation and water as the denitrosating nucleophile. A common, elevated temperature was used for all decompositions to allow ready comparison of the data and to compensate for the large half-lives of the *N*-nitrosotosylamide and the nitrosocarboxamides with simpler acyl portions.[1d,5a,7f] Further, the "H-bridging" (that would encourage the acidic deamination) would be readily disrupted at this temperature.

Runs were performed in the presence and absence of pyridines as proton sponges. For the nitrosocarboxamides, pyridine was employed as the base because it was inert to the reagents and products. But for the nitrososulfonamides, 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) was used because pyridine was found to react with the sulfonate esters to form *N*-benzylpyridinium ions. This secondary reaction was eliminated through use of the sterically hindered DBMP.

The data (Table 1) show several noteworthy trends concerning the yield of amides, i.e., the extent of denitrosation. (1) It decreased in the presence of base, (2) it decreased with increasing steric bulk at the acyl position[8a] [indeed no denitrosation occurs in the pivaloyl (= trimethylacetyl) series], and (3) it increased with the rising strength of the acid from which the acyl moiety is derived (carboxylate to tosylate, to triflate).[8a]

The Effect of the Acidity of the Medium on Thermal Denitrosations. In thermolyses of nitrosotriflamides, denitrosation accounts for 40% of the products in the absence of base but for only 15% in the presence of DBMP (Table 1). For nitrosotosylamides, however, denitrosation accounts for 25% of the products in the absence of base, but only ~5% in the presence of DBMP (Table 1). Similar diminutions in amide yields in

the presence of base are observed in the *N*-nitrosocarboxamide series (Table 1).

This result indicates that like the denitrosations in aqueous acid, the thermal nonaqueous reaction under near-neutral conditions is acid-catalyzed. The formation of the N-conjugate acid, **2b**, in the low acidity of the current media *especially when pyridines are employed*, however, does not appear reasonable. Hence, a difference between the denitrosative mechanisms in aqueous acid and the present nonaqueous, near-neutral system would appear to exist. Evidently, the reaction is still acid-catalyzed, but (1) denitrosation is occurring at low acidity and hence (2) the site of protonation leading to denitrosation is not the weakly basic amidic N. To the extent that this is true, the conjugate acid along the reaction path is not the N-conjugate as in the aqueous systems,[3,4] and further, the protonation obviously involving a modestly basic site would be fast. The only reasonable sites for protonations are the nitrosyl O or the acyl O (vide infra). Unlike in the aqueous system, two distinct species will arise from O- vs N-protonation (vide supra).[3,4]

Electronic Effects in Thermal Denitrosation. From the sensitivity of the yield of amide to the variation in the acyl unit from carboxyl to tosyl to triflyl, it appears that the extent of denitrosation depends, at least in part, on the acid-derived moiety in the starting nitrosoamide. Two properties of the acyl moiety may be relevant to this observation: (1) the basicity of the acyl O's and (2) the electron-withdrawing ability of acyl group. With respect to the relative basicities of the acyl O's, although the carbonyl-O of the carboxamides is presumably more basic than the sulfonyl-O's of the sulfonamide, the O-protonations are unlikely to be the step that distinguishes the behavior of the carboxamides from the sulfonamides. This interpretation is likely to be true since, with few exceptions,[9a,b] proton transfer to oxygen bases is very fast and essentially proceeds on encounter.[9c] In terms of electron-withdrawing effects, however, when the sulfonamide is protonated it ostensibly acts as a better electron-sink than the conjugate acid of the carboxamide (due to classical charge dispersal via resonance, induction, and sheer size).

Since the extent of denitrosation under these conditions depends on the electron-withdrawing ability of the acyl moiety, it would appear that the rate-determining step or one preceding it (but after the initial rapid protonation) for thermal denitrosation involves a step in which electron density is actively shunted (by resonance) into the acyl unit. If this is true, then initial protonation of the nitrosoamide probably occurs at the acyl O rather than the nitrosyl O, thus enhancing the flow of electron density into the acyl group.[8c]

The Effect of Added Nucleophiles on Denitrosation. *N*-Benzyl-*N*-nitrosotosylamide was allowed to decompose in DMSO-d_6 at ambient and elevated temperatures; in some cases, selected nucleophiles were added. Despite its higher thermal stability[7a,d] the *N*-nitrosotosylamide was chosen because of its ability to generate relatively large yields of amide via denitrosation (Table 1). DMSO was chosen because of its high polarity, which tends to accelerate nitrosoamide decomposition[7a] and encourage dissolution of the salts; it is also inert to the added nucleophiles.[7a] The nucleophiles employed were Br^-, CN^-, and I^- (n = 5.7, 6.8, and 7.4, respectively),[10] which were utilized as their Et_4N^+ salts. The *N*-nitrosotosylamide (at δ 4.97, which undergoes no detectable deamination after 48 h at 50 °C in DMSO) was incubated separately in DMSO with 1 molar equiv of the tetraethylammonium salts at 20 °C in the dark. No reaction was observed in the X = Br^- case; for X = CN^- and I^-, however, benzyl alcohol (δ 4.50) and *N*-benzyltosylamide (δ 3.93) (48%:52% and 40%:60%, respectively) were observed.

Since no deamination is occurring at this temperature, the reaction products must arise from an independent pathway that is sensitive to the nucleophilicity of the added species (vide supra). We propose that the active nucleophiles attack the *N*-nitrosotosylamide as in paths "a" and "b" in Scheme 3. Path "a" ostensibly offers less steric hindrance than does path "b", which would explain why the bulky iodide has a greater preference for it than does the smaller cyanide ion. Interestingly, neither water (n = 0) nor bromide (n = 5.8) appear sufficiently nucleophilic to attack the *N*-nitrosotosylamide under these conditions. The similarity of the % amide and % alcohol as well as the similarities in relative yields with the different active nucleophiles suggest that nucleophilic attacks on the nitrosyl and sulfonyl groups have similar rate constants. Interestingly, neither benzyl bromide, benzyl cyanide, nor benzyl iodide was detected (absence of signals at δ 4.53, 4.05, and 4.75, respectively), indicating that the potential pathway "c" (Scheme 3) is not competitive here.

When solutions of the *N*-nitrosotosylamide in DMSO were incubated at 20 °C in the presence of Br^-, I^-, and CN^-, significant nitrosoamide hydrolyses[7d] to benzyl alcohol occurs in the polar, deliquescent DMSO. The observed benzyl alcohol probably also derives somewhat from path "b" (Scheme 3) to a small extent, but largely from hydrolysis of the labile nitrosoamides under these conditions. Superimposed upon alcohol formation is denitrosation leading to amide formation.

Interestingly, at higher salt and nitrosoamide concentrations, the rate of nitrosoamide disappearance fell linearly with decreasing concentrations of the *N*-nitrosoamide and of the active salt (Table 2), suggesting a first order dependence on both [nitrosoamide] and [salt]

(8) (a) The aqueous acidities of the acetic acid derivatives fall slightly with increasing steric bulk. Thus, for the series $MeCO_2H$, $EtCO_2H$, $^iPrCO_2H$, and $^tBuCO_2H$, the pK_a values are 4.8, 4.9, 4.9, and 5.0, respectively.[8b] Thus, the acidity and steric features are not truly independent variables but may be treated roughly as such because of the following: (i) the ΔpK_a of 0.2 would appear to be less important than the significant increase in bulk from Me to ^{t}Bu, (ii) despite the increase in bulk from Et to ^{i}Pr, no change in pK_a occurs, and (iii) the yield of amide rises dramatically in the series carboxylate (p$K_a \sim 4.9$) to tosylate (p$K_a \sim -6.5$) to triflate (p$K_a \sim -10$) indicating that the suggested dependence of % denitrosation on the acidity of the acyl moiety is valid. (b) *Stability Constants* and *Stability Constants Supplement*; The Chemical Society, London, 1964 (Special Publication 17) and 1971 (Special Publication 25); No. 1. (c) The possibility exists of an equilibrium involving proton transfer between the acyl O and the amidic nitrogen especially at elevated temperatures (which disrupts H-bonding) in a fairly nonpolar solvent (which may enhance proton acidity). However, the fact that denitrosation is significant at 20 °C in DMSO in the presence of CN^- and I^- would suggest that such an equilibrium would not be important. (d) When the nitrosotosylamide is heated in $CDCl_3$ dried by distillation from P_2O_5 no denitrosation occurs.

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Scheme 3. Pathways for Reaction of Nucleophiles with N-nitrosoamides

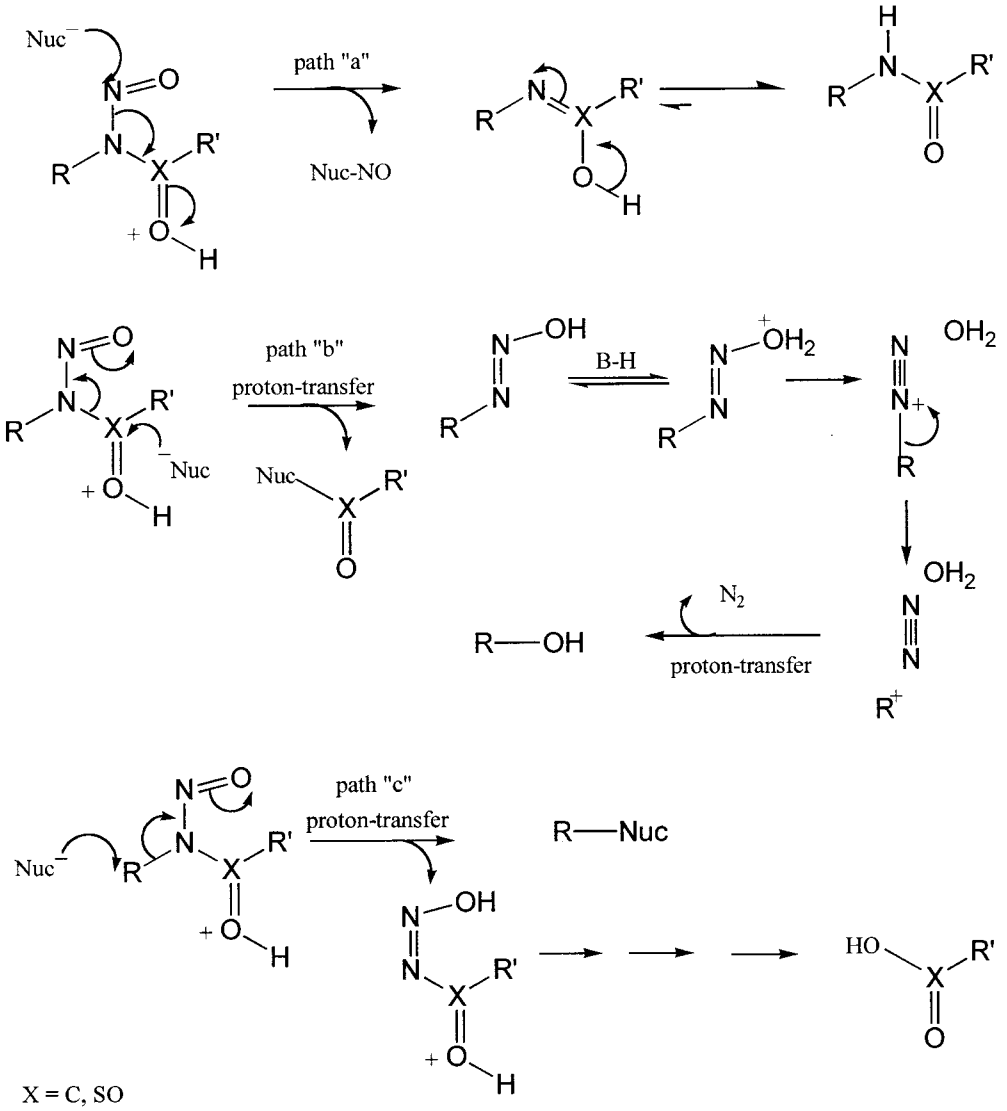
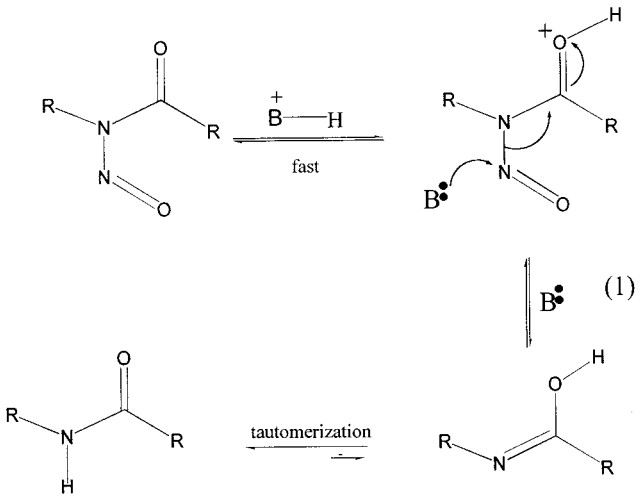


Table 2. Kinetic Data[a,b] for Reaction of *N*-Benzyl-*N*-nitrosotosylamide with Cyanide in DMSO at 20 °C

$[NTS^c]_o$ (M)	$[CN^-]_o$ (M)	Δ(% NTS)/Δt (min^{-1})	approximate[d] relative rate
0.0625	0.125	3.9[e]	1
0.125	0.125	4.0[e]	1
0.25	0.125	4.0[e]	1
0.125	0.25	4.3[e]	1
0.25	0.25	8.2[e]	2
0.25	0.5	16.3	4

[a] Method of initial rates used; decomposition after only 1 min (~5% reaction) was considered. [b] Runs were performed in at least triplicate. [c] NTS = *N*-Benzyl-*N*-nitrosotoluenesulfonamide. [d] Rounded to nearest whole number. [e] Standard deviation ~1.0.

(vide supra; eq 1).[11] It is to be noted, however, that the reaction rate levels off and becomes essentially constant at lower [nitrosoamide] and [salt] concentrations (Table 2). Ostensibly, in this concentration-insensitive phase, denitrosation does not compete with nitrosoamide hydrolyses.[7d] The insensitivity of the system to [salt] in this phase of the plot further supports the belief that path "b", Scheme 3 is poorly competitive in these reactions.



(1)

(11) The formation of amide but no ester (i.e., denitrosation without deamination) is due, in part, to a smaller activation energy for the former process. Additionally, since deamination is first order in the nitrosoamide[5h,7a] and zero order in the nucleophile, its rate is unaffected by the concentration of the nucleophile. Conversely, denitrosation is first order in both the nitrosoamide and nucleophile and thus a high concentration of the latter further enhances the denitrosative pathway over the deaminative one. Nitrosoamide hydrolyses however, which are also zero order in the nucleophile do successfully compete with denitrosation and at low [salt] when denitrosation essentially ceases only nitrosoamide hydrolysis occurs.

Table 3. Dependence of Yield of Amide[a] on the Nucleophilicity[b] of Added Anions[c] for Decomposition of *N*-Benzyl-*N*-nitrosotosylamide in DMSO at 80 °C

anion[c]	nucleophilicity[b]	relative % amide[a]
I^-	7.4	87.2
CN^-	6.8	42.0
Br^-	5.7	35.6

[a] Yield relative to total amt of ester + amide. [b] Data from ref 10. [c] Anions employed as $Et_4N^+X^-$.

Additionally, the extent of denitrosation (and hence the rate of amide formation), as evidenced by the yield of amide, rose systematically with the nucleophilicity of the ion (Table 3). These results suggest that both the nitrosoamide and the added salt (= nucleophile) are involved prior to, or at the rate-determining step (RDS) leading to denitrosation.

Steric Effects in Thermal Denitrosation. With respect to steric effects in the reaction, as the size of the acyl group rises from methyl to ethyl, to isopropyl, to *tert*-butyl, the yield of amide falls from 8.2 to 4.2, to 0.5, to 0, respectfully, in the absence of base (Table 1). Evidently, denitrosation is discouraged by steric hindrance at the acyl group. Ostensibly, steric inhibition of resonance between the *N*-nitroso moiety and the amido carbonyl group mitigates against the efficient transmission of electron-density between them. It is interesting that although steric crowding at the *N*-nitroso moiety encourages thermal deamination,[1d,5h] it inhibits the competitive thermal denitrosation.

A Proposed Mechanism for Thermal Denitrosation. The dependence of thermal denitrosation upon the electron withdrawing ability and size of the acyl moiety, the improbability of N-protonation under nonaqueous, near-neutral conditions,[8c] and the sensitivity of amide formation to the identity and concentration of added nucleophiles suggest that the mechanism of thermal denitrosation occurs as follows. The first step is a rapid protonation of the nitrosoamide at the acyl O; the resultant O-conjugate acid then suffers attack at the nitrosyl N by an appropriate nucleophile (e.g., adventitious moisture).[8d,12a,b] This latter reaction is encouraged by electron donation into the acyl moiety. Such π-interaction is apparently required to generate the tautomer of the resultant amide (eq 1).

Protogenesis under Near-Neutral Conditions. The proposed mechanism for thermal denitrosation requires a fast, initial protonation of the acyl oxygen of the nitrosoamide (eq 1). The question arises, however, as to the source of the protons under these near-neutral conditions.

Interestingly, in the *N*-nitrosotosylamide decompositions [but not the *N*-nitrosoacetamide ones (vide infra)] in the presence of added iodide at 80 °C, the ratio of [% amide/% ester (alcohol)[12c] (vide infra)] is not constant over the course of the reaction (Table 4). Additionally, although plots of % nitrosoamide vs time yield very good binomial curves ($R^2 = 0.963-0.997$), the data are slightly better fit ($R^2 = 0.990-0.997$, respectively) to trinomial curves (although the highest order contribution is small, $\sim 10^{-3}$; Figure 1). In these *N*-nitrosotosylamide cases though, the related plots of ln(%nitrosoamide) vs time give straight lines (e.g., Figure 2; $R^2 = 0.992$). These observations suggest that although the *N*-nitrosotosylamide thermolyses approach simple-order ones, perhaps some autocatalytic process is involved in the *N*-nitrosotosylamide case to the extent that as the reaction progresses, agents are produced that accelerate the *N*-nitrosoamide decomposition. We believe that these "agents" are acidic.

Acids could conceivably be produced during nitrosoamide thermolyses from reversible deprotonation of the diazonium ion by its nascent counterion to yield the diazoalkane/acid pair.[13a] This reaction sequence is competitive when the alkyl group of the diazonium ion (e.g., Me)[13a] is incapable of forming a stable carbocation,[5d] thus allowing the diazonium ion to persist for bimolecular collision with the counterion.[13a,b] However, for mono- and diaryldiazomethanes when the putative cation (e.g.,

Table 4. Time-Dependent Ratio of % Amide[a]/% Ester (Alcohol)[b,c] for Decomposition of *N*-Benzyl-*N*-nitrosoamides in the Presence of Iodide in DMSO at 80 °C

	[% amide[a]/% ester (alcohol)[b,c]][d]	
time (min)	*N*-nitrosotosylamide	*N*-nitrosoacetamide
5		0.089
10		0.089
45	11.8	0.091
80	3.5	
120	2.9	0.089
180	3.1	0.088
240	3.1	0.088
310	2.7	0.089
370	2.5	

[a] The amide arises from denitrosation. [b] The esters (= benzyl acetate for the *N*-nitrosoacetamide and benzyl tosylate for *N*-nitrosotosylamide) are products of the deaminative pathway. [c] Benzyl tosylate hydrolyses to benzyl alcohol under these conditions; benzyl acetate is stable. [d] Runs performed in at least duplicate; maximum standard deviation ~0.2.

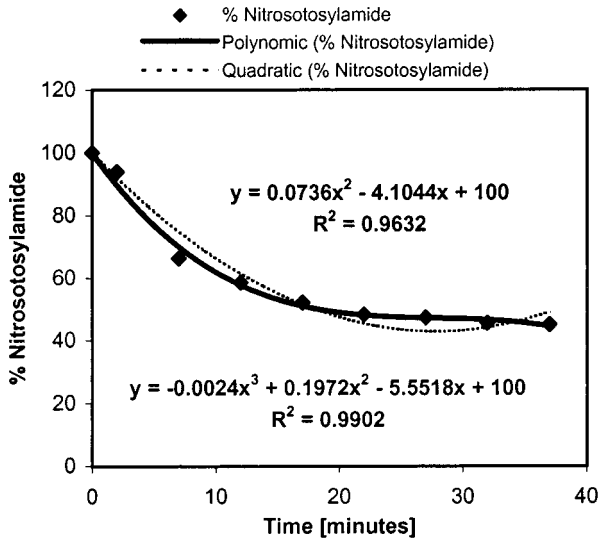


Figure 1. Overlay plot % *N*-nitrosoamide vs time (min) for decomposition of *N*-benzyl-*N*-nitrosotosylamide in DMSO and $Et_4N^+CN^-$ at 20 °C.

(12) (a) An alternative second step after rapid O-protonation is spontaneous denitrosation of the O-conjugate acid to form NO^+ and the tautomer of the amide. Although, this option is indeed a possibility, the formation of NO^+ in a solvent of only modest polarity such as $CDCl_3$ (in the present study) and in nonpolar solvents such as benzene[12b] and hexane[12b] appears unlikely. (b) Darbeau, R. W. Ph.D. Thesis, The Johns Hopkins University, Baltimore, MD, 1996. (c) In the thermolyses of the *N*-nitrosocarboxamides trace benzyl alcohol is formed from hydrolysis of the starting material. The ester is stable under these conditions and does not undergo appreciable hydrolysis.[7d] Benzyl tosylate, however, derived from *N*-nitrosotosylamide thermolyses, is labile under these conditions and decomposes into benzyl alcohol.

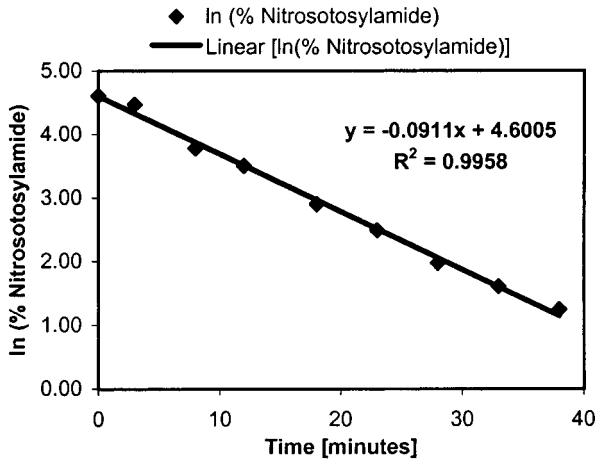


Figure 2. Plot of ln(% *N*-nitrosoamide) vs time (min) for decomposition of *N*-benzyl-*N*-nitrosotosylamide in DMSO and $Et_4N^+CN^-$ at 20 °C.

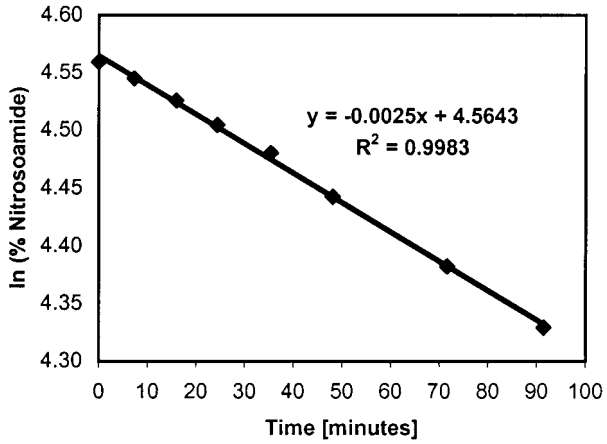


Figure 3. Plot of ln(% *N*-nitrosoamide) vs time (min) for decomposition of *N*-4-methoxybenzyl-*N*-nitrosopivalamide in cyclohexane-d_{12} at 18 °C.

benzyl and diphenylmethyl) is stable, the rate constant for dediazoniation is much faster than that for proton transfer and the diazonium−diazoalkane equilibrium is not competitive.[13c,d]

A likely initial source of protons is trace moisture present in the modestly hygroscopic chloroform or the deliquescent DMSO. Further, since chloroform undergoes slow hydrolysis in the presence of moisture to produce HCl, then the substrates in chloroform-based solution would be exposed to trace acids. It should be borne in mind that pyridinium ions are also mild acids so that even in the presence of pyridines as proton sponges, a proton source is readily available for protonation of the nitrosoamides.

Additionally, however, in the *N*-nitrosotosylamide case, facile hydrolysis of benzyl tosylate is clearly operational at elevated temperatures as evidenced by the absence of this ester as a reaction product and the appearance of large yields of benzyl alcohol. Consequently, as the reaction progresses, *p*-toluenesulfonic acid is generated which in turn effects more efficient protonation of the *N*-nitrosotosylamide than did the water molecules that formed them. Thus, although the number of acids in the system may be roughly the same, the acidity of the medium rises and so the reaction accelerates as it progresses.

Evidently, the corresponding hydrolysis of the carboxylate esters is not competitive here since benzyl acetate is stable under these conditions[7d,12c] and because no enhanced yields of benzyl alcohol are observed. Additionally, the % amide/% ester ratio is essentially constant over the course of the reaction (Table 4) and a plot of ln(%nitrosoamide) vs time yields a straight line (Figure 3; $R^2 = 0.998$).

Summary

While the considerable body of data concerning the acid-catalyzed denitrosations of *N*-nitrosoamides in the presence of aqueous acids appears valid, there is evidently a mechanistic divergence for thermal denitrosations occurring in nonaqueous, near-neutral conditions. It would appear that the reaction occurs by initial, rapid formation of an *O*-conjugate acid from protonation of the acyl O, followed by a rate-limiting bimolecular nucleophilic attack at the nitrosyl group to form an intermediate that tautomerizes to the amide (eq 1). Evidently, whereas thermal denitrosations of *N*-nitrosocarboxamides follows third-order kinetics as described, such reactions of *N*-nitrosotosylamides (and presumably any *N*-nitrosoamide that generates an ester that easily hydrolyzes into a strong acid) are prone to autocatalysis.

In addition to the well-documented external effects such as pH and temperature,[3,4] the thermal denitrosation reaction is subject to intramolecular effects as well. Thus steric crowding at the acyl moiety diminishes the extent of denitrosation whereas strongly electron-withdrawing acyl groups encourage amide formation.

Experimental Section

Materials and Methods. All commercial reagents were reagent grade and were used without further purification. Spectra were recorded on 300 MHz FT- NMR, FT-IR and UV−vis spectrometers.

Stability of *N*-Benzyl-*N*-nitrosoamides: Handling and Storage. *N*-Benzyl-*N*-nitrosocarboxamides are thermolabile oils and were stored under N_2 in sealed tubes immersed in liquid nitrogen. The nitrososulfonamides, which are solid and more stable, were stored in desiccators at −50 °C. They are labile in the presence of acids, bases, and moisture; being photolabile they were handled in the dark. **Caution!** Nitrosoamides should be handled with extreme care because of their possible mutagenicity[14a] and carcinogenicity (local and systemic).[14b] Efficient fume hoods and appropriate personal protection (chemical-resistant gloves, safety glasses, lab coat, etc.) are recommended when handling these compounds.

***N*-Alkylcarboxamides, *N*-Alkylsulfonamides, and *N*-Nitrosoamides.** The toluenesulfonamide was prepared using the method of Holmes and Ingold[15a] and nitrosated using the approach of Overberger and Anselme.[15b] All other amides were prepared using the method of Heyns and von Bebenburg.[15c] The preparations and physical properties of these compounds

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(14) (a) Lee, K.; Gold, B.; Mirvish, S. *Mutat. Res.* **1977**, *48*, 131. (b) Preussman, R.; Stewart, B. W. In *Chemical Carcinogenesis*, Searle, C., Ed.; ACS Monograph No. 182; American Chemical Society: Washington, DC, 1984; p 643.

(15) (a) Holmes, E. L.; Ingold, C. K. *J. Chem. Soc.* **1925**, *127*, 1800. (b) Overberger, C. G.; Anselme, J. *J. Org. Chem.* **1963**, *28*, 592. (c) Heyns, K.; v. Bebenburg, W. *Chem. Ber.* **1953**, *86*, 278. (d) White, E. H. *J. Org. Chem.* **1954**, 77, 6008.

and of their *N*-nitroso derivatives (prepared by the method of White[15c]) have been previously reported in refs 1a (the triflamide series), 7f (the pivaloyl series), and 7d (all other compounds).

Decomposition of *N*-Nitrosoamides. In a typical run, ~10 mg of *N*-nitrosoamide and 2 equiv of pyridine (or 2,6-di-*tert*-butyl-4-methylpyridine for the sulfonamides), as required, were dissolved in 500 μL of the appropriate solvent (DMSO-d_6 or $CDCl_3$) in an NMR tube. The NMR tube was then attached to a special holder on a vacuum line. Prior to evacuation at oil pump vacuum, the solution was frozen in liquid N_2 and then degassed and finally evacuated again and flame-sealed while still under vacuum. The sealed tube was then incubated at 80 °C until decomposition was complete (as verified by the absence of starting material by ^{1}H NMR).

Kinetic Analyses of *N*-Nitrosoamide Denitrosations. In most typical runs, ~10 mg of nitrosoamide and the required 1 molar equiv of tetraethylammonium salt were dissolved in 500 μL of DMSO at room temperature in an NMR tube. In the Method of Initial Rates, 500 μL of a stock solution containing the requisite amount of $Et_4N^+CN^-$ in DMSO was added to an equal volume of a stock solution of the *N*-nitrosotosylamide in DMSO in an NMR tube. The tube was then rapidly shaken. For the runs at 20 °C, a t_0 ^{1}H NMR spectrum was taken and ^{1}H NMR spectra were recorded at intervals during the decomposition. For runs at elevated temperatures, the sample tube was loaded into the NMR probe at ambient temperature and then heated rapidly to the appropriate temperature after which a t_0 ^{1}H NMR spectrum was recorded. As before, ^{1}H NMR spectra were then recorded at intervals. From the data, rates were calculated in the usual fashion.

Proof of the Absence of Benzyl Cyanide, Benzyl Bromide, and Benzyl Iodide from Decompositions in the Presence of Et_4N X (X = Br, CN, I). The absence of these compounds was shown by comparisons of their chemical shifts with those from decomposition mixtures and by spiking such mixtures with the authentic compounds when new peaks were observed. The chemical shifts of the benzylic methylene protons of benzyl bromide, iodide, and cyanide in DMSO are δ 4.53, 4.75, and 4.00, respectively.

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