those of others[33] follow this trend.

The lack of experimental data for bridged [n]annulene and [n]annulene ions is indicative of the difficulties in attempting to prepare these species. This correlates well with our predictions of low aromatic stability which anticipate problems in making the annulene ions of both variety.

Acknowledgment. We are thankful to Professors E. Vogel (Cologne), G. Hohlneicher (Cologne), and L. T. Scott (Reno) for very useful discussions about the chemical and physical properties of bridged annulenes. In addition, we thank the referees for their comments.

Registry No. 3, 2443-46-1; **3** radical cation, 78037-43-1; **3** radical anion, 35533-21-2; **3** dication, 77984-15-7; **3** dianion, 77966-07-5; **4**, 14458-51-6; **4** radical cation, 78085-70-8; **4** radical anion, 78085-71-9; **4** dication, 77966-08-6; **4** dianion, 77966-09-7; **5**, 78038-55-8; **5** radical cation, 78038-56-9; **5** radical anion, 78037-44-2; **5** dication, 68630-17-1; **5** dianion, 77984-14-6; **6**, 77965-99-2; **6** radical cation, 77966-00-8; **6** radical anion, 78037-45-3; **6** dication, 77966-10-0; **6** dianion, 77966-11-1; **7**, 77966-01-9; **7** radical cation, 77966-02-0; **7** radical anion, 78037-46-4; **7** dication, 78018-23-2; **7** dianion, 77966-12-2; **8**, 77966-03-1; **8** radical cation, 77966-04-2; **8** radical anion, 78037-47-5; **8** dication, 77966-13-3; **8** dianion, 77966-14-4; [n]polyacene (n = 10), 91-20-3; [n]polyacene (n = 14), 120-12-7; [n]polyacene (n = 18), 92-24-0; [n]polyacene (n = 22), 135-48-8; [n]polyacene (n = 26), 258-31-1; [n]polyacene (n = 30), 258-38-8; [n]annulene (n = 10), 3227-76-7; [n]annulene (n = 14), 2873-14-5; [n]annulene (n = 18), 2040-73-5; [n]annulene (n = 22), 3227-79-0; [n]annulene (n = 26), 3332-39-6; [n]annulene (n = 30), 3332-40-9; [n]annulene (n = 10) dication, 59975-80-3; [n]annulene (n = 10) dianion, 59947-29-4; [n]annulene (n = 14) dication, 59975-82-5; [n]annulene (n = 14) dianion, 77984-16-8; [n]annulene (n = 18) dication, 77984-17-9; [n]annulene (n = 18) dianion, 77984-18-0; [n]annulene (n = 22) dication, 77984-19-1; [n]annulene (n = 22) dianion, 77984-20-4; [n]annulene (n = 26) dication, 77984-21-5; [n]annulene (n = 26) dianion, 77984-22-6; [n]annulene (n = 30) dication, 78003-76-6; [n]annulene (n = 30) dianion, 77984-23-7; [n]annulene (n = 10) radical cation, 78037-48-6; [n]annulene (n = 10) radical anion, 78037-49-7; [n]annulene (n = 14) radical cation, 78037-50-0; [n]-annulene (n = 14) radical anion, 78037-51-1; [n]annulene (n = 18) radical cation, 78037-52-2; [n]annulene (n = 18) radical anion, 78037-53-3; [n]annulene (n = 22) radical cation, 77966-05-3; [n]-annulene (n = 22) radical anion, 78037-54-4; [n]annulene (n = 26) radical cation, 77966-06-4; [n]annulene (n = 26) radical anion, 78037-55-5; [n]annulene (n = 30) radical cation, 78037-56-6; [n]-annulene (n = 30) radical anion, 78037-57-7.

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Reactions of Nitrosoureas and Related Compounds in Dilute Aqueous Acid: Transnitrosation to Piperidine and Sulfamic Acid

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Received February 20, 1981

The transnitrosation reactions of four classes of nitrosamides in dilute aqueous acid were studied. Trialkyl nitrosoureas and nitrosoguanidines were found to react very rapidly in transnitrosations to piperidine, giving high yields (70–90%) of nitrosopiperidine at pH 1.7 (perchloric acid) or pH 3.3 (formate buffer). Methylnitrosourea reacted more slowly than either the trialkylnitrosoureas or the nitrosoguanidines and gave moderate yields (48%) of nitrosopiperidine at pH 1.7 and low yields (6%) at pH 3.3. Nitrosourethanes gave high yields at pH 1.7 and moderate yields at pH 3.3. Denitrosation rates (transnitrosation to a nitrite trap) are given for a series of monoalkyl- and trialkylnitrosoureas. An increase in the size of the alkyl group at N_1 decreased the rate of denitrosation. The kinetics of nucleophile-catalyzed transnitrosation from trialkylnitrosoureas to piperidine at pH 1.7 for a series of four trialkylnitrosoureas have been studied. Both the denitrosation of the donor and the nitrosation of the recipient were studied with respect to thiocyanate ion concentration. The denitrosation step was affected only at high [SCN^-], while the nitrosation step showed a first-order dependence on thiocyanate at most concentrations, with a "leveling off" effect observed at high [SCN^-]. The denitrosation step does not exhibit a true dependence on thiocyanate concentration but merely reflects the rapid rate of the nitrosation of the recipient piperidine at high [SCN^-] as a consequence of mass action. The behavior of nitrosoureas in transnitrosation reactions is compared with that of alicyclic nitrosamines. The latter differ from nitrosoureas in that they react more slowly, require a nucleophilic catalysis at the denitrosation step, and do not always nitrosate strongly basic amines.

The ability of a nitrosamine to act as a nitrosating agent (i.e., to effect transnitrosation) has been demonstrated for aromatic nitrosamines,[1,2] which can react via direct and indirect mechanisms, in organic and aqueous media.[3] Many aliphatic nitrosamines will transnitrosate under mild conditions in dilute aqueous acid with nucleophilic catalysts.[4,5]

Nitrosamides are less stable than nitrosamines in acid.[6] While much is known about the potential alkylating ability of nitrosamides in base via alkyl diazonium ion formation, the acid hydrolysis reactions and, in particular, the nitrosating ability of nitrosoureas have received little attention. Challis and co-workers studied the denitrosation and deamination reactions of *N*-nitrosopyrrolidone[7] and *N*-butyl-*N*-nitrosoacetamide,[8] and Williams has studied the denitrosation reactions of 1-methyl-1-nitroso-*p*-toluenesulfonamide.[9] In both cases, proton transfer from

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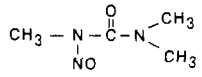
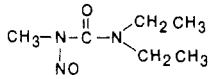
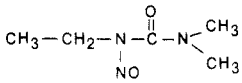
Chart I



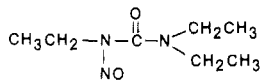
1,3,3-trimethyl-1-nitrosourea (TMNU)



1-methyl-1-nitroso-3,3-diethylurea (MDENU)



1-ethyl-1-nitroso-3,3-dimethylurea (EDMNU)



1,3,3-triethyl-1-nitrosourea (TENU)

solvent was the rate-limiting step; the denitrosation was unaffected by nucleophilic catalysts.

Hallett and Williams recently reported a study of the kinetics and mechanism of nitrosation and denitrosation of nitrosomethylurea (NMU) including the effects of nucleophilic catalysts on these reactions.[10] Their results are in accord with earlier work on nitrosamides[7-9] and clearly show that nitrosation and the reverse reaction of methylurea are first order in acid, methylurea, and nitrite and are not catalyzed by nucleophiles. They offer an explanation for these results based on an analysis of the individual steps in each reaction with the application of a limiting condition to both the forward and the reverse reactions.[10] The appearance of nitrous acid in denitrosation experiments was followed by trapping freed nitrous acid with *p*-chloroaniline and quantitating the coupling product formed with 3-hydroxynaphthalene-2,7-disulfonic acid. The results showed that formation of HNO_2 was almost complete at acidities ranging from 1.07 to 2.69 M H_2SO_4; i.e., under these conditions denitrosation was the only reaction; no deamination or other hydrolysis reactions occurred.

Snyder and Stock[11] have reported on both acid- and base-catalyzed decompositions of 1-methyl-1-nitrosourea (NMU) and *sym*-dimethyl- and 1,3,3-trimethylnitrosourea (TMNU)[12] in aqueous solutions (see Chart I). The acid-catalyzed decompositions of the mono- and trialkylnitrosoureas differed considerably. Denitrosation was the principal reaction of 1-methyl-1-nitrosourea (NMU) at pH <2. At pH 2–4, the compound was reported to undergo hydrolysis but not denitrosation. In contrast, trimethylnitrosourea was found to undergo predominantly denitrosation at all acid pH's. The authors studied the hydrolysis and denitrosation reactions of the three 1-methyl-1-nitrosoureas in some detail and found that methylamine was a principal product of the denitrosation reaction of NMU, but methanol was obtained from TMNU.

We present data for transnitrosation to piperidine and/or sulfamic acid for several nitrosoureas and related compounds. These compounds are of potential biological interest because of their carcinogenic[14] and mutagenic activity.[15] Because many nitrosoureas are potential contaminants in the food chain,[16] the study of their chemistry in aqueous acid is of particular interest in terms of possible in vivo reactivity. The results of Hallett and Williams[10] and of Snyder and Stock[11] are generally in accord with our observations with alkylnitrosoureas in transnitrosation reactions, although some minor differences are noted.

Table I. Transnitrosation to Sulfamic Acid at pH 1.5[a]

donor, *N*-nitroso-	τ, min[b]	k, s^{-1}[c]	k, s^{-1} (with NaSCN)
N-methylurea	25	4.78×10^{-4}	
N-propylurea	57	2.43×10^{-4}	
N-isobutylurea	160	7.90×10^{-4}	
N-(2-hydroxyethyl)urea	69	1.99×10^{-4}	
N-methylurethane	110	1.48×10^{-4}	
N-ethylurethane	87	1.61×10^{-4}	
N,N',N'-trimethylurea	18.8	6.03×10^{-4}	
N-methyl-*N',N'*-diethylurea	19	7.38×10^{-4}	8.30×10^{-4}
N-ethyl-*N',N'*-dimethylurea	31	3.81×10^{-4}	
N,N',N'-triethylurea	38	3.05×10^{-4}	2.76×10^{-4}

[a] Reaction conditions: 0.05 M nitrosourea, 0.1 N $HClO_4$, 0.05 M HSO_3NH_2. Reactions of monoalkylnitrosoureas were run at 50 °C; the nitrosourethanes and the trialkyl nitrosoureas were run at 20 °C. [b] Half-lives determined from a plot of concentration vs. time for the disappearance of the nitrosourea. [c] First-order rate constant for disappearance of the nitrosourea.

Results and Discussion

We studied the reactions in aqueous acid of four classes of nitrosamides, including four monoalkylnitrosoureas, two nitrosourethanes, two nitrosoguanidines, and four trialkylnitrosoureas. Two types of reactions were studied: denitrosation (transnitrosation to a nitrite trap to give gaseous products, which makes the reaction irreversible) and transnitrosation (transfer of the nitroso group from the nitrosourea to an amine such as piperidine to form a stable product).

Denitrosation. Denitrosation provides a convenient method for studying the first step in a transnitrosation reaction, the loss of the nitroso group from the donor. All denitrosations were carried out in 0.1 N $HClO_4$. The nitroso compound and the sulfamic acid trap were equimolar at 0.05 M. The pH of the reaction mixture was 1.5. Denitrosations of the monoalkylnitrosoureas were run at 50 °C, while others were carried out at 20 °C. Data are presented in Table I.

When all the reactions were treated as first order, rate constants could be obtained from a least-squares treatment of the data ($\ln a/x$ vs. t, where a is the initial concentration of the nitrosourea and x is the value at time t), with correlation coefficients in all cases being >0.990. However, when half-lives were determined from a plot of concentration vs. time, a plot of half-life vs. initial concentration did not always produce a line of slope = 0 (which is the case when first-order kinetics are followed). The trialkylnitrosoureas and NMU obeyed first-order kinetics by this criterion, but *N*-methyl-*N*-nitrosourethane obeyed zero-order kinetics, and all the other nitrosoureas gave fractional orders (less than 1) for 30–50% of the reaction period (i.e., ≤1 half-life) with a gradual change to first-order kinetics. One possible explanation of this behavior

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(12) Abbreviations used in this paper are as follows: 1-methyl-1-nitrosourea, NMU; 1-methyl-1-nitroso-3,3-dimethylurea, TMNU; 1-ethyl-1-nitroso-3,3-dimethylurea, EDMNU; 1-methyl-1-nitroso-3,3-diethylurea, MDENU; 1-ethyl-1-nitroso-3,3-diethylurea, TENU. Structures are shown in Chart I.
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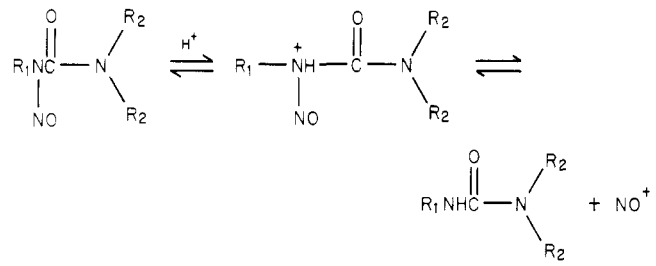
Scheme I



is that more than one reaction is being observed, such as a hydrolysis reaction competing with denitrosation. It is also possible that for some of these compounds renitrosation of the urea competes favorably with reaction of the free [NO^+] with the sulfamic acid trap.

It is apparent from the data that for both mono- and trialkylnitrosoureas increasing the size of the alkyl group at N_1 retards the loss of the nitroso group. This observation may be rationalized as anticipated behavior if the mechanism proceeds by protonation of N_1 as the slow step in the reaction (Scheme I), as proposed by Challis and Jones[7] for denitrosation of nitrosamides and later verified by Williams et al.[9]

When R_1 is large, protonation at N_1 may be somewhat hindered. Examination of models indicates that minor changes in structure (e.g., when methyl is replaced by ethyl at R_1 or R_2) have a considerable steric effect, producing crowding around the N–CO–N core. Snyder and Stock[13] examined the NMR and IR spectra of a number of mono-, di-, and trialkylnitrosoureas. They found that increasing the steric bulk of R_2 substituents led to changes in the IR spectra that could be interpreted as arising from a compressional distortion of the $C–N_3$ bond (as opposed to a torsional distortion). In any event, the magnitude of the change in denitrosation rates with increasing steric bulk at R_1 seems contrary to expectation were relief of steric strain the only consideration. It is possible that steric strain is not greatly different in the urea and corresponding nitrosourea but that strain in the transition state, with the protonating species attacking N_1 is great, and hence protonation when R_1 is large is not favored.

Transnitrosation. Transnitrosation refers to the transfer of a nitroso group from a nitroso compound to a suitable recipient, usually an amine, to form a new nitroso compound. While many nitroso compounds undergo this reaction, only diphenylnitrosamine is known to undergo a direct, uncatalyzed reaction in aqueous solution.[3] Many alicyclic nitrosamines have been found to undergo transnitrosation at moderate acid pH's (1–3), in the presence of a nucleophilic catalyst such as halide or thiocyanate ion.[4,5] These reactions have been shown to proceed via protonation of the donor nitrosamine followed by nucleophilic attack by [SCN^-] to produce a small steady-state concentration of the powerful nitrosating agent NOSCN. If no recipient amine or trap is present, denitrosation of the donor does not proceed further. The net effect is that nitrosamines are quite stable in dilute acid.

A transnitrosation reaction involving aliphatic nitrosamines is an equilibrium process, governed by the relative rates of nitrosation of the recipient amine and the renitrosation of the donor amine. Thus, if the donor nitrosamine is 4-methyl-1-nitrosopiperazine (derived from a weak and therefore easily nitrosated base) and the recipient amine is piperidine (a strong base which is nitrosated much more slowly than a piperazine), no transnitrosation takes place.

The behavior of nitrosoureas is not at all like that of nitrosamines. All the nitrosoureas studied were found to

Table II. Transnitrosation to Piperidine at pH 1.7[a]

donor, *N*-nitroso-	$\tau_{1/2}$,[b] min	% nitrosopiperidine at 1τ	% nitrosopiperidine at 18 h	10^4k_1,[c] s^{-1}
N-methylurea	495	21(6 h)	48	
N-methyl-*N'*-nitroguanidine	9	16	76	
N-methylurethane	34		53	
N-ethylurethane	27	15	57	3.16
N,N',N'-trimethylurea	19	26	71	2.44
N-methyl-*N',N'*-diethylurea	20	23	56	3.52
N-ethyl-*N',N'*-dimethylurea	24	30	70	4.86
N,N',N'-triethylurea	22	29	76	6.68

[a] $NaNO_2$ (0.05 M) plus 0.5 M NaSCN: percent nitrosopiperidine = 32% at 1τ and 80% at 18 h; 10^4k_1 = 58.7. [b] Reactions run at 50 °C. Concentrations of reactants: nitroso compound, 0.05 M; piperidinium perchlorate, 0.5 M; NaSCN, 0.5 M. [c] k_1 is the first-order rate constant for appearance of nitrosopiperidine.

Table III. Transnitrosations to Piperidine at pH 3.3 with Formic Buffer (I = 0.05)[a]

donor, *N*-nitroso-	% remaining donor, 300 min	% remaining donor, 18 h	% yield of nitrosopiperidine, 300 min	% yield of nitrosopiperidine, 18 h
N-methylurea	70	24	2.3	6
N-methyl-*N'*-nitroguanidine	*b*		56	
N-methylurethane	77	34	3.5	19
N-ethylurethane	72	53	6	55
N-ethyl-*N',N'*-dimethylurea	59	9	29	90
N,N',N'-triethylurea	66	7	40	93
N,N',N'-trimethylurea	55	7	40	93
N-methyl-*N',N'*-diethylurea	25		58	

[a] Reactions run at 50 °C. Concentrations of reactants: nitroso compound, 0.05 M; piperidinium formate, 0.5 M; NaSCN, 0.5 M. [b] Not determined.

nitrosate piperidine readily at pH's from 1 to 4, despite the fact that the ureas themselves are nitrosated far more rapidly than piperidine. (Data for transnitrosation to piperidine at pH 1.7 and 3.3 are given in Tables II and III.)

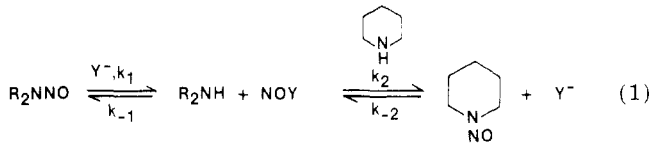
Of the nitrosamides studied, NMU was the least effective nitrosating agent, having a half-life for disappearance of 4.5 min and giving a 48% yield of nitrosopiperidine after 18 h. Three of the four trialkylnitrosoureas and 1-methyl-1-nitroso-3-nitroguanidine (MNNG) all gave yields of nitrosopiperidine of 16–30% in 1 half-life (9–24 min) and yields of 70–76% in 18 h. The first order rate constant for appearance of nitrosopiperidine, obtained from a plot of $\ln x_\infty - x$ vs. t, where x_∞ is the infinity concentration for nitrosopiperidine (taken at 18 h with no nitrosourea remaining) and x is the concentration at time t, shows some variation that may reflect some dependence on the donor nitrosourea in terms of reversibility or side reactions. All rate constants were about one order of magnitude slower than the rate constant for nitrosation of piperidine by 0.05 M $NaNO_2$ and 0.5 M NaSCN at pH 1.7.

At pH 3.3, in formate buffer, the transnitrosation reaction from nitrosamides to piperidine is much slower than at pH 1.7. However, trialkylnitrosoureas and nitroso-

guanidines give high yields of nitrosopiperidine at this pH, with conversion generally being quantitative. At pH 1.7, yields were somewhat lower, which can at least in part be attributed to the reaction of some of the nitrosating species with thiocyanate to give a sulfur precipitate. This precipitate was not seen at the higher pH.

Nitrosoureas are far more effective transnitrosating agents than nitrosamines, and this may well be a reflection of different mechanisms operating in each case. It is clear that many nitrosoureas can undergo transnitrosation very rapidly, indeed, far more rapidly than even the most labile alicyclic nitrosamines. But it is also true that ureas are nitrosated very rapidly at pH 1.7. In a competitive nitrosation experiment, 1-methyl-3,3-diethylurea (0.5 M) and piperidine (0.5 M) were treated with a deficiency of nitrite (0.05 M) at pH 1.7. A 100% yield of MDENU[12] was obtained immediately. MDENU then slowly disappeared as nitrosopiperidine was formed by transnitrosation.

The problem remains as to why nitrosoureas, no matter how rapidly they denitrosate, transnitrosate to piperidine, while only the least labile alicyclic nitrosamines nitrosate piperidine. The probable explanation may be found in a comparison of the mechanisms of denitrosation of the two classes of nitroso compounds. Aliphatic nitrosamine transnitrosation occurs only in the presence of a suitable recipient and a nucleophilic catalyst (Y^-). The freed nitrosating agent (NOY) is present only in a small, steady-state concentration. If the donor nitrosamine is a derivative of a weak base, then *renitrosation* of that base occurs far faster than *nitrosation* of the recipient piperidine, and no nitrosopiperidine is formed, i.e., $k_{-1} \gg k_2$ (eq 1). If



(1)

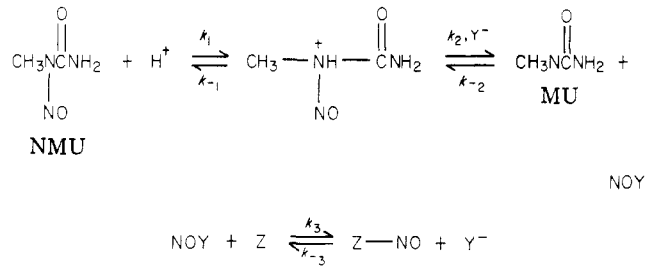
R_2NH is a base of strength comparable with that of piperidine, i.e., if k_2 does not differ greatly from k_{-1}, some nitrosopiperidine will form. Piperidine effectively removes NOY from the reaction mixture; i.e., k_{-2} is very small, and nitrosopiperidine will slowly accumulate.

Nitrosourea denitrosation differs from nitrosamine denitrosation in that nucleophilic catalysis does not take place.[16] By analogy to Williams' work with 1-methyl-1-nitroso-*p*-toluenesulfonamide,[9] one would expect the denitrosation of nitrosoureas to be independent of the nitroso recipient. At the pH's used in this study, dependence on the recipient was observed. At pH 1.5 a nitrosourea forms a pool of [NO^+] immediately. If no recipient is present (as in "decomposition" reactions), renitrosation can occur, and the [NO^+] can be lost eventually through reactions with the nitrosourea that lead to hydrolysis or by formation of oxides of nitrogen that will be lost as gas. This entire process is relatively slow, as one can see from a comparison of the half-lives for the disappearance of the nitrosoureas in the decomposition studies (typically times of 21–65 h at pH 2 for the four trialkylnitrosoureas were found by Lijinsky and Taylor[14]) with any of the reactions involving a recipient where typical half-lives are 20–40 min for the same group of compounds. Nitrosoureas can react very rapidly when a recipient such as piperidine is present; both the piperidine and the urea resulting from denitrosation compete for the nitrite pool. When [SCN^-] is present, the piperidine nitrosation will be catalyzed (vide infra), and the entire transnitrosation process will then be accelerated by mass action, even though the thiocyanate is not directly involved in the nitrosourea denitrosation.

Table IV. Formation of NOSCN

MDENU		MeON(NO)Me	
time, min	absorbance	time, min	absorbance
on mixing	0.056	on mixing	0.0131
1	0.078	1	0.0131
3	0.106	2	0.0134
6	0.118	3	0.0136
12	0.127	60	0.0185
20	0.159		
36	0.213		

Scheme II[a]



[a] When Z = piperidine, Z-NO = nitrosopiperidine; when Z = NaN_3, $N_2H_5^+SO_4^-$, NH_2SO_3H, or $NH_2SO_3NH_4$, Z-NO is unstable and yields gaseous products. Y^- = Br^- or SCN^-.

The following experiment was done to demonstrate the existence of a "NO^+ pool" in nitrosourea denitrosation as opposed to a steady-state NOSCN formation from a nitrosamine. MDENU (0.1 M), and NaSCN (0.1 M) were dissolved in 0.1 M $HClO_4$. The visible absorbance of this mixture was monitored at 460 nm, the λ_{max} for NOSCN.[19] *N*-Nitroso-*N*-methoxymethylamine, an aliphatic nitrosamine which transnitrosates very readily, was treated similarly (Table IV). The absorbance of NOSCN derived from MDENU increased rapidly, while that from the nitrosamine increased very slowly, never approaching the levels obtained with the nitrosourea.

Measurement of the formation of nitrosyl thiocyanate in this situation should provide a qualitative method for following the denitrosation reaction of the nitrosourea without directly affecting the reaction being studied, i.e., without driving the reaction forward. Also, there should not be any interfering absorbances at 460 nm, as there can be in following in the NN=O UV absorbance at ca. 350 nm.

Kinetics of Transnitrosation. The kinetics of nitrosourea transnitrosation are extremely complex. Mirvish[16] has shown that the experimentally observed form of the rate equation for nitrosation of methylurea (MU), using the method of initial rates, is as shown in eq 2. This result

$$\text{rate} = k[HNO_2][MU][H^+] \quad (2)$$

was verified recently by Hallett and Williams[10] and Casado et al.[17] Hallett and Williams[10] also studied the effect of nucleophilic catalysts (Br^- and SCN^-) on nitrosation of *N*-methylurea and denitrosation of NMU (Scheme II). They derived the following full rate expression for denitrosation of nitrosomethylurea [with hydrazine sulfate as the recipient (eq 3)] by using a steady-state treatment for

$$k_0 = \frac{k_1 h_A k_2[Y^-]k_3[Z]}{(k_{-1} + k_2[Y^-])k_3[Z] + k_{-2}k_{-1}[MU]} \quad (3)$$

the concentration of [NOY] and [$NMUH^+$]. This equation was then verified in part by the observation of a linear

(19) Stedman, G.; Whincup, P. A. E. *J. Chem. Soc.* **1963**, 5796–5799.

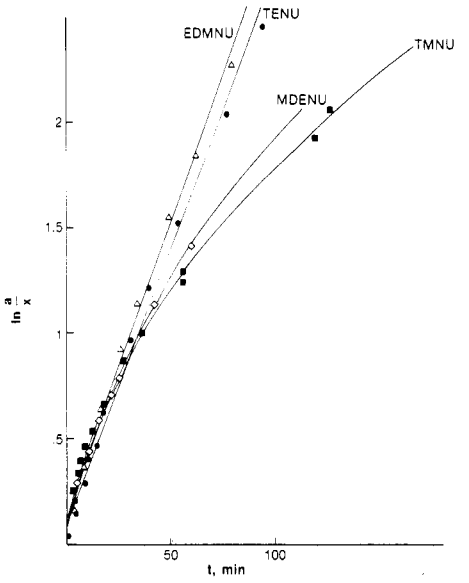


Figure 1. Disappearance of four different trialkyl nitrosoureas[12] in a transnitrosation to piperidine plotted as first-order processes. Only EDMNU and TENU exhibit first-order behavior (ln a/x vs. t is linear) in this situation.

relationship when k_0 was plotted against added *N*-methylurea. The authors also comment that the Y^- term is present since the nitrosation of Z (hydrazine sulfate in their example) will always be catalyzed by Y^-.

The kinetic expressions derived by Hallett and Williams[10] are, of course, for reactions of forms identical with those that we have studied. When Z is piperidine, k_3 is not as rapid as k_{-2}, but since k_{-3} is vanishingly small for all practical purposes, the formation of nitrosopiperidine is an irreversible step. In the subsequent discussion we will relate our kinetic results to the expression given in eq 3.

We have studied transnitrosation to piperidine for a number of nitrosoureas and related compounds. We have been particularly interested in the chemistry of the trialkylnitrosoureas which are relatively stable in both acid and basic solutions and are carcinogenic[14,20] but not direct-acting mutagens.[15] The four trialkylnitrosoureas studied were chosen because they have been subjected to biological tests, and some differences in behavior that may be related to structural differences have been observed.[14,15,20] In carcinogenicity studies the trimethyl- and methyl-3,3-diethylnitrosoureas were found to induce tumors in the central nervous system of the Fisher rat, while triethylnitrosourea produced mainly mammary adenocarcinomas (malignant tumors of the mammary glands).[20] In mutagenesis tests, only the triethyl- and trimethylnitrosoureas were mutagenic (on activation with rat liver S-9 microsomes).[15]

In Tables II and III we have presented the data on transnitrosation to piperidine in a very general form because product studies and attempted kinetic analyses of our data have implied that several side reactions occur after the initial stages of the reactions. Thus, simple kinetic treatments which may be valid for one compound are not necessarily valid for another. Even within the group of trialkylnitrosoureas there were interesting variations in kinetic behavior. When the disappearance of nitrosourea was followed (by high-pressure LC) and treated as a first-order process (ln a/x vs. t), TENU and EDMNU[12] followed first-order behavior (see Figure 1). MDENU and TMNU deviated from first-order behavior after approximately 1 half-life. If the data were plotted as $1/c$ vs. t (second-order behavior), TMNU gave a linear plot, TENU and EDMNU curved well away from the TMNU line, and MDENU gave a curve intermediate between the two extremes. A plot of half-life vs. initial concentration for the disappearance of each trialkylnitrosourea confirmed that the two nitrosoureas with methyl groups at N_1 exhibited first-order behavior.

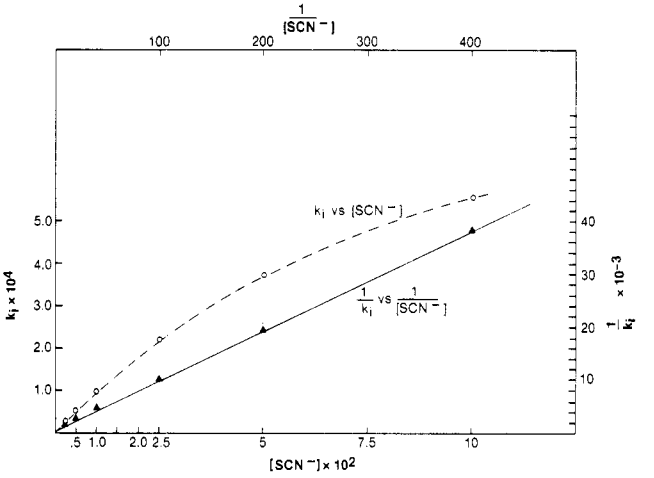


Figure 2. Thiocyanate-catalyzed transnitrosation from triethylnitrosourea to piperidine at varying thiocyanate concentrations. The plot of initial rate of formation of nitrosopiperidine (k_i, mol/min) vs. the thiocyanate concentration (molar, O) shows a deviation from linearity at high [SCN^-]. The double reciprocal ($1/k_i$ vs. $1/[SCN^-]$, ▲) is linear throughout the range studied.

We also studied nucleophilic catalysis in trialkylnitrosourea transnitrosations to piperidine, where one would expect to see catalysis of the nitrosation of piperidine but not of the denitrosation of the nitrosourea.[10] We found the anticipated catalysis of the piperidine nitrosation but also an apparent catalysis of the nitrosourea denitrosation at high thiocyanate concentration.

Triethylnitrosourea (TENU), which exhibited simple first-order behavior for denitrosation (vide supra) was used for this study. Kinetics were followed at 50 °C, in perchloric acid at pH 1.7. The concentration of piperidinium perchlorate was 0.50 M, that of triethylnitrosourea was 0.10 M, and the thiocyanate concentration was varied from 0.10 to 0.0025 M. Figure 2 shows a plot of k_i (initial rate) for formation of nitrosopiperidine vs. thiocyanate concentration. Values of k_i at 0.0025–0.025 M SCN^- reflect first-order dependence on thiocyanate while above 0.05 M the leveling-off effect of high [SCN^-] is seen. A double-reciprocal plot of $1/k_i$ vs. $1/[SCN^-]$ yields a straight line of slope 9.5×10^{-5} (also shown in Figure 2).

In contrast, data obtained for the denitrosation of TENU in this reaction exhibited a limited dependence on thiocyanate concentration when the catalyst is present at 0.025–0.1 M concentrations; at catalyst concentrations below 0.01 M the dependence disappears. The plot of ln a/x vs. t for 0.1 M NaSCN shows a deviation from linearity that may be attributed to a change in the kinetic expression at this high concentration of thiocyanate ($k_2[Y^-]$ becomes an important term). Diethylnitrosamine is not a prominent product in this transnitrosation reaction, although trace amounts are formed at late stages of the reaction. One might expect the formation of diethylnitrosamine to be a more prominent reaction in the "decomposition" reactions of TENU, i.e., reactions in

(20) Lijinsky, W.; Reuber, M. D.; Blackwell, B.-N. *J. Natl. Cancer Inst.* **1980**, *65*, 451–453.

(21) A product study of this reaction and related reactions of TENU are in progress and will be reported in a subsequent publication.

which TENU is placed in acid with no recipient amine or nitrite scavenger present. We were able to detect small amounts of diethylnitrosamine (<1%) in such situations. Snyder and Stock[11] reported that dimethylnitrosamine was found at long reaction times in their studies of the decompositions of TMNU. We have reported previously that diethylnitrosamine can be found in pH 1.5 and 3.5 solutions of MDENU after 66 h at ambient temperature.[23]

Conclusions

The various nitrosamides studied in this work all denitrosate sufficiently rapidly at pH 1.7 to allow them to participate in transnitrosation reactions. All are apparently capable of transnitrosating to sulfamate, morpholine, or piperidine.[22] This is in contrast to nitrosamines, for which the relative rates of nitrosation of amine recipient and the parent amine of the donor govern whether transnitrosation occurs.[5]

At pH 3.3, the transnitrosation reaction of these nitrosamides is slower than at pH 1.7 but much faster than the transnitrosation reactions of nitrosamines at the latter pH.[5] Furthermore, when trialkylnitrosoureas or nitrosoguanidines are donors, reactions give very high yields (≥90%) at the higher pH. Even *N*-methyl-*N*-nitrosourea gave a 6% yield of nitrosopiperidine under these conditions which indicates that, for this compound, some denitrosation occurs at this pH, although Snyder and Stock[11] have reported that the only reaction of NMU in the pH range 2–4 is hydrolysis. For several nitrosoureas, increasing the bulk of the alkyl group at N_1 retarded the reaction rate for transnitrosation. This supports the findings of Challis[7,8] and Williams[9,10] and their co-workers that protonation at N_1 is the slow step in nitrosamide denitrosation if steric crowding hinders approach to N_1.

The kinetic studies we have reported here on the effect of thiocyanate ion concentration on nitrosourea transnitrosation reactions show that the transnitrosation reaction to a recipient amine is favored by the presence of a nucleophilic catalyst; the loss of the nitroso group from the donor is not directly affected. In contrast, presence of a nucleophilic catalyst is essential in transnitrosation from a nitrosamine donor. It is clear that nitrosoureas and nitrosamines denitrosate by very different mechanisms and as a result behave very differently in transnitrosation reactions, the nitrosoureas being far more effective nitrosating agents. We would not make any sweeping generalization of this result in relation to the carcinogenicity of nitrosoureas. There is no obvious relation between rate of denitrosation and carcinogenicity. Those nitrosoureas which denitrosate the most rapidly (the trialkylnitrosoureas) are as potent carcinogens as those that denitrosate more slowly (the monoalkylnitrosoureas). Monoalkylnitrosoureas often give tumors at the site of application, as well as at distant sites when they are administered in the diet. This observation strongly suggests that despite the acid lability of these compounds, they are either transported to their site of action intact or they are converted to a metabolite which is then transported to their site of action. The possibility that a transnitrosation reaction is involved in one of these biochemical steps exists, of course.

Experimental Section

Caution: The alkylnitrosoureas are believed to be carcinogenic, and should be handled only with suitable precautions.

Materials. Organic chemicals were obtained from Aldrich or Eastman and were not generally purified further. Inorganic chemicals were Fisher ACS reagent grade. The solvents used were Burdick and Jackson "Distilled in Glass" grade.

The nitrosoureas used in this study were synthesized by standard methods described elsewhere.[14,23]

Kinetics. Rate constants for denitrosation were determined in the following manner. The nitrosourea (0.25 mequiv) and sulfamic acid (0.25 mequiv) were dissolved in 0.1 N $HClO_4$ (5 mL). Aliquots were taken at timed intervals, and the reaction was quenched by 1/50 dilution with water. Kinetics were followed by monitoring the disappearance of the nitrosourea peak by high-pressure LC (254 nm) on an Altex Ultrasphere ODS column (5 μm, 150 × 4.6 mm) at a flow rate of 1 mL/min of water/methanol, with a percentage of the latter sufficient to elute the nitrosourea in 4–6 min. Trialkylnitrosourea and nitrosourethane denitrosations were studied at 20 °C. Monoalkylnitrosoureas reacted more slowly, and were studied at 50 °C.

Transnitrosations to piperidine at pH 1.7 were carried out in the following manner. The nitrosourea (0.25 mequiv) was mixed with prewarmed (50 °C) solutions of piperidinium perchlorate (2.5 M, 1 mL), NaSCN (2.5 M, 1 mL) and $HClO_4$ (0.1 M, 3 mL), and kept in a temperature controlled bath at 50 °C. Aliquots were taken at timed intervals, and the reaction mixture was quenched and analyzed as described for the denitrosation reactions. The reactions at pH 3.3 were run in the same way except that pH 3.3 formate buffer (I = 0.05) was used rather than perchloric acid, and piperidine was present as the formate salt.

Kinetics of Transnitrosation from TENU to Piperidine (pH 1.7). Reaction conditions were as described above except that the concentration of TENU was 0.1 M in all cases, and the concentration of NaSCN was varied from 0.100–0.0025 M.

Formation of NOSCN from a Nitrosamine and a Nitrosourea. MDENU and NaSCN were dissolved in 0.1 N $HClO_4$ to make a solution that was 0.10 M in each reactant. In a parallel experiment *N*-nitroso-*N*-methoxymethylamine and NaSCN were dissolved in 0.1 N $HClO_4$. The absorbance of each mixture was followed at 460 nm for 1 h.

Acknowledgment. We thank Drs. G. M. Singer, C. J. Michejda, and W. Lijinsky for many helpful discussions. We also thank Dr. Lijinsky for providing some of the compounds used. This work was supported by Contract No. NO1-CO-75380 with the National Cancer Institute, NIH, Bethesda, MD.

Registry No. *N*-Nitroso-*N*-methylurea, 684-93-5; *N*-nitroso-*N*-propylurea, 816-57-9; *N*-nitroso-*N*-isobutylurea, 760-60-1; *N*-nitroso-*N*-(2-hydroxyethyl)urea, 13743-07-2; *N*-nitroso-*N*-methylurethane, 615-53-2; *N*-nitroso-*N*-ethylurethane, 614-95-9; *N*-nitroso-*N*,*N*′,*N*′-trimethylurea, 3475-63-6; *N*-nitroso-*N*-methyl-*N*′,*N*′-diethylurea, 50285-72-8; *N*-nitroso-*N*-ethyl-*N*′,*N*′-dimethylurea, 50285-71-7; *N*-nitroso-*N*,*N*′,*N*′-triethylurea, 50285-70-6; *N*-nitroso-*N*′-nitroguanidine, 21829-46-9; nitrosopiperidine, 100-75-4; *N*-nitroso-*N*-methoxymethylamine, 16339-12-1; NOSCN, 3985-25-9; NaSCN, 540-72-7; piperidinium perchlorate, 57367-18-7; piperidine formate, 77984-65-7; sulfamic acid, 5329-14-6.

(22) Singer, S. S. *IARC Sci. Publ.* **1980**, *31*, 111–118.
(23) Elespuru, R. K.; Lijinsky, W. *Food Cosmet. Toxicol.* **1973**, *11*, 807–817.