

adducts. Repeated preparative TLC resulted in the isolation of the major adduct as a difficultly crystallizable material which was recrystallized from chloroform-hexane: mp 273-276 °C; NMR (CDCl₃) δ 0.98 (dd, *J* = 7.8 and 3.4 Hz, H₁₀), 1.17 (t, *J* = 7.2 Hz, CH₂CH₃), 1.62 (dd, *J* = 7.8 and 6.8 Hz, H₈), 1.82 (br s, =CCH₃), 2.34 (d, *J* = 9.2 Hz, H₄), 2.63 [d(d), *J* = 6.0 Hz (*J*_{gem} not observable), H₆], 2.66 (dd, *J* = 19.0 and 7.2 Hz, H₃), 2.69 [d(d), *J* = 2.6 Hz (*J*_{gem} not observable), H₇], 2.82 (dd, *J* = 6.8 and 3.4 Hz, H₉), 2.99 (dd, *J* = 19.0 and 9.2 Hz, H₂), 3.37 (ddd, *J* = 9.2, 6.0, and 2.6 Hz, H₅), 3.53 (q, *J* = 7.2 Hz, OCH₂CH₃), 3.71 (dd, *J* = 9.2 and 7.2 Hz, H₁), 7.3 (m, aromatic H); mass spectrum, exact mass calcd for C₂₉H₂₈N₂O₅, *m/e* 484.199; found, 484.195.

The NMR spectrum of the crude reaction mixture showed two broad singlets at δ 1.82 and 1.88 in a ratio of 4:1.

Acknowledgment. The authors wish to thank Professor T. Fehner of our department for running the PES spectra and the Computing Center of the University of Notre Dame for providing computer time.

Registry No. 6, 4544-26-7; 7a, 108-31-6; 7b, 941-69-5; 8a, 73261-95-7; 8b, 73261-96-8; 9a, 73307-14-9; 9b, 73306-82-8; 11a/12a, 73261-97-9; 11b/12b, 73261-98-0; 14, 73261-99-1; 15, 73262-00-7; 17, 73262-01-8; 18, 73262-02-9; 19, 73262-03-0.

Reactions of Alkylnitrosoureas in Aqueous Solution¹

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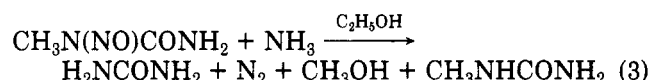
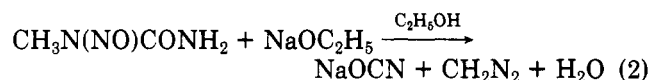
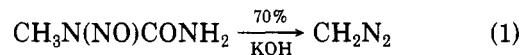
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Received September 20, 1979

The acid- and base-catalyzed decompositions of *N*-methyl-, *N,N'*-dimethyl-, and *N,N,N'*-trimethyl-*N*-nitrosourea in aqueous solution have been studied. Below pH 2, the *N*-methyl compound undergoes both denitrosation and hydrolysis. The denitrosation yields methylurea and nitrous acid. The hydrolysis yields largely methylamine, nitrogen, and carbon dioxide. The acid-catalyzed denitrosation and hydrolysis of the trimethylnitrosourea are somewhat more rapid than the corresponding reactions of *N*-methyl-*N*-nitrosourea. The denitrosation of this compound yields trimethylurea and nitrous acid. The hydrolysis yields methanol, dimethylamine, nitrogen, and carbon dioxide. The solvent isotope effect, *k*_{H₂O}/*k*_{D₂O} = 1.3, and the absence of chloride ion catalysis suggest that the denitrosation reaction proceeds by a rate-determining proton transfer which is followed by the rapid loss of the nitroso group. The results for the hydrolysis reaction are compatible with a formulation in which a hydrate of the nitrosourea is protonated in a rate-determining step to form a tetrahedral intermediate which subsequently decomposes to yield methyldiazonium hydroxide and a carbamic acid derivative. The base-catalyzed reactions of the mono-, di-, and trimethylnitrosoureas are first order in hydroxide ion over a broad pH range. The hydrolysis of *N*-methyl-*N*-nitrosourea yields methanol and derivatives of carbamic acid. Salt effects on the reaction rate are negligible except for the influence of lithium ion. The rate constants for the hydrolysis of the mono- and dimethyl compounds depend upon the buffer concentration at pH 9.5. These constants reach limiting values. The rate constants for the hydrolysis of the trimethyl compound also depend upon the buffer concentration, but a limiting value is not achieved. The solvent isotope effect for the base-catalyzed reaction, the exchange reaction of water-¹⁸O with the carbonyl group of the urea, and the fact that *N*-methyl-*N*-nitrosourea is hydrolyzed about 2.2 × 10⁴ times more rapidly than *N,N,N'*-trimethyl-*N*-nitrosourea suggest that the hydrolysis occurs by a mechanism in which a tetrahedral intermediate is formed. Often, the formation of this intermediate is rate limiting. However, under certain conditions, its decomposition to methyldiazonium hydroxide and a carbamate anion which decompose to form methanol and the other products may be rate determining.

N-methyl-*N*-nitrosourea and other *N*-alkyl-*N*-nitrosoureas have been implicated in chemical carcinogenesis.² Most workers in this field have focused attention on the alkylation of the nucleic acids by these substances.^{3,4} However, the nature of the alkylation reaction is unclear. Uncertainty exists, in part, because the *N*-alkyl-*N*-nitrosoureas have such a rich, diverse chemistry. In early work, Werner found that methylnitrosourea decomposed thermally to give nitrogen, methyl isocyanate, and water.⁵

He also found that it reacted with concentrated sodium hydroxide solution to produce diazomethane, with ethoxide ion in ethanol to give diazomethane, sodium cyanate, and water, and with ammonia in ethanol to yield urea, nitrogen, methanol, and some methylurea and dimethylurea⁵ (see eq 1-3). Boivin and Boivin subsequently reported that



methylnitrosourea decomposed in boiling water to give a stoichiometric yield of nitrogen.⁶ They also found that *N*-nitroso-*N,N'*-dimethylurea decomposed in a similar manner to give a quantitative yield of nitrogen, methyl isocyanate, and methanol.⁶ The nitrosoureas reacted with

(1) This research was supported by Grant No. CA20049, awarded by the National Cancer Institute, DHEW, and by the Illinois Division of the American Cancer Society. The NMR work was assisted by Grant No. CA-14599, awarded by the National Cancer Institutes of the Public Health Service.

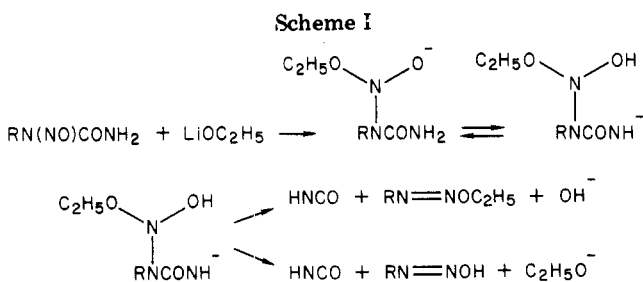
(2) (a) Lijinsky, W.; Garcia, H.; Keefer, L.; Loo, J.; Ross, A. E. *Cancer Res.* 1972, 32, 893. (b) Druckrey, H.; Preussmann, R.; Ivankovic, S.; So, B. T.; Schmidt, C. H.; Bucheler, J. Z. *Krebsforsch.* 1966, 68, 87. (c) Ivankovic, S.; Druckrey, H.; Preussmann, R. *Ibid.* 1965, 66, 541.

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(4) The influence of cyanate ion is discussed by: Knox, P. *Nature (London)* 1976, 259, 671.

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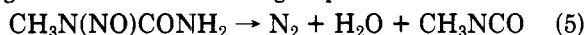
(6) Boivin, J. L.; Boivin, P. A. *Can. J. Chem.* 1951, 29, 478.



primary and secondary amines in boiling water to provide substituted ureas in good yield (eq 4). These results

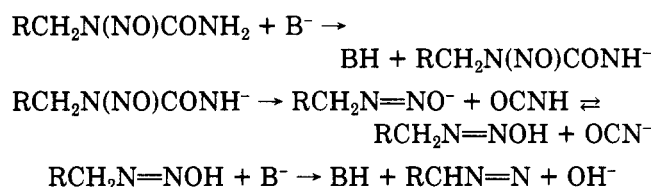
$$\text{CH}_3\text{N(NO)CONH}_2 + \text{RR}'\text{NH} \rightarrow \text{RR}'\text{NCONH}_2 + \text{N}_2 + \text{CH}_3\text{OH} \quad (4)$$

indicated that isocyanic acid or methyl isocyanate were among the decomposition products. Clusius and Endtinger investigated the spontaneous decomposition of methyl-nitrosourea at room temperature⁷ (eq 5). They showed that the methyl group in the urea was transferred to the nitrogen atom of the amido group.



In more recent work, Jones and his associates studied the reactions of bases with *N*-(2,2-diphenylcyclopropyl)-*N*-nitrosourea in organic solvents.⁸ They established that ethyl carbamate was not formed in the reaction with lithium ethoxide in ethanol and that lithium (2,2-diphenylcyclopropyl)diazotate, the intermediate which would form in the reaction of the ethoxide ion at the carbonyl carbon atom, was stable under the experimental conditions. These observations and other lines of evidence led them to propose that the ethoxide ion reacted at the nitrosyl group rather than at the carbonyl group (Scheme I). Hecht and Kozarich also studied the reactions of the nitrosoureas with strong bases in organic solvents.⁹ They found that *N*-methyl-*N*-nitrosourea reacted with sodium hydride in 1,2-dimethoxyethane to give diazomethane in quantitative yield as well as hydrogen and sodium cyanate. Observations of this kind prompted them to suggest that these reactions occurred following an initial proton abstraction (Scheme II).

Scheme II



The hydrolytic reactions of these nitrosoureas in water at ambient temperature have not received sufficient attention to permit the description of the reaction mechanism. McCalla and his associates reported that *N*-methyl-*N*-nitrosourea decomposed rather rapidly in acidic (pH 2) and basic (pH 9) solution but that the compound was more stable in dilute aqueous acid solutions.¹⁰ They suggested that the nitrosourea decomposed in the presence of acid by initial protonation on the nitrosyl oxygen atom with subsequent expulsion of the protonated nitrosyl

group. They did not propose a pathway for the reaction in basic solution. Garrett and his associates studied the rate of decomposition of several *N*-alkyl-*N*-nitrosoureas in buffered aqueous solution from pH 5.95 to 7.75.¹¹ They found that the rates of hydrolysis did not depend importantly on the structure of the alkyl group. They also reported that the reaction was not catalyzed by the buffers and that there were no appreciable salt effects. They proposed that the reaction occurred by the addition of hydroxide ion to the carbonyl group to form a tetrahedral intermediate which decomposed to form a diazonium ion and carbamic acid.¹¹ In related work, Lijinsky and Taylor studied the rates of hydrolysis of several trialkylnitrosoureas, including *N,N,N'*-trimethyl-*N*-nitrosourea.¹² They found that this urea was much less reactive than *N*-methyl-*N*-nitrosourea.

These investigations have not resolved the central problems concerning the manner in which these small but highly functional molecules decompose in water. The observations quite strongly suggest that the hydrolysis reaction has a distinctive pH rate profile. However, it is not clear whether the key reactions occur with the ureide protons or with the nitrosyl or carbonyl groups. The diverse results obtained for the reactions in organic solvents suggest that the reactions proceed by several paths with attendant variations in the product distribution. This information does not provide a suitable basis for the discussion of the reaction in water. Considerations of this kind and our interest in the possibility that the decomposition reactions of *N*-alkyl-*N*-nitrosoureas might be strongly influenced by the purine or pyrimidine constituents of the nucleic acids prompted us to examine the hydrolysis more thoroughly to define the rate-limiting step in the reaction with more confidence prior to an investigation of the influence of added nucleophilic reagents.

Results

Decomposition in Acid Solution. Preliminary work established that the methylnitrosoureas decompose in acid solution by both denitrosation and hydrolysis reactions. The relative importance of these reaction paths depends upon the pH of the solution. The denitrosation reaction yields compounds, presumably nitrogen oxides, which absorb near 210 nm. Nevertheless, the rates of disappearance of the methylnitrosoureas can be measured accurately spectrophotometrically between 225 and 245 nm.

The decomposition reactions of both methyl- and trimethylnitrosourea are first-order processes from pH 3 to 7. The rate constants are summarized in Table I.

The data indicate that the rate of disappearance of *N*-methyl-*N*-nitrosourea is independent of the acid strength from pH 2 to 4 and inversely proportional to the acid strength at higher pH. In contrast, the rate of disappearance of *N,N,N'*-trimethyl-*N*-nitrosourea depends upon the acid strength over the entire pH range. The uncatalyzed and base-catalyzed reactions of the monomethyl compound will be discussed subsequently.

The product distribution for the reaction of trimethylnitrosourea was studied in unbuffered deuterium oxide by NMR spectroscopy at 270 MHz. After 13% of the nitrosourea had disappeared, the only detectable product was trimethylurea, the denitrosation product. After 85% of the nitrosourea had disappeared, the product distribution was somewhat different. Trimethylurea accounted for about 70% of the starting material, and di-

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(9) (a) Hecht, S. M.; Kozarich, J. W. *Tetrahedron Lett.* 1972, 5147. (b) Hecht, S. M.; Kozarich, J. W. *J. Org. Chem.* 1973, 38, 1821.

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(11) Garrett, E. R.; Goto, S.; Stubbins, J. F. *J. Pharm. Sci.* 1965, 54, 119.

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Table I. Observed First-Order Rate Constants for the Disappearance of the Methylnitrosoureas from pH 2 to 7 in Water at 25 °C

| pH ^a | rate const, k_{obsd} , s ⁻¹ | |
|-------------------|-------------------------------------------------|-----------------------|
| | methylnitrosourea | trimethyl-nitrosourea |
| 7.07 | 1.10×10^{-4} | 4.03×10^{-8} |
| 6.05 | 1.30×10^{-5} | 1.49×10^{-7} |
| 5.01 | 1.43×10^{-6} | |
| 4.97 | | 7.15×10^{-7} |
| 4.28 | 6.73×10^{-7} | |
| 3.99 | | 3.42×10^{-6} |
| 3.09 | 7.08×10^{-7} | |
| 3.03 | | 2.01×10^{-5} |
| 2.06 ^b | | 4.66×10^{-5} |

^a Sodium phosphate-citric acid buffers were used.

^b Hydrochloric acid, 0.009 M.

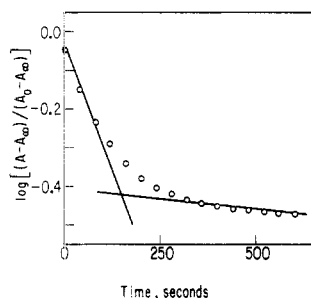


Figure 1. Relationship between $\log [(A - A_{\infty})/(A_0 - A_{\infty})]$ and time for the decomposition of *N,N',N'*-trimethyl-*N*-nitrosourea in 1.145 M hydrochloric acid at 25 °C. The data for the initial and final stages of the reaction were used to estimate the first-order rate constants for denitrosation, k_a , and hydrolysis, k_b , presented in Table IV.

methylamine and methanol accounted for the remainder. Careful examination of the spectra revealed that the latter hydrolysis products were not present in the initial stages of the reaction.

The reactions of the nitrosoureas in more acidic solution, pH < 2, were more complex. The results shown in Figure 1 for the reaction of the trimethylnitrosourea are typical of the data obtained in this pH region.

The complex kinetic behavior is also reflected in the changing product distribution (Table II).

The products obtained in the reactions of the two methylnitrosoureas are comparable. In the initial stages of the reaction, *N*-methyl-*N*-nitrosourea yields methylurea, and *N,N',N'*-trimethyl-*N*-nitrosourea yields trimethylurea. Nitrous acid is formed simultaneously. Subsequently, the products of the hydrolysis reaction, methylamine or dimethylamine and methanol, are observed. The relative quantities of these materials increase as the reaction proceeds until in the late stages of the reaction they are the dominant products. It is pertinent that neither dimethylurea (from the reaction of methylamine with methylnitrosourea) nor tetramethylurea (from the reaction of dimethylamine with trimethylnitrosourea) are formed.

These results suggest that the first, more rapid reaction is denitrosation and that the second, slower reaction is hydrolysis. The denitrosation is reversible, and the ultimate products are formed from the hydrolysis reaction. To test this idea, we measured the rate of disappearance of *N*-methyl-*N*-nitrosourea in 1.145 M hydrochloric acid solution in the presence of excess urea and methylurea. When urea is present in large excess, the decomposition is a first-order reaction. The rate constant for this process is 28.0×10^{-5} s⁻¹. When methylurea is present in large excess compared to *N*-methyl-*N*-nitrosourea, the disap-

Table II. Reaction Products of the Decomposition of *N*-Methyl-*N*-nitrosourea and *N,N',N'*-Trimethyl-*N*-nitrosourea in Aqueous Acid Solution at 25 °C

| % reactn | % products | | |
|------------------------------------------------------------------------------------------------------|------------------|-----------------|----------|
| | methylurea | methyl-amine | methanol |
| For <i>N</i> -Methyl- <i>N</i> -nitrosourea in 0.111 M DCl in D ₂ O ^a | | | |
| 10 | 31 | 69 | trace |
| 30 | 16 | 79 | 5 |
| 52 | 12 | 82 | 6 |
| 74 | 9 | 84 | 7 |
| 89 | 8 | 84 | 8 |
| 99 | 7 | 86 | 7 |
| For <i>N</i> -Methyl- <i>N</i> -nitrosourea in 1.11 M DCl in D ₂ O | | | |
| 3 | 100 | | |
| 19 | 18 | 82 | |
| 79 | 5 | 95 | |
| 100 | 4 | 96 | trace |
| For <i>N,N',N'</i> -Trimethyl- <i>N</i> -nitrosourea in 1.145 M DCl in D ₂ O ^b | | | |
| 5 | 100 ^c | | |
| 6 | 100 ^c | | |
| 7 | 100 ^c | | |
| 23 | 51 ^c | 19 ^d | 30 |
| 34 | 40 ^c | 19 ^d | 41 |

^a Thin-layer chromatography indicated that urea is formed in trace amounts at long reaction times. ^b The material balance in later stages of this reaction was unsatisfactory because nitrosation of the amine occurs. Trimethylurea is stable under the experimental conditions. ^c Trimethylurea. ^d Dimethylamine.

Table III. Rate Constants for the Denitrosation and Hydrolysis of *N*-Methyl-*N*-nitrosourea in 1.145 M Hydrochloric Acid Solution at 25 °C

| [Ur]/[MNU] ^a | denitrosation rate const, s ⁻¹ | [MeUr]/[MNU] | hydrolysis rate const, s ⁻¹ |
|-------------------------|-------------------------------------------|--------------|----------------------------------------|
| 10.0 | 27.5×10^{-5} | 4.0 | 2.6×10^{-5} |
| 60.0 | 28.5×10^{-5} | 8.0 | 2.8×10^{-5} |

^a MNU is *N*-methyl-*N*-nitrosourea and Ur is urea. The other nitrosoureas are designated in a similar way in the other tables.

pearance of the starting material is less rapid. The rate constant for the hydrolysis reaction is about 2.8×10^{-5} s⁻¹. The observations are summarized in Table III.

The dependence of these reactions on the concentration of the acid, salts, and chloride ion was investigated. The approximate first-order rate constants, k_a and k_b , estimated from the initial and final slopes of diagrams of $\log [(A - A_{\infty})/(A_0 - A_{\infty})]$ vs. time (Figure 1), are summarized in Table IV.

Decomposition in Basic Solution. Denitrosation is unimportant in basic solution. Accordingly, the hydrolysis reactions of the mono-, di-, and trimethylnitrosoureas can be studied spectrophotometrically without the interference of nitrogen oxides over an extensive pH range. The rate data adhere with excellent precision to a first-order rate law over the entire extent of the reaction. The results for *N*-methyl-*N*-nitrosourea at pH 7.5 (Figure 2) are representative of the data obtained in this phase of the study. The reaction of this compound is quite rapid at pH 10, and we, therefore, studied the less reactive *N,N*-dimethyl- and *N,N',N'*-trimethyl-*N*-nitrosoureas in the more basic solutions. Each of these reactions is first-order in hydroxide ion concentration. Representative second-order rate constants for the base-catalyzed reactions are presented in Table V.

Table IV. Kinetic Observations for the Acid-Catalyzed Denitrosation and Hydrolysis of *N*-Methyl-*N*-nitrosourea and *N,N',N'*-Trimethyl-*N*-nitrosourea in Aqueous Solution at 25 °C

| catal, salt (concn, N) | $10^4 k_a / [H^+], M^{-1} s^{-1}$ | $10^5 k_b / [H^+], M^{-1} s^{-1}$ |
|------------------------------------------------------|-----------------------------------|-----------------------------------|
| For <i>N</i> -Methyl- <i>N</i> -nitrosourea | | |
| HCl (1.145) | 2.1 | 3.3 |
| H ₂ SO ₄ (1.018) | 2.6 | 3.7 |
| DCl (1.11) | 1.7 | 1.7 |
| HCl (1.145), KCl (1.00) | 2.7 | 3.4 |
| H ₂ SO ₄ (1.018), KCl (1.00) | 2.4 | 3.4 |
| HCl (1.145), LiCl (1.00) | 2.4 | 3.2 |
| HCl (0.115) | 2.3 | 1.6 |
| H ₂ SO ₄ (0.102) | 2.3 | |
| HCl (0.115), KCl (1.00) | 2.5 | |
| HCl (0.0090) | 3.0 | 6.5 |
| For <i>N,N',N'</i> -Trimethyl- <i>N</i> -nitrosourea | | |
| HCl (1.145) | 58 | 22 |
| HCl (0.102) | 42 | 56 |

Table V. Representative Second-Order Rate Constants for the Hydrolysis of the Methylnitrosoureas at 25 °C

| pH | $k_1, M^{-1} s^{-1}$ | | |
|-------------------|---------------------------------|-------------------|------------------------------------|
| | MNU | DMNU | TMNU |
| 7.8 ^a | 9.95×10^2 | 5.25 | |
| 8.1 ^a | 9.66×10^2 | 4.20 | |
| 9.0 ^a | 9.56×10^2 ^e | 2.81 | 5.96×10^{-2} |
| 9.3 ^b | 9.16×10^2 ^e | | 3.02×10^{-2} |
| 9.6 ^b | 7.45×10^2 | 2.08 | 2.66×10^{-2} |
| 9.9 ^b | 6.84×10^2 | 2.08 ^e | 2.68×10^{-2} ^e |
| 11.6 ^c | | 1.17 | 2.26×10^{-2} |
| 12.2 ^c | | 1.06 | 2.19×10^{-2} |
| 14.0 ^d | | | 2.59×10^{-2} |

^a Sodium borate and borax buffer. ^b Sodium borate buffer. ^c Sodium phosphate buffer. ^d Sodium hydroxide, 1.0 M. ^e Extrapolated to zero buffer concentration; see Figure 4.

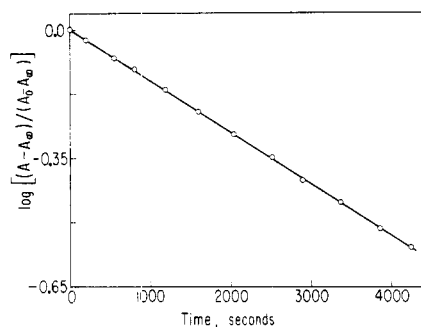


Figure 2. Relationship between $\log [(A - A_\infty)/(A_0 - A_\infty)]$ and time for the decomposition of *N*-methyl-*N*-nitrosourea in sodium dihydrogen phosphate buffer at pH 7.50.

The second-order rate constants for the monomethyl compound decrease by a factor of 2 from pH 7 to 10, the values for the dimethyl compound decrease by a factor of 5 from pH 7 to 12, and the values for the trimethyl compound decrease by a factor of 2 from pH 9 to 14. These decreases are small when the pH range is considered. Similar decreases in second-order rate constants for the hydrolyses of esters and amides have been observed by other investigators.¹³ Nevertheless, we thought it prudent to study the influences of ionic strength and buffer cation on the reaction rate to probe the magnitude of possible salt

Table VI. Influence of Ionic Strength on the Rate of Hydrolysis of *N*-Methyl-*N*-nitrosourea in 0.1 M Sodium Borate Buffer at pH 9.75 at 25 °C^a

| [KCl], M | ionic strength | $10^2 k_{obsd}, s^{-1}$ |
|----------|----------------|-------------------------|
| 0.000 | 0.080 | 5.25 |
| 0.020 | 0.100 | 5.11 |
| 0.040 | 0.120 | 5.13 |
| 0.060 | 0.140 | 5.12 |
| 0.080 | 0.160 | 5.10 |
| 0.100 | 0.180 | 5.18 |

^a Under these conditions, the reaction rate is independent of the buffer concentration as shown in Figure 3.

Table VII. Influence of Buffer Cation on the Rate of Hydrolysis of *N*-Methyl-*N*-nitrosourea in 0.1 M Borate Buffer at pH 9.75 at 25 °C^a

| buffer cation | ionic strength | $10^2 k_{obsd}, s^{-1}$ |
|---------------|----------------|-------------------------|
| lithium | 0.080 | 6.25 |
| sodium | 0.080 | 5.25 |
| potassium | 0.080 | 5.21 |

^a Under these conditions, the reaction rate is independent of the buffer concentration as shown in Figure 3.

Table VIII. Influence of Phosphate Buffer Concentration on the Rate of Hydrolysis of *N*-Methyl-*N*-nitrosourea at 25 °C

| pH | concn range, M | $10^4 k_{obsd}, s^{-1}$ |
|------|----------------|-------------------------|
| 6.43 | 0.039-0.078 | 0.255-0.265 |
| 7.20 | 0.002-0.010 | 1.17-1.40 |
| 7.50 | 0.059-0.117 | 3.82-3.92 |

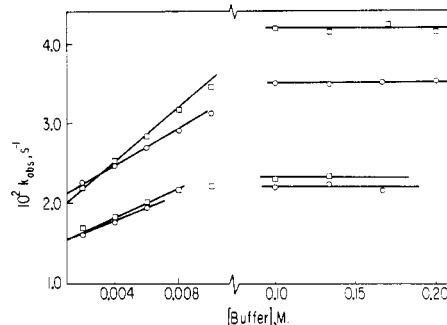


Figure 3. Relationship between the observed first-order rate constant for the hydrolysis of *N*-methyl-*N*-nitrosourea and the concentration of the buffer at pH 9.40 and 9.75. The concentration of sodium glycinate is noted with squares and the concentration of sodium borate is noted with circles. The ionic strength was constant in all these experiments.

effects. Certain typical results are summarized in Tables VI and VII.

These results and other related experiments establish that the reaction rate is not especially sensitive to the ionic strength of the reaction solution. However, the reaction is specifically enhanced by lithium ion.

General-Base Catalysis. Garrett and his associates reported that the hydrolysis of *N*-methyl-*N*-nitrosourea was not catalyzed by the buffer components in the pH range 5.95-7.85.¹⁴ We reexamined this aspect of the problem by a study of the three nitrosoureas in three different buffer solutions from pH 6.4 to 9.8. We confirmed the conclusion of the earlier work that the reaction is not general-base catalyzed in near neutral solutions. The observed first-order rate constant is not dependent upon low, 0.002-0.01 M, intermediate, 0.04-0.08 M, or high,

(13) Illustrations of this phenomena are provided by: (a) Bunton, C. A.; Spatcher, D. N. *J. Chem. Soc.* 1956, 1079; (b) Bunton, C. A.; Nayak, B.; O'Connor, C. *J. Org. Chem.* 1968, 33, 572.

(14) The concentration range of the buffer was not specified in ref 11.

Table IX. Rate Constants^a for General-Base Catalysis of the Hydrolysis of the Methylnitrosoureas in Water at 25 °C

| general base | nitroso-urea | $k_2, \text{M}^{-1} \text{s}^{-1}$ | k_L, s^{-1} |
|-----------------------------|--------------|------------------------------------|-----------------------|
| pH 9.40 | | | |
| sodium glycinate | MNU | 2.62 | 2.32×10^{-2} |
| sodium borate | MNU | 0.76 | 2.20×10^{-2} |
| pH 9.75 | | | |
| sodium glycinate | MNU | 3.27 | 4.26×10^{-2} |
| sodium borate | MNU | 1.31 | 3.38×10^{-2} |
| lithium borate ^b | MNU | 1.93 | 4.39×10^{-2} |
| sodium glycinate | DMNU | 3.89×10^{-3} | 1.19×10^{-4} |
| sodium borate | DMNU | 2.22×10^{-3} | 1.10×10^{-4} |
| sodium glycinate | TMNU | 3.16×10^{-6} | 1.80×10^{-6} |
| sodium borate | TMNU | 1.84×10^{-6} | 1.80×10^{-6} |

^a The rate constants are defined in eq 6. ^b The ionic strength was maintained at 0.163. In this case, the ionic strength was adjusted with lithium chloride.

Table X. First-Order Rate Constants for the Hydrolysis of the Methylnitrosoureas in Water and Heavy Water at 25 °C

| nitroso-urea | pH ^a | $k_{\text{obsd}}^{\text{H}_2\text{O}}, \text{s}^{-1}$ | $k_{\text{obsd}}^{\text{D}_2\text{O}}, \text{s}^{-1}$ | $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ |
|--------------|-----------------|-------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------|
| MNU | 6.85 | 6.89×10^{-5} | 7.14×10^{-5} | 0.96 |
| MNU | 9.72 | 2.72×10^{-2} | 4.83×10^{-2} | 0.56 |
| DMNU | 9.72 | 7.61×10^{-5} | 1.46×10^{-4} | 0.52 |
| TMNU | 9.72 | 1.43×10^{-6} | 2.24×10^{-6} | 0.64 |

^a The apparent values for deuterium oxide are shown.³³

0.06–0.12 M, concentrations of phosphate buffers at pH 7.2, 6.4, and 7.5, respectively (Table VIII).

Further study of the reaction at higher pH revealed that the reaction is catalyzed by borate and glycinate anions. The results obtained for *N*-methyl-*N*-nitrosourea at pH 9.4 and 9.75 are illustrated in Figure 3.

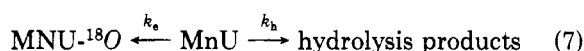
The experimental results at low buffer concentration were analyzed on the basis of eq 6. The parameters k_1 ,

$$k_{\text{obsd}} = k_1[\text{OH}^-] + k_2[\text{B}^-] + k_{\text{BH}}[\text{BH}] \quad (6)$$

k_2 , and k_{BH} represent the hydroxide ion catalyzed reaction, the buffer anion catalyzed reactions, and the buffer catalyzed reactions, respectively. The value of k_{BH} is too small to measure. The values of the slope and intercept were determined by least-squares analysis. The k_1 values predicted by the intercepts were in reasonable agreement with the values presented in Table V. The k_2 values and the limiting rate constant, k_L , observed at high buffer concentration are presented in Table IX.

Solvent Isotope Effect. The kinetic solvent isotope effect was measured at pH 6.85 and 9.72 for *N*-methyl-*N*-nitrosourea and at pH 9.72 for *N,N'*-dimethyl-*N*-nitrosourea and *N,N'*-trimethylnitrosourea. The results are presented in Table X.

Carbonyl Oxygen Exchange. The oxygen atoms in C-, *N*-, and *O*-nitroso groups exchange with water in acid-catalyzed reactions. The reactions are undetectably slow in basic solution.¹⁵ In this situation, it was practical to investigate the exchange of the carbonyl oxygen atom of *N*-methyl-*N*-nitrosourea with water (eq 7). In one



(15) (a) Dahn, H.; Wyss, P. *Bull. Soc. Vaudoise Sci. Nat.* 1967, 69, 385. (b) Aoyama, M.; Takahashi, T.; Minato, H.; Kobayashi, M. *Chem. Lett.* 1976, 245.

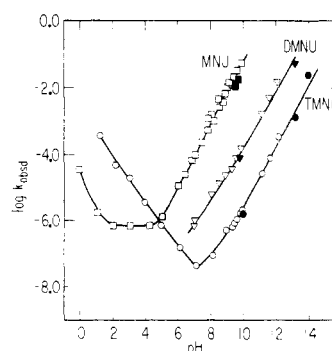


Figure 4. Relationship between the logarithms of the observed first-order rate constants for the disappearance of the nitrosourea and the pH of the solution. The data points shown in black have been obtained in the absence of a buffer or have been extrapolated to zero buffer concentration.

experiment at pH 6.84, the reaction was allowed to proceed to 40% completion in 24% ¹⁸O-enriched water. The unreacted nitrosourea was recovered from this experiment. Mass spectroscopy revealed that this substance contained less than 0.5% ¹⁸O. Knowledge of the detection limits established that the exchange rate ratio, k_h/k_a , is greater than 8. In another experiment initiated at pH 9.6, the reaction was allowed to proceed to 60% completion in 40% ¹⁸O-enriched water. The nitrosourea recovered from this experiment contained 0.86% excess ¹⁸O. This result indicates that k_h/k_a is 28.0 ± 2.8 .

Reaction Products. The products of the decomposition of *N*-methyl-*N*-nitrosourea were determined at several pH values by NMR spectroscopy, thin-layer chromatography, and other qualitative methods.

In neutral or modestly acidic solution, this nitrosourea decomposed to form methanol quantitatively. The methanol obtained from the reaction in deuterium oxide did not contain deuterium atoms.

At pH 9.7, *N*-methyl-*N*-nitrosourea also decomposed to produce methanol quantitatively. Spot tests indicated carbonate and carbamate ions were present. Cyanate ion, urea, and methylurea, which are stable under the experimental conditions, were absent. In 0.1 M sodium hydroxide, carbamate ion was produced quantitatively.

The course of the reaction of *N,N'*-dimethyl-*N*-nitrosourea in unbuffered deuterium oxide was also studied by NMR spectroscopy. Essentially quantitative yields of methanol and *N,N'*-dimethylurea (0.5 mol of the urea/mol of methanol) were obtained upon completion of the reaction. At intermediate stages, the product mixture consisted of the starting material, methanol, *N*-methylcarbamate ion, and *N,N'*-dimethylurea. The sum of the areas of the methyl resonances of the urea and the carbamate was equal to the area of the methyl resonance of methanol and fully accounted for the disappearance of the nitrosourea. The variations in the relative intensities of the signals indicate that dimethylurea is formed via the carbamate.

Discussion

Decomposition Reactions. The relationship between the logarithms of the observed first-order rate constants and the pH is shown in Figure 4.

For *N*-methyl-*N*-nitrosourea there are three distinct regions of reactivity. In the first region, the decomposition is apparently first-order in the concentration of the acid. The product studies establish that denitrosation and hydrolysis occur competitively. In an intermediate region between pH 2 and 4, this compound undergoes hydrolysis, but not denitrosation, in a reaction which is independent of pH. In the third region, the reaction is first-order in

Table XI. Observations for the Acid-Catalyzed Denitrosation of *N*-Nitroso Compounds in Water at 25 °C

| observation | <i>N</i> -nitroso compd | | | |
|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| | amine ^{a,b} C ₆ H ₅ N(CH ₃)NO | amide ^b CH ₃ CON(C ₄ H ₉)NO | sulfonamide ^c CH ₃ C ₆ H ₄ SO ₂ - N(CH ₃)NO | urea ^d H ₂ NCON(CH ₃)NO |
| rate const, 10 ⁴ k ₂ , M ⁻¹ s ⁻¹ (acid; concn, M) | 0.30 (H ₂ SO ₄ , 2.5) | 0.12 (HClO ₄ , 1.0) | 510 (HCl, 0.16) | 2.5 (HCl, 1.1) |
| k _{H₂O} /k _{D₂O} | 0.5 | 1.8 | 1.4 | 1.3 |
| halide ion catalysis | yes | no | no | no |
| O ¹⁸ exchange, 10 ⁶ k ₂ , M ⁻¹ s ⁻¹ | 1.0 ^e | | | |

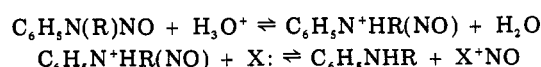
^a Reference 17. ^b Reference 18. ^c Reference 19. ^d This study. ^e Reference 15b.

the base. The products obtained in basic solution indicate that the hydrolysis reaction is predominant. For *N,N',N'*-trimethyl-*N*-nitrosourea there are two regions of reactivity. In the acidic region, the decomposition is probably first-order in the concentration of the acid. The product analyses establish that denitrosation is the predominant reaction. In the basic region, the decomposition reaction is first-order in base, and the hydrolysis reaction is the dominant process. *N,N'*-Dimethyl-*N*-nitrosourea behaves similarly in the basic region.

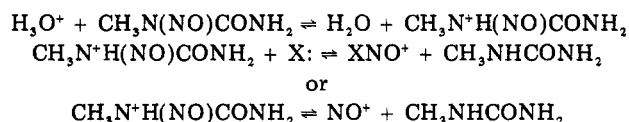
Acid-Catalyzed Reaction. The kinetic information and the product distributions observed for the decomposition of *N*-methyl-*N*-nitrosourea and *N,N',N'*-trimethyl-*N*-nitrosourea (Tables I–IV) establish that the acid-catalyzed decomposition reactions occur by independent denitrosation and hydrolysis reactions. The rate constants for denitrosation in 1.1 M hydrochloric acid could be estimated by the addition of excess urea which cleanly scavenges nitrous acid and renders the denitrosation effectively irreversible. The second-order constant for the denitrosation of *N*-methyl-*N*-nitrosourea is about $2.2 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$. Although the rate constants for the slower denitrosation in 0.1 and 0.01 M hydrochloric acid solution could not be defined with equal confidence, the estimated second-order constants, 2.3×10^{-4} and $2.4 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, for these solutions are within experimental error of the more accurate datum for 1.1 M acid.¹⁶ Essentially the same rate constants are observed for the reaction in sulfuric acid and in the presence of added chloride salts. Hence, chloride ion does not catalyze the denitrosation. The solvent kinetic isotope effect for this reaction of methylnitrosourea is 1.3.

In contrast to the results for the monomethyl derivative, the decomposition of the trimethyl compound is acid catalyzed over a broad pH range. The product distribution at low and neutral pH suggests that the denitrosation reaction is dominant. The second-order rate constants for this reaction, $k_{\text{obsd}}/[\text{H}^+]$, increase somewhat as the pH of the solution increases. This variation apparently results from the fact that the renitrosation of trimethylurea is acid catalyzed and is a more significant reaction in the more acidic solutions. The denitrosation of the trimethyl compound is about 25-fold more rapid than that of the monomethyl compound under comparable conditions.

Challis and Williams and their associates have investigated the acid-catalyzed denitrosation reactions of several *N*-nitroso compounds.^{17–19} Several lines of evidence have

Scheme III^a

^a X: = H₂O, halide ion, etc.

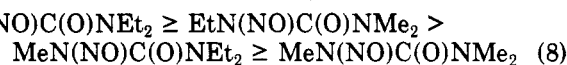
Scheme IV^a

been presented to define the most probable reaction path. Certain of their observations are presented in Table XI for convenient comparison with the information obtained for the nitrosoureas.

The reactions of the *N*-nitrosoamines are quite different than the reactions of the other compounds. The most striking differences are the solvent isotope effect and the influences of nucleophilic reagents, e.g., halide ion, thio-urea, etc., on the reaction rate. These observations have prompted Challis and Williams and their students to conclude that the reaction proceeds in two steps and that the second step is generally rate limiting^{17–19} (Scheme III). It is pertinent that the addition of excess bromide ion to the reaction of *N*-nitrosodiphenylamine leads to a situation in which the reaction rate is independent of the concentration of bromide ion and for which the solvent isotope effect increases to 1.25.^{17d} This finding is good evidence that the proton-transfer reaction can be rate limiting in appropriate circumstances.^{17–19}

The general features of the reactions of the amides, the sulfonamide, and the ureas are strikingly similar. The available evidence, therefore, suggests that the reactions of the nitrosourea occur by a slow proton-transfer reaction followed by a rapid displacement reaction (Scheme IV). This formulation accounts for the observations that the more basic trimethyl derivative is more reactive, that the reaction is not accelerated by nucleophilic reagents, and that the solvent isotope effect is greater than 1.

The relative reactivity of *N*-methyl-*N*-nitrosourea and *N,N',N'*-trimethyl-*N*-nitrosourea can be rationalized on the basis of this formulation. Presumably, the additional methyl groups increase the reactivity of the trialkyl compound by an increase in its basicity and reactivity in the slow proton-transfer reaction (eq 8). The relative re-



activity of the mono- and trimethyl compounds and of the

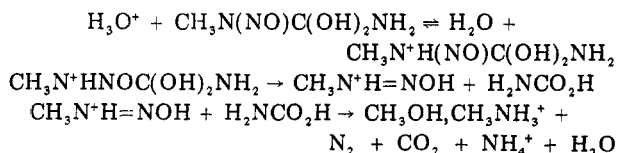
(16) The observed rate constant for the catalyzed reaction in 0.01 M acid has been corrected for the concomitant uncatalyzed hydrolysis reaction.

(17) (a) Challis, B. C.; Osborne, M. R. *J. Chem. Soc., Perkin Trans. 2* 1973, 1526. (b) Biggs, I. D.; Williams, D. L. H. *Ibid.* 1975, 107. (c) Williams, D. L. H. *Ibid.* 1975, 655. (d) Williams, D. L. H. *Ibid.* 1977, 128. (e) Thompson, J. T.; Williams, D. L. H. *Ibid.* 1977, 1932. (f) Crampton, M. R.; Thompson, J. T.; Williams, D. L. H. *Ibid.* 1979, 18.

(18) (a) Berry, C. N.; Challis, B. C. *J. Chem. Soc., Perkin Trans. 2* 1974, 1638. (b) Challis, B. C.; Jones, S. P. *Ibid.* 1975, 153.

(19) Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* 1976, 1838.

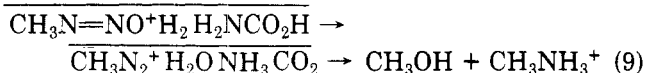
Scheme V



trialkylated compounds studied by Lijinsky and Taylor¹² at pH 2 is in accord with a simple interpretation based on the direct polar effects of the ethyl and methyl groups. However, the matter is probably not so simple because structural models suggest that the additional alkyl groups distort the N(C=O)N core with a resultant decrease in NC double bond character and an increase in basicity.

The hydrolysis reaction which accompanies the denitrosation of methylnitrosourea is about tenfold less rapid. The reaction also appears to be first-order in the concentration of acid. Like the denitrosation, this process is not accelerated by salt effects and exhibits a solvent isotope effect which is about 2.²⁰ The isotope effects for the denitrosation and hydrolysis reactions differ. Consequently, it seems unreasonable to postulate that the reactions proceed via a common intermediate. It is not unreasonable, however, to postulate that the slow proton transfer is made to a hydrate of the nitrosourea present in low concentration. One of several alternative formulations is presented in Scheme V.²¹

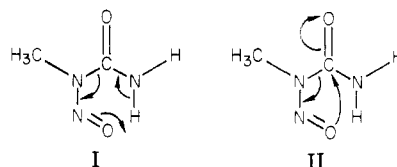
The ultimate products of the reactions are formed in rapid reactions which follow the rate-determining reaction. Product formation in the denitrosation is apparently straightforward. The product distribution is more complex in the hydrolysis reaction. The *N*-methyl group of the monomethyl derivative is converted to methylamine. In contrast, the *N*-methyl group of the trimethyl derivative is converted to methanol. The product distribution also depends upon the pH of the solution, with less methylamine formed in the less acidic solution. Presumably, the intermediates decompose to yield derivatives of methyl-diazonium hydroxide and carbamic acid (Scheme V). These unstable compounds decompose very rapidly in acid solution to produce methyl-diazonium ion and water and carbon dioxide, ammonia, and water, respectively (eq 9).



The finding that more methylamine is obtained in the more acidic solutions indicates that the initial products do not achieve equilibrium with their surroundings prior to the recombination reactions which produce methanol and the amine. These observations prompt the suggestion that the initial intermediates which are derivatives of methyl-diazonium hydroxide and carbamic acid immediately decompose to form an equally reactive group of molecules which react before they diffuse. The decomposition reactions of the intermediates are more rapid in acid solution, and more methylamine than methanol is produced. This interpretation also accounts for the different course of the hydrolysis of the trimethyl compound.

In this instance, the additional methyl groups presumably slow the rate of decomposition of the carbamate and the fragment recombination rate. Other information supports this interpretation. First, the decomposition of carbamic acid is very rapid in acid solution. The initial products are reported to be ammonia and carbon dioxide.²² Second, the decomposition of methyl-diazonium hydroxide is also acid catalyzed. The decomposition products of molecules of this class react very rapidly with surrounding molecules and ions at rates which are competitive with the rates of diffusion and rotation.²³

Uncatalyzed Reaction. There is a narrow pH range over which the reaction rate of *N*-methyl-*N*-nitrosourea is independent of the concentration of acid or base (Figure 4). The behavior of this molecule contrasts sharply with the behavior of the trimethyl compound. To decide whether or not this reaction proceeded via a cyclic transition state such as the ones produced by Huisgen and Montgomery and their associates^{24,25} (I and II), we exam-



ined the rate of the reaction in chloroform and methanol at 25 °C. *N*-Methyl-*N*-nitrosourea was stable for several weeks in these anhydrous solvents. The observation that the reaction proceeds rapidly only in the polar solvent and the fact that the reaction of the trimethyl compound does not proceed by an uncatalyzed pathway prompt our conclusion that the uncatalyzed decomposition of the monomethyl compound occurs by the rate-determining reaction of a water molecule with the carbonyl center of the nitrosourea (or the kinetic equivalent of the reaction of the conjugate acid with hydroxide ion) to yield a tetrahedral intermediate which decomposes to give the reaction products. More work will be necessary to verify this suggestion.

Base-Catalyzed Reaction. The three methylnitrosoureas undergo base-catalyzed hydrolysis over a broad pH range. The kinetic data, observations of buffer catalysis, the solvent kinetic isotope effect, oxygen-18 exchange data, the modest salt effects, and the products provide a basis for the description of the principal reaction path. The reactions of the monomethyl and trimethyl compounds are strictly first order in the concentration of hydroxide ion. In contrast, the second-order rate constant for the dimethyl compound at pH 7 is about fivefold greater than the rate constant for this compound at pH 12. Although the differences in the rate constants are not exceptionally large when the pH range is considered, we believe that the somewhat larger variations observed in the rate constants for the dimethyl compound are real and that the diminution in the apparent second-order rate constant should be attributed to the formation of the unreactive conjugate base of *N,N*-dimethyl-*N*-nitrosourea at high pH.^{26,27}

(22) Adams, P.; Baron, F. A. *Chem. Rev.* 1965, 65, 567.

(23) Moss, R. A. *Acc. Chem. Res.* 1974, 7, 421.

(24) Huisgen, R.; Reimlinger, H. *Justus Liebigs Ann. Chem.* 1956, 599, 183. See also other articles in that series.

(25) Montgomery, J. A.; James, R.; McCaleb, G. S.; Johnston, T. P. *J. Med. Chem.* 1967, 10, 668.

(26) Similar phenomena have been observed in the hydrolytic reactions of amides and have been attributed to the formation of the conjugate base.²⁷ The pK_a of the amido protons of *N,N*-dimethyl-*N*-nitrosourea, we estimate, is between 12 and 13. Thus, the concentration of the conjugate base would be significant at high pH.

(20) The solvent isotope effect was estimated from the rate constants for the slower hydrolysis reactions which accompany the denitrosation reactions. These rate constants are not as precisely defined, and, as a consequence, there is an element of uncertainty in the value of this isotope effect.

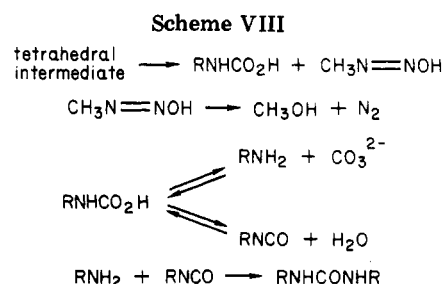
(21) Other possibilities include rate-determining addition of the proton to another site in the molecule or rate-determining addition of the proton to a hydrogen-bonded adduct of water and the nitrosourea rather than to the hydrate.

compound suggests that the rate of decomposition of the intermediate to the products is significantly larger than that for the less sterically encumbered compounds. It is also pertinent that the sodium glycinate buffered reaction of *N,N,N'*-trimethyl-*N*-nitrosourea does not reach a limiting value. This observation suggests that the decomposition of its tetrahedral intermediate is catalyzed by this buffer. Bifunctional catalysis may be important in this instance as in other circumstances.²⁹

The exchange reaction between the oxygen atoms of water and the carbonyl group of the nitrosourea could be determined because the exchange reaction with the nitroso group is slow¹⁵ (Scheme VII). The exchange was examined in 0.1 M borate buffer, pH 9.75. Under these conditions the decomposition of the tetrahedral intermediate is the rate-limiting process. The hydrolysis reaction is favored by a factor of about 28 compared to the exchange reaction. Thus, even though the reverse reaction is significant, there is little exchange. The results of a previous study suggest that the nitrosoureas have a strong internal hydrogen bond.³⁰ According to the stereoelectronic theory of Deslongchamps, the reaction of this compound with hydroxide ion should proceed along a preferred reaction path to yield a tetrahedral intermediate in which the entering group, ¹⁸OH₂, and the nitrogen atom lone pair are anti-periplanar.³¹ Expulsion of ¹⁸OH⁻ occurs along the same reaction path. Conversion of A to B is required for the expulsion of the unlabeled hydroxyl group. This conversion may be slow relative to the other modes of decomposition of the intermediate because the inversion at the nitrogen atom requires the disruption of the hydrogen bond structure with attendant changes in the conformation of the molecule. A proton transfer is also required for ¹⁸O exchange to occur. It seems unlikely that this process is slow compared to the rate of conformational change or to the rate of expulsion of the leaving group. It should also be noted that the intermediate has six electronegative atoms and that hydrogen bonding between these atoms and the solvent molecules must be substantial. Thus, the role played by the solvent in determining the relative rates of the various processes must be significant. Unfortunately, at the present, there is no adequate method to assess its role.

The salt effects observed in the basic hydrolysis of *N*-methyl-*N*-nitrosourea (Table VIII) are quite modest and quite specific. At higher pH the second-order rate constants for the reaction are somewhat greater for lithium ion than for sodium or potassium ions. The addition of lithium ion to solutions containing a large excess of potassium ion also causes a small rate acceleration. These results suggest that there is a very specific interaction between the lithium ion and the nitrosourea. One possible interpretation is that the carbonyl group is less solvated in the more basic solutions with a corresponding decrease in its electrophilicity. Neither sodium ions nor potassium ions can compensate for this change. Lithium ion, however, is a better coordination agent and, in part, compensates for the variation in solvation of the incipient anion.

The products of the decomposition of the nitrosoureas are formed in several reactions which occur after the rate-determining step. The information obtained in the course of this study indicates that carbamic acid derivatives are often produced during the course of the reaction. The data strongly infer that methyldiazonium hydroxide derivatives are also formed as first intermediates. In basic



solution, the diazonium hydroxide decomposes to form methanol as the predominant product. The fate of the carbamate depends upon the pH of the solution and the time allotted for the attainment of equilibrium as outlined in Scheme VIII.³² This scheme accounts for the observations, including the fact that the base-catalyzed decomposition of *N,N'*-dimethyl-*N*-nitrosourea first gives the *N*-methylcarbamate ion but eventually provides *N,N'*-dimethylurea as the dominant product.

Conclusion

This research indicates that the decomposition reactions of the *N*-methyl-*N*-nitrosoureas in acid solution proceed by both denitrosation and hydrolysis reactions and that the denitrosation is more rapid. A slow proton transfer is the key step in the reaction. These observations correspond nicely with the results obtained in the study of other *N*-nitroso compounds by Challis and Williams and their associates. The product distribution in the acid-catalyzed reaction is unusual because the *N*-methyl group of the nitrosourea is converted to methylamine. The facts suggest that this product is formed from a diazonium hydroxide and a carbamic acid derivative in a solvent cage.

The base-catalyzed decomposition reactions apparently proceed via a tetrahedral intermediate. The reaction with hydroxide ion is much more rapid than the general-base-catalyzed reactions of other buffer anions. The *N*-methyl group of the nitrosoureas is converted to methanol under the conditions of our experiments. The decomposition products also include ureas, cyanates, carbamates, and carbonates. The relative quantities of these materials depend upon the reaction time and conditions. Our conclusion that the reactions of the nitrosoureas in basic solution proceed via a tetrahedral intermediate contrasts with the suggestions of Hecht and Kozarich⁹ and of Jones and his co-workers.⁸ These investigators presented evidence that the reactions with strong bases in nonaqueous solutions proceeded, at least in some cases, by the abstraction of an amido proton (Scheme II) or by the reaction of the base at the nitroso group (Scheme I). Several lines of evidence favor the view that the reactions of the three compounds examined in this study do not proceed in this way in aqueous solution. There is no discernible difference in the character of the reactions of the monomethyl and the trimethyl compounds for which the elimination reaction is impossible. For both these molecules, the reactions are bimolecular over a broad pH range, are insensitive to salt effects, respond similarly to changes in the concentration of the buffers, and exhibit identical kinetic solvent isotope effects. This information and the product distribution data eliminate serious consideration of a reaction

(29) Jencks, W. P. *Chem. Rev.* 1972, 72, 705.

(30) Snyder, J. K.; Stock, L. M. *J. Org. Chem.* 1980, 45, 886.

(31) Deslongchamps, P. *Tetrahedron* 1975, 31, 2463.

(32) The reactions of the sodium and ammonium salts of cyanate, carbonate, and carbamate ions have been studied for many years. Although uncertainties remain, the rates of most of the reactions important for an understanding of the product distribution in the decomposition of the carbamate ion have been measured. The recent articles by K. J. Hall and D. W. Watts [*Aust. J. Chem.* 1977, 30, 781, 903] contain many leading references.

at the nitroso group in basic aqueous solution. Rather, the available information strongly supports the conclusion that the reaction occurs via a tetrahedral intermediate over a broad pH range.

Experimental Section

Caution: The alkylnitrosoureas are suspected to be carcinogenic substances. Suitable precautions must be observed in work with these compounds.

Materials. The methods for the preparation of the ureas and nitrosoureas used in this work have been recently described.³⁰ *N*-Methyl-*N*-nitrosourea (mp 123–124 °C), *N,N*-dimethyl-*N*-nitrosourea (mp 95–96 °C), and *N,N,N*-trimethyl-*N*-nitrosourea (a yellow oil) were freed of traces of residual urea by extraction of a chloroform solution with chilled water. Quite pure samples of the mono- and dimethyl derivatives were obtained directly. However, the trimethyl derivative required further purification by preparative thin-layer chromatography on silica gel with chloroform–methanol (8:1). The spectroscopic properties of the compounds were studied to examine the purity of the samples prior to kinetic work.

Kinetic Experiments. Solutions of the alkylnitrosoureas were prepared in very carefully dried methanol. These solutions were stored at –9 °C. Control experiments established that these stock solutions were stable for months. An aliquot of the stock solution (0.02–0.2 mL) was subsequently dissolved in a buffer solution (50 mL) at constant ionic strength at 25 °C. The concentrations of the alkylnitrosoureas in the kinetic experiments were about 10^{-3} – 10^{-4} M. The ionic strength of the solution was usually adjusted with 2 M potassium chloride solution.

The reaction rates were studied spectrophotometrically at the absorption maxima of the nitrosoureas (235, 224, and 237 nm, respectively, for the mono-, di-, and trimethyl derivatives). The experiments were conducted at 25 °C. The hydrolysis reactions were followed to a minimum of 2 half-lives. The absorbance after a minimum of 6 half-lives was adopted as A_{∞} . This value was generally between 0.00 and 0.01 absorbance units. When the reactions were very slow and it was impractical to measure A_{∞} directly, the average A_{∞} value determined for the more rapid reactions of the compound was adopted. Typical rate data are shown in Figures 1 and 2. All the rate constants presented in the tables are based on replicate experiments.

Kinetic Solvent Isotope Effect. Solutions of the buffer salts were prepared by the addition of boric anhydride or sodium phosphate to 99.8% deuterium oxide. The buffer concentrations were comparable to the concentrations used in the work with water. The pD was adjusted to the desired value by the addition of sodium deuterioxide or deuterium chloride solutions. The pD was determined by the method of Glasoe and Long.³³ The reaction solutions were prepared and studied as previously described.

The kinetic solvent isotope effect was also determined for the reaction in the presence of hydrogen chloride in water and deuterium chloride in deuterium oxide. The concentrations of the acids were determined by the Volhard method. The reactions were studied as previously described.

Isotope-Exchange Experiments. The exchange between water enriched in ^{18}O and *N*-methyl-*N*-nitrosourea was first studied in nearly neutral solution. A suitable experimental procedure was developed in preliminary work with unlabeled compounds. A phosphate buffer was employed because the oxygen atom exchange rate is slow for this anion.³⁴ *N*-Methyl-*N*-

nitrosourea (0.048 mmol) was dissolved in methanol (0.1 mL), 90% ^{18}O -enriched water (0.53 mL) was added, and the volume was adjusted to 2 mL with the phosphate buffer solution (0.1173 M, pH 7.50). The pH of this solution was 6.64. After 1.55 h, an aliquot (0.1 mL) of the reaction solution was withdrawn and diluted to 10 mL with water. Measurement of the absorbance of the remaining nitrosourea indicated that the reaction was 40.2% complete. The remainder of the solution was extracted with ether (5 × 5 mL). The ether solution was washed with water (10 mL) and brine solution (2 × 10 mL) and then dried over sodium sulfate. The mixture was filtered, and the ether was removed in vacuo. The isotopic composition of the residue was studied by mass spectroscopy. There was no discernible enhancement of the signal at *m/e* 105. Control experiments suggested that an ^{18}O content of 0.5% in the methylnitrosourea could have been readily determined. These results indicate that k_h/k_e is greater than 8 for water with 100% ^{18}O .

The exchange reaction was also examined in basic solution by using a borate buffer. A proportionately greater amount of ^{18}O was used in this experiment to compensate for the slow rate of the exchange reaction with the nitrosourea and for the rapid rate of the exchange reaction of borate anion.³⁴ *N*-Methyl-*N*-nitrosourea (0.054 mmol) was dissolved in methanol (0.1 mL), 90% ^{18}O -enriched water (1.0 mL) was added, and the volume was adjusted to 2 mL with the borate buffer solution (0.200 M, pH 9.53). The pH of this solution was 9.53. The reaction was allowed to proceed for 30 s. Control experiments indicated that the reaction was 60% complete at this time. The residual *N*-methyl-*N*-nitrosourea was isolated as described previously and studied by mass spectroscopy. The spectrum indicated that the ratio of the *m/e* 103 and 105 signals was increased to 0.86%. These results define k_h/k_e to be 28.0 ± 2.8 for water with 100% ^{18}O .

Reaction Products. Several methods were employed to determine the product distributions. In one method, the nitrosourea (0.1 mmol) was dissolved in an aqueous buffer solution (2 mL). Aliquots of the solution were studied by thin-layer chromatography on silica gel (eluent, 1:5 methanol–chloroform). The nitrosoureas were monitored by study of the plates under ultraviolet light. The ureas and methylureas were monitored visually after treatment of the plate with *p*-(dimethylamino)benzaldehyde.³⁵ Aliquots of the reaction solution were also analyzed for isocyanate, carbonate, and carbamate ions by known procedures.³⁶ When the chromatographic analysis indicated that the reaction was complete, the mixture was distilled to separate methanol from the other reaction products. The quantity of methanol produced in the reaction was determined by NMR spectroscopy. The concentrated residue was dissolved in deuterium oxide or dimethyl- d_6 sulfoxide for the examination of the NMR spectrum.

In a second approach, a known quantity of the nitrosourea (about 3.5 mg) was dissolved in deuterium oxide (about 0.5 mL) or a solution of deuterium chloride in deuterium oxide. The progress of the reaction was monitored by NMR at 270 MHz. The reaction products were identified by the appearance of characteristic resonance signals which had been established by the study of authentic compounds under identical conditions.

The curious product distributions observed in acid solution prompted us to examine the behavior of methylurea and trimethylurea under the same reaction conditions. It was found that these molecules were unchanged after prolonged contact with 0.01, 0.1, and 1 M hydrochloric acid.

Registry No. MNU, 684-93-5; TMNU, 3475-63-6; DMNU, 13256-32-1.

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