The Chemistry of Nitroso-compounds. Part IX.[1] General Acid Catalysed Decomposition of *N*-Nitroso-2-pyrrolidone, an Example of Amide Hydrolysis *via* S_N2 Displacement on the *N*-Conjugate Acid

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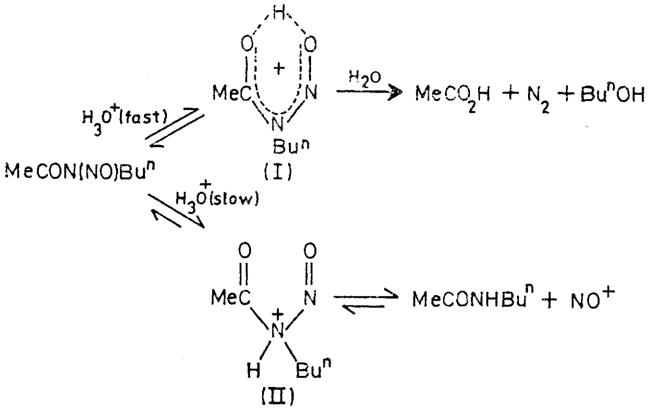
Decomposition of *N*-nitroso-2-pyrrolidone in mildly acidic aqueous solutions proceeds by concurrent pathways resulting in either denitrosation or deamination. The acid-catalysed component of both pathways is shown to involve a common rate limiting step, which is an unusually slow protonation of the amino nitrogen atom: the *N*-conjugate acid then rapidly partitions *via* the two decomposition pathways to products. In aqueous buffer solutions of CF_3CO_2H, $Me_3\overset{+}{N}CH_2CO_2H$, Cl_2CHCO_2H, and $ClCH_2CO_2H$ Brønsted general acid catalysis is observed and the results lead to a common Brønsted plot for both deamination and denitrosation with $\alpha = 0{\cdot}64$. With high concentrations of the buffer components, the rates reach a limiting value for both decomposition pathways, which shows that neither deamination nor denitrosation of the *N*-conjugate acid intermediate requires an additional molecule of base. For denitrosation, decomposition of the *N*-conjugate acid is a unimolecular process: for deamination, however, decomposition is bimolecular involving the solvent water, which is well able to compete with the weakly basic buffer anions. The results provide the first authenticated example of an amide hydrolysis reaction proceeding *via* an *N*-conjugate acid species. Reasons for the preference of this pathway (instead of *via* the more usual *O*-conjugate acid) are discussed in terms of the cyclic amide structure rather than the presence of an *N*-nitroso-group. Further, the results show that *N*-nitroso-amides may undergo denitrosation as well as deamination under mild conditions which has an important bearing on carcinogenesis by these compounds.

We have shown[1] that *N*-n-butyl-*N*-nitrosoacetamide decomposes in aqueous $HClO_4$ and H_2SO_4 by two concurrent acid-catalysed pathways (Scheme 1) involving either deamination or denitrosation. The deamination reaction is believed to proceed *via* the *O*-conjugate acid (I), formed in a rapid pre-equilibrium step, whereas denitrosation involves rate-limiting protonation of the amino nitrogen atom to give (II), which rapidly decomposes to release nitrous acid (NO^+) and *N*-n-butylacetamide. Deamination is the principal decomposition pathway at low acidity, whereas denitrosation predominates at $[HClO_4] \geqslant 4{\cdot}8$M.[1] The most remarkable feature of the denitrosation reaction is that proton transfer from the solvent to the amino nitrogen atom is rate limiting. With the exception of one or two recent examples,[2] proton transfer to either oxygen or nitrogen bases is usually rapid, more often than not proceeding on encounter.[3] The exceptional behaviour of *N*-n-butyl-*N*-nitrosoacetamide may be attributed to the strong electron-withdrawing ability of the nitroso-substituent. Our evidence for this slow H^+ transfer came from several kinetic parameters, in particular the positive solvent deuterium isotope effect $[k_0^{NO}(H_2SO_4)/k_0^{NO}(D_2SO_4)$ *ca.* 1·9] in sulphuric acid.[1] Although general acid catalysis would also be expected for this reaction it was not possible to demonstrate this phenomenon (apart from noting a faster rate in H_2SO_4 relative to $HClO_4$) for *N*-n-butyl-*N*-nitrosoacetamide because at low acidity decomposition occurred exclusively by the deaminative pathway.



Scheme 1 Acid catalysed deamination and denitrosation of *N*-n-butyl-*N*-nitrosoacetamide

We have therefore turned our attention to another substrate, *N*-nitroso-2-pyrrolidone, in which steric constraints might impede both the thermal[4] and spontaneous (water catalysed) deamination reactions. Denitrosation could then be effected under very mild conditions conducive to the observation of general acid catalysis. Examination of general acid catalysis for bases other than carbon promises useful information about the origin of the ‘ intrinsic energy barrier ’ invoked by Marcus[5] to account for the widely different rates of H^+ transfer reactions. Further the denitrosation of *N*-nitroso-amides under mild conditions is relevant to the induction of cancer by these compounds.[6] The decomposition of *N*-nitroso-2-pyrrolidone is complicated, however, by the concurrence of several pathways and here we concentrate on establishing the mechanism of the acid catalysed decomposition reactions.

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[1] Part VIII, C. N. Berry and B. C. Challis, *J.C.S. Perkin II*, 1974, 1638.

[2] M. L. Bade, *J. Amer. Chem. Soc.*, 1971, **93**, 949; F. Hibbert, *J.C.S. Chem. Comm.*, 1973, 463.

[3] M. Eigen, *Angew. Chem.*, 1964, **3**, 1.

[4] E. H. White and D. J. Woodcock, ‘ Chemistry of the Amino Group,. ed. S. Patai, Wiley, London, 1968, p. 407.

[5] R. A. Marcus, *J. Amer. Chem. Soc.*, 1969, **91**, 7224, and earlier papers cited therein.

[6] B. C. Challis and M. R. Osborne, *J.C.S. Perkin II*, 1973, 1526.

EXPERIMENTAL

Substrates and Reagents.—*N*-Nitroso-2-pyrrolidone was prepared by nitrosation of the parent lactam following the procedure of Huisgen and Reinertshofer.[7] Thus 2-pyrrolidone (15 g, 0·177 mol) in HCl (50 ml; 4N) was cooled to −5° when a solution of $NaNO_2$ (15 g, 0·218 mol) was added slowly while stirring the mixture. The resulting yellow solution was stirred for a further 30 min at −5°. The organic components were extracted into CH_2Cl_2, which was then washed repeatedly with H_2O before drying over $MgSO_4$. After removing CH_2Cl_2 under vacuum at room temperature, the residual red oil was distilled at 84—86° and 0·3 Torr to give *N*-nitroso-2-pyrrolidone (*ca.* 18 g, 89%) (lit.,[7] 86° at 0·3 Torr). The product analysed for $C_4H_6N_2O_2$ and showed the following spectral properties: $\nu_{max.}$ (thin film) 1760 cm^{-1}, $\lambda_{max.}$ (H_2O) 253 (log ε 3·868) and 426 nm (1·953), τ ($CDCl_3$) 6·23 (2H, m), 7·15 (2H, m), and 7·78 (2H, m).

AnalaR H_2SO_4, $HClO_4$, $NaNO_2$, $NaClO_4$, $Na_2B_4O_7,10H_2O$, $ClCH_2CO_2H$, and Cl_2CHCO_2H were used without further purification other than vacuum drying where appropriate. Reagent grade CF_3CO_2H was found on titration against standard NaOH to require no further purification. Reagent grade $Me_3\overset{+}{N}CH_2CO_2H\ Cl^-$ was twice recrystallised from EtOH–H_2O before use, and its purity also checked by titration.

TABLE 1

Independence of product ratios and reaction rates on the concentration of HNO_2 trap for decomposition of *N*-nitroso-2-pyrrolidone at 25°. Initial [*N*-nitroso-2-pyrrolidone] *ca.* 2 × 10^{-4}—10^{-3}M

$[HClO_4]$/M	[Salt]/M	$10^4[p\text{-}ClC_6H_4NH_2]$/ M	$\%[HNO_2]_\infty$	10^5k_0 *	$10^5k_0^{NO}$ *	$10^5k_0^{N_2}$ *
0·01				5·28		
0·01		10		5·12		
0·01	1·0 $MgCl_2$	1	7·5	4·15	0·31	3·84
0·01	1·0 $MgCl_2$	5	8·0	4·17	0·33	3·84
0·01	1·0 $MgCl_2$	10	7·3	4·12	0·30	3·82
0·01	1·5 $NaClO_4$		10·1	2·16	0·19	1·97
0·01	1·5 $NaClO_4$	10	12·2	1·61	0·20	1·42

* k_0, k_0^{NO}, and $k_0^{N_2}$ in s^{-1}.

Kinetics.—Overall decomposition rates were measured mainly from the decrease in absorption of the substrate by monitoring the reaction solution at either 253 or 426 nm. Details of the method have been described.[1] The amount of HNO_2 released by the reaction was ascertained by coupling with sulphanilamide (Shinn's method [8]) or with *p*-chloroaniline. Details of Shinn's method have also been described.[1]

Modified Shinn's Method.—Because diazotisation of sulphanilamide (the normal Shinn's reagent [8]) is slow and incomplete at pH >1·0, the more reactive *p*-chloroaniline was used to estimate the released HNO_2 by a colorimetric procedure involving the formation of an azo dye. With *p*-chloroaniline, diazotisation was complete within 30 min, and the resultant *p*-chlorobenzenediazonium ion proved to be stable for at least 48 h in aqueous solution at 25°. The diazonium ion was coupled with disodium 3-hydroxynaphthalene-2,7-disulphonate in borax solution (pH 9·2) to give an orange azo dye, $\lambda_{max.}$ 495 nm (log ε 4·36). Experiments summarised in Table 1 showed that the presence of *p*-chloroaniline had no effect on either the rate of decomposition of *N*-nitroso-2-pyrrolidone or the product ratio.

RESULTS

The overall decomposition of *N*-nitroso-2-pyrrolidone (the sum of the denitrosation and deamination reactions) followed equation (1). The results for a typical kinetic

$$\text{Rate} = k_0[N\text{-Nitroso-2-pyrrolidone}] \qquad (1)$$

experiment carried out in 0·05M-$HClO_4$, using the u.v. method at λ 426 nm to follow the reaction, are shown in Table 2, where k_0 is reasonably constant to *ca.* 90% reaction. Further, values of k_0 were independent of the presence of an HNO_2 trap (either sulphanilamide or *p*-chloroaniline) as were the amounts of HNO_2 released (Table 1). This demonstrates that reversibility of the denitrosation reaction is not important and, as for *N*-n-butyl-*N*-nitrosoacetamide reported earlier,[1] deamination and denitrosation result from concurrent first-order processes. Thus first order rate coefficients for each of these decomposition pathways (k_0^{NO} and $k_0^{N_2}$, respectively) were, as before, obtained from k_0 and the product ratio for each kinetic run by means of equations (2) and (3). Here, $\%[HNO_2]_t$ and $\%(\text{Reaction})_t$

$$k_0^{NO} = k_0\ \%[HNO_2]_t/\%(\text{Reaction})_t \qquad (2)$$

$$k_0^{N_2} = k_0 - k_0^{NO} \qquad (3)$$

refer to the amount of HNO_2 released and the overall extent of reaction, respectively, at time *t*. Where feasible, the

TABLE 2

Decomposition of *N*-nitroso-2-pyrrolidone in 0·05M-$HClO_4$–0·95M-$NaClO_4$ at 25°. Initial [*N*-nitroso-2-pyrrolidone] 4·8 × 10^{-3}M

t/min	*A*(426 nm)	% Reaction	$10^5k_0/s^{-1}$
0	0·428	0	
65	0·361	15·7	4·36
125	0·311	27·3	4·14
245	0·235	45·1	3·90
365	0·175	59·1	4·10
512	0·124	71·0	3·90
634	0·093	78·3	4·00
752	0·069	83·9	4·15
872	0·053	87·6	3·74
∞	0		

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[7] R. Huisgen and J. Reinertshofer, *Annalen*, 1952, **575**, 197.

[8] M. B. Shinn, *Ind. Eng. Chem. Analyt.*, 1941, **13**, 33; N. F. Kershaw and N. S. Chamberlin, *ibid.*, 1942, **14**, 312.

product ratio was assessed at complete reaction (t ∞) to minimise error. Both the derivation and application of equations (2) and (3) have been discussed previously.[1]

TABLE 3

Decomposition rates of *N*-nitroso-2-pyrrolidone in dilute $HClO_4$ at 25°. Initial [*N*-nitroso-2-pyrrolidone] 2—8 × 10^4M

$[HClO_4]$/M	$[NaClO_4]$/M	$10^5k_0/s^{-1}$	$\%[HNO_2]_\infty$	$10^5k_0^{NO}/s^{-1}$	$10^5k_0^{N_2}/s^{-1}$
0·01		5·28	3·3	0·18	5·11
0·05		6·30	11·9	0·75	5·56
0·10		8·48	21·9	1·86	6·63
0·20		12·0	27·8	3·33	8·67
0·30		16·2	36·0	5·83	10·4
0·40		19·7	42·9	8·45	11·2
0·01	0·99	2·70	7·9	0·24	2·47
0·05	0·95	4·03	25·3	1·02	3·02
0·07	0·93	5·25	27·9	1·48	3·77
0·10	0·90	6·40	33·6	2·15	4·25

The reaction of *N*-nitroso-2-pyrrolidone was examined in this way for various aqueous acidic and buffer solutions at 25°. Experimental values of k_0 and $\%[HNO_2]_\infty$ are listed in Tables 3—9, together with k_0^{NO} and $k_0^{N_2}$ derived from these data. For $HClO_4$ (Table 3), results for low concentrations (⩽0·4M) only are reported and the kinetic behaviour at high acidities will be dealt with subsequently. For buffer solutions of CF_3CO_2H, Cl_2CHCO_2H, and $ClCH_2CO_2H$ (Tables 4—6), decomposition was examined at two different buffer ratios so that any contribution to the deamination reaction from a nucleophilic or base-catalysed pathway could be assessed. Catalyses by both Cl_2CHCO_2H and $ClCH_2CO_2H$ were also examined in the presence of a fairly high, constant $[HClO_4]$, and these results are given in Table 7. Under these conditions, the chloroacetic acids are present overwhelmingly in their un-ionised forms, so this is equivalent to measuring their catalysis with an infinitely high buffer ratio ($[HA]/[A^-]$). For decomposition in betaine buffers ($Me_3\overset{+}{N}CH_2CO_2H \rightleftharpoons Me_3\overset{+}{N}CH_2CO_2^- + H_3O^+$), considerable difficulty was experienced in obtaining reproducible results which appeared to be linked to interaction between betaine and the nitrous acid trap. Reproducible data were obtained for the buffer ratio, $[Me_3\overset{+}{N}CH_2CO_2H]/[Me_3\overset{+}{N}CH_2CO_2^-] = 0·903$, and these are given in Table 8.

TABLE 4

Decomposition rates of *N*-nitroso-2-pyrrolidone in CF_3CO_2H buffers at 25°. Initial [*N*-nitroso-2-pyrrolidone] *ca.* 1—4 × 10^{-3}M, μ 1·0 ($NaClO_4$)

$[CF_3CO_2H]$/M	$10^5k_0/s^{-1}$	$\%[HNO_2]_\infty$	$10^5k_0^{NO}/s^{-1}$	$10^5k_0^{N_2}/s^{-1}$
Buffer ratio ($[HA]/[A^-]$) 0·309				
0·095	10·95	32·6	3·57	7·37
0·142	12·2	33·2	4·05	8·15
0·177	13·1	35·8	4·67	8·38
0·213	14·5	35·4	5·11	9·33
0·284	16·6	36·1	5·99	10·6
0·354	17·1	38·8	6·60	10·5
Buffer ratio ($[HA]/[A^-]$) 0·578				
0·33	21·5	41·0	8·61	12·9
0·385	23·8	40·5	9·52	14·3
0·44	25·2	38·6	9·72	15·6
0·55	29·9	39·8	12·0	18·0

No acid catalysed decomposition, either denitrosation or deamination, could be detected in buffer solutions of acids weaker than HCO_2H (pK_a 3·75),[9] but deamination did proceed by a nucleophilic/general base catalysed pathway as shown by the results in Table 9. The absence of any

TABLE 5

Decomposition rates of *N*-nitroso-2-pyrrolidone in Cl_2CHCO_2H buffers at 25°. Initial [*N*-nitroso-2-pyrrolidone] 1—4 × 10^{-3}M, μ 1·0 ($NaClO_4$)

$[Cl_2CHCO_2H]$/M	$10^5k_0/s^{-1}$	$\%[HNO_2]_\infty$	$10^5k_0^{NO}/s^{-1}$	$10^5k_0^{N_2}/s^{-1}$
Buffer ratio ($[HA]/[A^-]$) 1·7				
0·189	5·08	28·9	1·47	3·61
0·378	7·20	31·5	2·27	4·93
0·504	8·25	32·3	2·67	5·59
0·629	9·19	34·3	3·16	6·04
0·755	10·7	32·6	3·47	7·18
0·881	9·68	33·7	3·22	6·45
1·007	9·79	32·6	3·19	6·59
Buffer ratio ($[HA]/[A^-]$) 0·519				
0·102	4·45	15·1	0·67	3·78
0·205	5·53	17·4	0·96	4·56
0·273	6·42	17·7	1·14	5·29
0·342	6·76	19·0	1·28	5·47
0·410	6·97	19·3	1·35	5·64
0·478	7·23	19·1	1·38	5·86

TABLE 6

Decomposition rates of *N*-nitroso-2-pyrrolidone in $ClCH_2CO_2H$ buffers at 25°. Initial [*N*-nitroso-2-pyrrolidone] 1—4 × 10^{-3}M, μ 1·0 ($NaClO_4$)

$[ClCH_2CO_2H]$/M	$10^5k_0/s^{-1}$	$\%[HNO_2]_\infty$	$10^5k_0^{NO}/s^{-1}$	$10^5k_0^{N_2}/s^{-1}$
Buffer ratio ($[HA]/[A^-]$) 11·01				
0·551	3·42	12·6	0·43	2·98
0·826	3·88	14·2	0·55	3·33
1·101	4·38	14·3	0·63	3·75
1·378	4·42	16·5	0·73	3·68
Buffer ratio ($[HA]/[A^-]$) 2·32				
0·210	3·31	4·81	0·16	3·15
0·419	3·58	6·27	0·22	3·36
0·629	4·17	6·56	0·27	3·89
0·838	4·64	7·26	0·34	4·30
1·048	4·61	7·05	0·33	4·28
1·257	4·90	6·89	0·34	4·56

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[9] From the compilation by G. Kortüm, W. Vogel, and K. Andrussow, ' Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961.

significant acid catalysis by either HCO_2H or $MeCO_2H$ was further confirmed by showing that addition of these acids had no effect on the rates or products of decomposition in dilute $HClO_4$ (Table 7).

DISCUSSION

Decomposition of *N*-nitroso-2-pyrrolidone in acidic media is similar to that of *N*-n-butyl-*N*-nitrosoacetamide reported previously [1] in that two products are obtained (from either deamination or denitrosation of the substrate) by processes each bearing a first-order dependence on the nitrosamide concentration [equation (4)]. Both compounds have a similar overall decomposition rate (in 0·1M-$HClO_4$, $k_0 = 1{\cdot}7 \times 10^{-5}$ and $6{\cdot}4 \times 10^{-5}$ s^{-1} for

$$\text{Rate} = (k_0^{\mathrm{NO}} + k_0^{\mathrm{N_2}})[N\text{-Nitroso-2-pyrrolidone}] \quad (4)$$

N-n-butyl-*N*-nitrosoacetamide and *N*-nitroso-2-pyrrolidone, respectively) but denitrosation is much more important for *N*-nitroso-2-pyrrolidone: for example, in 0·1M-$HClO_4$ denitrosation contributes 22% to the decomposition of *N*-nitroso-2-pyrrolidone but nothing to that of *N*-n-butyl-*N*-nitrosoacetamide.[1] This difference prevails in more mildly acidic media and makes feasible the observation of general acid catalysis.

TABLE 7

Effect of added buffer acids on the decomposition rates of *N*-nitroso-2-pyrrolidone in $HClO_4$ at 25°

$[\mathrm{Cl_2CHCO_2H}]$/M	$[\mathrm{HClO_4}]$/M	$10^5k_0/s^{-1}$	$\%[\mathrm{HNO_2}]_\infty$	$10^5k_0^{\mathrm{NO}}/s^{-1}$	$10^5k_0^{\mathrm{N_2}}/s^{-1}$
0·10	1·0	46·4	46·7	21·7	24·8
0·50	1·0	45·3	52·9	24·0	22·5
0·75	1·0	48·0	52·7	25·5	23·0
1·00	1·0	47·7	53·4	25·5	22·2
1·25	1·0	48·5	54·9	26·8	21·8
1·50	1·0	49·8	53·8	26·8	22·9
$k^{\mathrm{NO}}_{\mathrm{Cl_2CHCO_2H}}$ $0{\cdot}35 \times 10^{-4}$ l mol^{-1} s^{-1}					
$[\mathrm{ClCH_2CO_2H}]$/M					
0·10	0·1	9·43	14·8	1·40	8·04
0·50	0·1	9·30	16·2	1·51	7·78
1·00	0·1	9·50	17·2	1·63	7·86
2·50	0·1	9·12	21·7	1·98	7·13
$k^{\mathrm{NO}}_{\mathrm{ClCH_2CO_2H}}$ $0{\cdot}023 \times 10^{-4}$ l mol^{-1} s^{-1}					

TABLE 8

Decomposition rates of *N*-nitroso-2-pyrrolidone in betaine buffers at 25°

$[\mathrm{Me_3\overset{+}{N}CH_2CO_2HCl^-}]$/M	$10^5k_0/s^{-1}$	$\%[\mathrm{HNO_2}]_\infty$	$10^5k_0^{\mathrm{NO}}/s^{-1}$	$10^5k_0^{\mathrm{N_2}}/s^{-1}$
Buffer ratio ([HA]/[A⁻]) 0·903				
0·095	3·30	9·2	0·31	2·99
0·190	3·43	10·2	0·35	3·08
0·142	3·68	10·6	0·39	3·29
0·237	3·95	10·9	0·43	3·52
0·285	4·81	9·3	0·45	4·36
0·332	5·09	9·3	0·47	4·62
0·380	5·01	9·1	0·46	4·55

Aqueous $HClO_4$.—Here only catalysis by H_3O^+ is expected and the decomposition kinetics are therefore simpler. The variation of k_0^{NO} and $k_0^{\mathrm{N_2}}$ with $HClO_4$ is shown in Figure 1. The zero intercept for denitrosation shows that only an acid catalysed pathway is important and equation (5) therefore follows. For the deamination

$$k_0^{\mathrm{NO}} = k_{\mathrm{H_3O^+}}^{\mathrm{NO}}[\mathrm{H_3O^+}] \quad (5)$$

reaction, however, there is clearly both an acid catalysed ($k_{\mathrm{H_3O^+}}^{\mathrm{N_2}}$) and a spontaneous uncatalysed ($k_{\mathrm{spont}}^{\mathrm{N_2}}$) component and the observed rate is expressed as equation (6). We believe that the spontaneous deamination comes from thermal decomposition [4] and

$$k_0^{\mathrm{N_2}} = k_{\mathrm{spont}}^{\mathrm{N_2}} + k_{\mathrm{H_3O^+}}^{\mathrm{N_2}}[\mathrm{H_3O^+}] \quad (6)$$

from catalysis by the solvent water mechanistically similar to that observed for both HCO_2^- and $MeCO_2^-$ (see above).

The most striking feature of Figure 1, however, is the close similarity of slopes for the k_0^{NO} and $k_0^{\mathrm{N_2}}$ plots and this is borne out by the almost identical values of $k_{\mathrm{H_3O^+}}^{\mathrm{NO}}$ and $k_{\mathrm{H_3O^+}}^{\mathrm{N_2}}$ summarised in Table 10. The

TABLE 9

Decomposition rates of *N*-nitroso-2-pyrrolidone in $MeCO_2H$ and HCO_2H buffers at 25°

$[\mathrm{HCO_2H}]$/M	$10^5k_0/s^{-1}$	$\%[\mathrm{HNO_2}]_\infty$	$10^5k_0^{\mathrm{NO}}/s^{-1}$	$10^5k_0^{\mathrm{N_2}}/s^{-1}$
Buffer ratio ([HA]/[A⁻]) 5·62				
0·505	3·30	1·99	0·07	3·23
1·006	3·93	1·92	0·08	3·75
1·502	4·80	0	0	4·80
2·00	5·30	0	0	5·30
2·50	5·90	0	0	5·90
Buffer ratio ([HA]/[A⁻]) 1·0				
0·25	4·23	0	0	4·23
0·50	7·35	0	0	7·35
0·75	10·8	0	0	10·8
1·00	13·4	0	0	13·4
$[\mathrm{MeCO_2H}]$/M				
Buffer ratio ([HA]/[A⁻]) 1·0				
0·25	5·81	0	0	5·81
0·50	9·48	0	0	9·48
0·75	14·5	0	0	14·5
1·00	20·3	0	0	20·3

implication is that, unlike *N*-n-butyl-*N*-nitrosoacetamide, H_3O^+ catalysed deamination and denitrosation of *N*-nitroso-2-pyrrolidone proceed *via* a common rate-limiting step, and *inter alia*, a common conjugate acid intermediate.

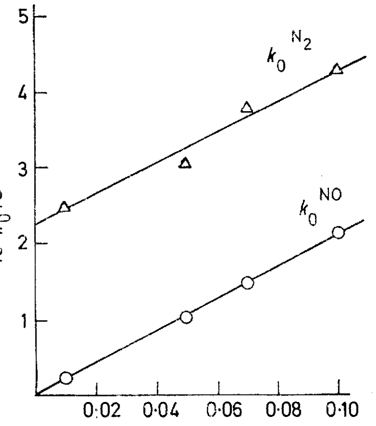


FIGURE 1 Rates of denitrosation (k_0^{NO}) and deamination ($k_0^{N_2}$) of *N*-nitroso-2-pyrrolidone in dilute $HClO_4$ ($\mu = 1{\cdot}0$) at 25°

TABLE 10

Catalytic rate coefficients for the decomposition of *N*-nitroso-2-pyrrolidone at 25°

Catalyst (HA)	pK_a (Catalyst)[9]	$10^4k_{HA}^{NO}$/ l mol^{-1} s^{-1}	$10^4k_{HA}^{N_2}$/ l mol^{-1} s^{-1}	$10^4k_{A^-}^{N_2}$/ l mol^{-1} s^{-1}
H_3O^+	−1·75	2·11	2·03	
CF_3CO_2H	0·22	1·71 (1·78)	1·58	1·71
Cl_2CHCO_2H	1·37	0·33 (0·33)	0·32	0·31
$Me_3\overset{+}{N}CH_2CO_2H\ Cl^-$	1·82	0·097		
$ClCH_2CO_2H$	2·87	0·03 (0·04)	0·07	0·49
HCO_2H	3·75			1·21
$MeCO_2H$	4·75			1·57

[a] Values in parentheses obtained from different buffer ratios.

Aqueous Buffer Solutions.—The above mechanistic deductions are strongly supported by the kinetic data for decomposition in aqueous buffer solutions. It is clear from Tables 4—6 that both deamination and denitrosation rates increase with increasing concentration of the buffer components, and, since these studies were made at constant pH, this is evidence of general acid catalysis. The derivation of catalytic rate coefficients for this general acid (HA) catalysis is simpler for the denitrosation pathway, for which there is no evidence of either base catalysis or a significant spontaneous rate. In this case the observed rate of denitrosation (k_0^{NO}) is related to the catalytic coefficients by equation (7), so the intercept and slope of

$$k_0^{NO} = k_{H_3O^+}^{NO}[H_3O^+] + k_{HA}^{NO}[HA] \qquad (7)$$

the plot of k_0^{NO} *versus* [HA] yield values of $k_{H_3O^+}^{NO}$ and k_{HA}^{NO}, respectively. For the deaminative pathway, however, the kinetic analysis is further complicated (over that for aqueous $HClO_4$) by an additional term corresponding to a contribution from catalysis by the buffer anion (A^-). The dependence of the observed rate on the buffer components is therefore given by equation (8), and for the usual plot of $k_0^{N_2}$ *versus* [HA]

$$k_0^{N_2} = k_{spont}^{N_2} + k_{H_3O^+}^{N_2}[H_3O^+] + k_{HA}^{N_2}[HA] + k_{A^-}^{N_2}[A^-] \qquad (8)$$

the intercept comprises the first two terms of equation (8) and the slope equals the sum of $k_{HA}^{N_2} + k_{A^-}^{N_2}[A^-]/[HA]$. From information obtained at two different buffer ratios ($[A^-]/[HA]$), however, both $k_{HA}^{N_2}$ and $k_{A^-}^{N_2}$ may be ascertained (see Table 10).

The variation of both $k_0^{N_2}$ and k_0^{NO} with $[Cl_2CHCO_2H]$, a typical example, is illustrated by Figures 2 and 3: the buffer ratios ($[Cl_2CHCO_2^-]/[Cl_2CHCO_2H]$), are 0·519 and 1·7, respectively. All four plots show the expected linear form at the lower buffer component concentrations, but clearly both $k_0^{N_2}$ and k_0^{NO} reach a limiting value when $[Cl_2CHCO_2^-] >$ *ca.* 0·6M. This diminution of buffer catalysis has important mechanistic implications which are discussed further below. Beforehand it is convenient to examine the linear portions of these and related plots for the other buffer solutions.

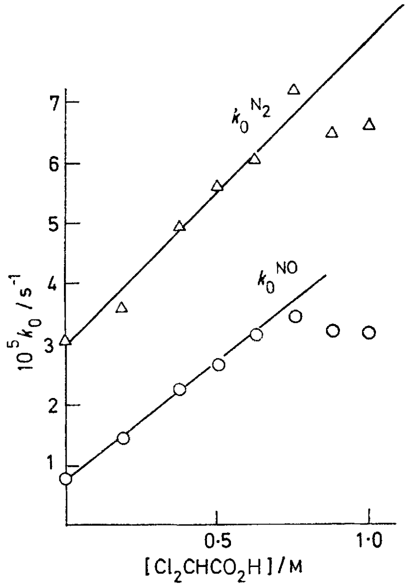


FIGURE 2 Rates of denitrosation (k_0^{NO}) and deamination ($k_0^{N_2}$) of *N*-nitroso-2-pyrrolidone in Cl_2CHCO_2H buffers at 25° with buffer ratio ($[HA]/[A^-]$) = 1·7

Second-order rate coefficients for Cl_2CHCO_2H catalysed denitrosation obtained from Figures 2 and 3 ($k^{NO}_{Cl_2CHCO_2H}$ $3{\cdot}29 \times 10^{-5}$ and $3{\cdot}33 \times 10^{-5}$ l mol^{-1} s^{-1} at $[Cl_2CHCO_2^-]/[Cl_2CHCO_2H]$ 0·519 and 1·7, respectively) are in reasonable agreement, indicating independently the absence of significant base catalysed denitrosation. Also, the intercepts for both these plots agree well with the value of $k_{H_3O^+}^{NO}$ obtained in dilute $HClO_4$. For deamination, however, the slopes in Figures 2 and 3 are substantially different, and solution of the relevant simultaneous equations leads to values of $k^{N_2}_{Cl_2CHCO_2H} = 3{\cdot}17 \times 10^{-5}$ and $k^{N_2}_{Cl_2CHCO_2^-} = 3{\cdot}11 \times 10^{-5}$ l mol^{-1} s^{-1}.

Plots similar to Figures 2 and 3 are obtained for decomposition of *N*-nitroso-2-pyrrolidone in CF_3CO_2H, $ClCH_2CO_2H$, and $Me_3\overset{+}{N}CH_2CO_2H$ buffer solutions. All show a limiting value for $k_0^{N_2}$ and k_0^{NO} at high buffer anion concentrations, but second-order catalytic rate coefficients have been evaluated as above from the linear portion of the curve at lower anion concentrations. These coefficients are summarised in Table 10 from which two significant points emerge. The first is that values of k_{HA}^{NO} are independent (within experimental error) of the buffer ratio, but clearly increase with the acid strength of HA. The second is that k_{HA}^{NO} and $k_{HA}^{N_2}$ are usually of similar magnitude, as for H_3O^+ catalysis: the exception for $ClCH_2CO_2H$ is where the base catalysed pathway makes an overwhelming (*ca.* >90%) contribution to the overall deamination rate and errors in the acid catalysed term are therefore likely to be large.

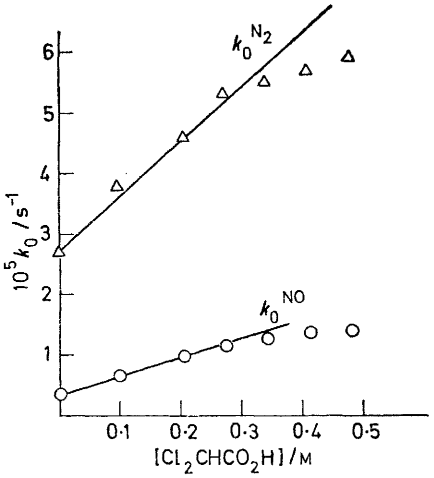


FIGURE 3 Rates of denitrosation (k_0^{NO}) and deamination ($k_0^{N_2}$) of *N*-nitroso-2-pyrrolidone in Cl_2CHCO_2H buffers at 25° with buffer ratio ($[HA]/[A^-]$) = 0·519

It is also evident from Table 10 that values of $k_{A^-}^{N_2}$ increase with the base strength of A^-, which accounts for the different kinetic behaviour observed in HCO_2H and $MeCO_2H$ buffers. In particular, these reactions show no evidence of either an acid catalysed decomposition (deamination or denitrosation) or a rate maximum at high buffer anion concentrations. Presumably, the fast base catalysed deamination precludes the observation of any acid catalysed reaction. In any event $k_0^{N_2}$ in HCO_2H and $MeCO_2H$ buffers shows a simple first-order dependence on either $[MeCO_2^-]$ or $[HCO_2^-]$ and the values of $k_{A^-}^{N_2}$ obtained are also listed in Table 10.

Mechanism of the General Acid Catalysed Decomposition Reactions.—Our kinetic investigations reveal a hitherto unrealised multiplicity in the decomposition reactions of *N*-nitroso-amides. Apart from the formation of two different sets of products arising, in the broadest sense, from either denitrosation or deamination of the substrate, it is clear that deamination may occur by several concurrent pathways. Here, we wish to concern ourselves primarily with the acid catalysed decomposition reactions.

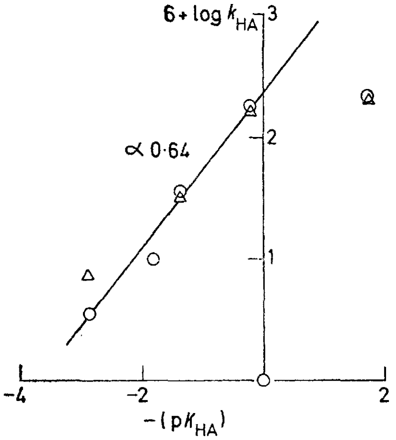
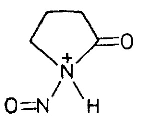


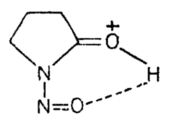
FIGURE 4 Brønsted plot for the acid catalysed denitrosation and deamination of *N*-nitroso-2-pyrrolidone at 25°: ○ k_{HA}^{NO}; △ $k_{HA}^{N_2}$

Denitrosation of *N*-nitroso-2-pyrrolidone is clearly catalysed by general acids in the Brønsted sense and the kinetic data, with the often-noted exception of H_3O^+, are collated by the Brønsted relationship[10] (Figure 4) with a slope (α) of 0·64. Bearing in mind that the denitrosation reaction is known[1,11] to be subject to a substantial primary deuterium isotope effect when carried out in deuteriated solvents, the only consistent mechanism is one involving a slow proton transfer to form a conjugate acid species. The results suggest, further, that the same rate limiting step applies to the acid catalysed deamination of *N*-nitroso-2-pyrrolidone. Both the k_{HA}^{NO} and $k_{HA}^{N_2}$ coefficients are remarkably similar for all the catalysts examined and these data lead to the generation of a common Brønsted plot as shown in Figure 4.

Two common conjugate acid species, (III) and (IV) may form from *N*-nitroso-2-pyrrolidone: (III) is the *N*-conjugate acid, (IV) an *O*-conjugate acid that may effect stabilisation by hydrogen bonding to both the



(III)



(IV)

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[10] J. N. Brønsted and K. J. Pedersen, *Z. phys. Chem.*, 1924, **108**, 185.

[11] B. C. Challis and S. P. Jones, to be published.

carbonyl and nitroso oxygen atoms. Both (III) and (IV) may, in principle, undergo the deamination and denitrosation reactions observed, but we have argued previously[1,12] why denitrosation is more likely to proceed *via* (III). In brief, the mainstay of the argument is that the rate of denitrosation is independent of the concentration of nucleophile added to trap HNO_2 (see Experimental section). Since denitrosation of (IV) could only be effected sensibly by nucleophilic attack on the nitroso nitrogen atom, it seems unlikely that this alternative would lead to the observed results. Further, slow proton transfer to form (III) is consistent with the low basicity of the amino nitrogen atom induced by electron withdrawal of the nitroso-substituent. We therefore believe that both denitrosation and deamination (hydrolysis) proceed *via* the *N*-conjugate acid (III).

We noted above that both $k_{\mathrm{HA}}^{\mathrm{N_2}}$ and $k_{\mathrm{HA}}^{\mathrm{NO}}$ reach limiting values at high buffer anion concentrations. The fact that these effects occur for both decomposition pathways concurrently is further evidence favouring a common rate limiting step. Their observation, however, has other important mechanistic implications which can be realised in terms of Scheme 2. This argument is easier to follow for the denitrosation pathway because there is independent evidence here (namely, that $k_{\mathrm{HA}}^{\mathrm{NO}}$ is independent of the concentration of the HNO_2 trap) that decomposition of the *N*-conjugate acid (III) must be a unimolecular process. In this event, the rate expression in terms of coefficients for the individual steps of Scheme 2 is described by equation (9), which

$$\text{Rate} = \frac{k_1 k_2'[N\text{-Nitroso-2-pyrrolidone}][\mathrm{HA}]}{k_{-1}[\mathrm{A}^-] + k_2'} \quad (9)$$

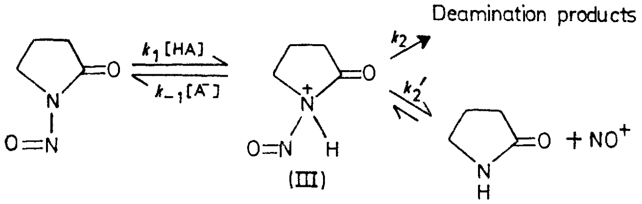
approximates to each of two limiting forms depending on the buffer anion concentration $[\mathrm{A}^-]$. Thus for low $[\mathrm{A}^-]$, $k_2' \gg k_{-1}[\mathrm{A}^-]$, and equation (10) showing a simple

$$\text{Rate} = k_1[N\text{-Nitroso-2-pyrrolidone}][\mathrm{HA}] \quad (10)$$

first order dependence on [HA] follows. For denitrosation, k_1 is equivalent to $k_{\mathrm{HA}}^{\mathrm{NO}}$ obtained from the linear portion of Figures 2 and 3. When $[\mathrm{A}^-]$ is large, however, $k_{-1}[\mathrm{A}^-] \gg k_2'$ and the rate expression approximates to equation (11). Accordingly, k_0^{NO} ($\simeq k_1k_2'/k_{-1}$)

$$\text{Rate} = \frac{k_1 k_2'[N\text{-Nitroso-2-pyrrolidone}][\mathrm{HA}]}{k_{-1}[\mathrm{A}^-]} \quad (11)$$

is then independent of [HA] but reaches a limiting value dependent on the magnitude of the fixed buffer ratio ($[\mathrm{HA}]/[\mathrm{A}^-]$).



SCHEME 2 General acid catalysed denitrosation and deamination of *N*-nitroso-2-pyrrolidone

Because $k_{\mathrm{HA}}^{\mathrm{N_2}}$ shows the same kinetic behaviour (*i.e.* limiting value) as $k_{\mathrm{HA}}^{\mathrm{NO}}$, it follows that deaminative breakdown (*i.e.* hydrolysis) of the *N*-conjugate acid (III) also cannot involve any significant catalysis by the buffer anion (A^-). This deduction is exceptional in as much as base catalysts are well known to facilitate the hydrolysis of neutral amides.[13] An explanation is forthcoming, however, from the rates of general base catalysed deamination of neutral *N*-nitroso-2-pyrrolidone (*i.e.* $k_{\mathrm{A^-}}^{\mathrm{N_2}}$) observed concurrently with the general acid catalysed pathway.

Preliminary data cited in Table 10 show that $k_{\mathrm{A^-}}^{\mathrm{N_2}}$ increases with base strength of A^- and, with the exception of the datum for $CF_3CO_2^-$, these results comply satisfactorily with the Brønsted relationship[10] (Figure 5) to give a slope (β) of *ca.* 0·2. The low β coefficient implies that even the neutral *N*-nitroso-2-pyrrolidone does not strongly discriminate between hydrolytic base catalysts of different strengths. This low selectivity will be attenuated further for hydrolysis of the more reactive *N*-conjugate acid and the outcome is that H_2O, present at 55·5M concentration, resoundingly overwhelms any catalysis by other basic species present even at the relatively high 1M level. The high efficiency of H_2O in attacking the carbonyl group of (III) manifests itself in other ways, such as salt effects and solvent deuterium isotope effects, to be reported subsequently.[11]

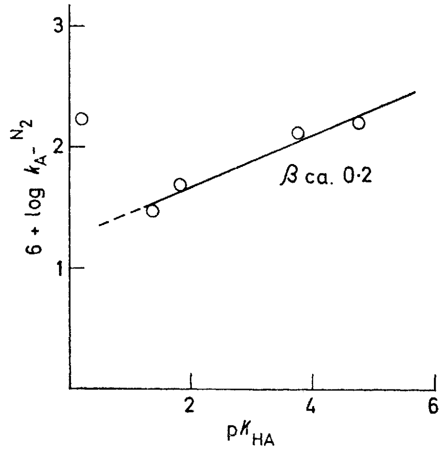


FIGURE 5 Brønsted plot for the base catalysed demination of *N*-nitroso-2-pyrrolidone at 25°

Amide Hydrolysis Reactions.—Continuing controversy[14] over the site of amide protonation in dilute acids has raised fundamental questions about the mechanism of amide hydrolysis and our results bear on this problem. There is some consensus[13,15] favouring

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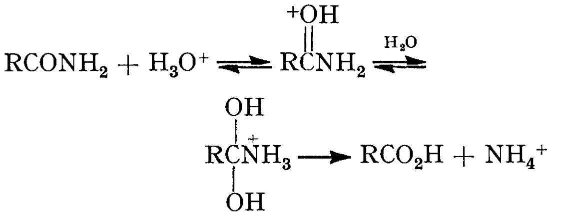
[12] B. C. Challis and S. P. Jones, *J.C.S. Chem. Comm.*, 1974, 748.

[13] B. C. Challis and J. A. Challis, ' Chemistry of the Amides,' ed. J. Zabicky, Wiley, London, 1971, p. 731.

[14] For example (*a*) M. Liler, *J.C.S. Perkin II*, 1972, 816; 1974, 71; (*b*) H. Benderly and K. Rosenhech, *J.C.S. Chem. Comm.*, 1972, 179; (*c*) R. B. Martin, *ibid.*, p. 793.

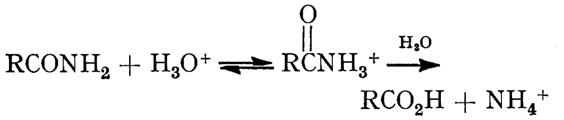
[15] C. J. O'Connor, *Quart. Rev.*, 1971, **24**, 553.

hydrolysis *via* an addition–elimination pathway of the *O*-conjugate acid [equation (12)], as suggested by Bender[16] several years ago. Many subsequent investigations[17] have provided indirect, but nonetheless substantial, support for Bender's hypothesis, although recently Liler[14a] has questioned this mechanism along with that of the site of amide protonation.



$$\mathrm{RCONH_2 + H_3O^+ \rightleftharpoons R\overset{{}^{+}OH}{\overset{\|}{C}}NH_2 \xrightleftharpoons{H_2O} R\underset{OH}{\overset{OH}{C}}\overset{+}{N}H_3 \longrightarrow RCO_2H + NH_4^+} \quad (12)$$

Amide hydrolyses *via* the alternative bimolecular pathway, a direct $S_{\mathrm{N}}2$ displacement on the *N*-conjugate acid [equation (13)], appear to be less common. This mechanism has been accepted for special cases, such as *N*-acetylimidazole,[18] *N*-acetylpyridinium ion,[19] and 2,2-dimethylquinuclidone[20] (where resonance interaction between nitrogen lone pair electrons and the carbonyl group is inhibited), but, with the exception noted above,[14a] not for simple amides, themselves. Bunton and his colleagues[21] have tentatively suggested, however, that the unusual acidity dependence of amide hydrolyses in concentrated acids may arise from the concurrence of both pathways.



$$\mathrm{RCONH_2 + H_3O^+ \rightleftharpoons R\overset{O}{\overset{\|}{C}}NH_3^+ \xrightarrow{H_2O} RCO_2H + NH_4^+} \quad (13)$$

Our results for *N*-nitroso-2-pyrrolidone constitute the first definitive evidence that amide hydrolyses may occur *via* the *N*-conjugate acid. It is not clear whether this pathway is favoured because of the cyclic amide system or the presence of the *N*-nitroso-group. However, we have deduced previously that hydrolysis (deamination) of *N*-n-butyl-*N*-nitrosoacetamide involves the *O*-conjugate acid.[1]

Carcinogenesis by N-*Nitroso-compounds*.—We have suggested[6] that certain *N*-nitroso-amines may act as proximate carcinogens by transferring their nitroso-groups to other compounds (transnitrosation). It is clear that this process may also occur for *N*-nitroso-2-pyrrolidone, although it is not possible to deduce whether transnitrosation occurs directly or *via* HNO_2 intermediates. Significantly, concurrent hydrolysis (deamination) produces a primary *N*-nitroso-amine, which may act as an alkylating agent. Both reactions proceed readily at the expected acidity of the stomach (pH 1—4), so *in vivo* experiments employing oral administration of these compounds such as *N*-nitroso-2-pyrrolidone may give misleading results.

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[4/1672 *Received*, 8*th August*, 1974]

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[17] For example, C. R. Smith and K. Yates, *Canad. J. Chem.*, 1972, **50**, 771.

[18] S. Marburg and W. P. Jencks, *J. Amer. Chem. Soc.*, 1962, **84**, 232.

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[20] H. Pracejus, *Chem. Ber.*, 1959, **92**, 988.

[21] C. A. Bunton, C. J. O'Connor, and T. A. Turney, *Chem. Ind.*, 1967, 1835; C. J. Hyland and C. J. O'Connor, *J.C.S. Perkin II*, 1973, 1402.