Acid-Catalysed Decomposition of *N*-Nitroso-2-pyrrolidone—A Rare Example of Amide Hydrolysis *via* S_N2 Displacement on the *N*-Conjugate Acid

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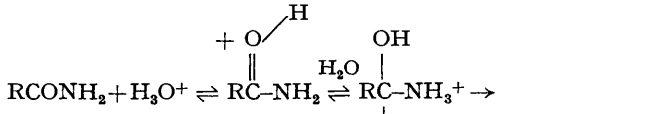
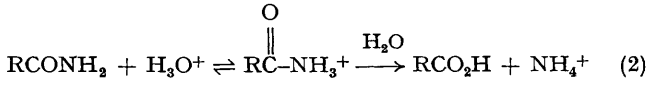
Summary The first definite proof that amide hydrolysis may proceed *via* a direct S_N2 displacement on the *N*-conjugate acid is reported for the acid-catalysed decomposition of *N*-nitroso-2-pyrrolidone.

THE site of amide protonation in dilute acids is still controversial[1] and raises fundamental questions about the mechanism of amide hydrolyses. For these, two distinct pathways can be envisaged, one involving an addition-elimination pathway for the *O*-conjugate acid [equation (1)] the other a direct S_N2 displacement on the *N*-conjugate



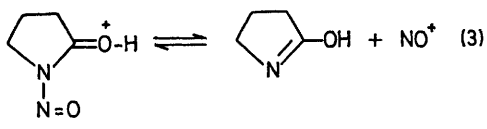
$$RCONH_2 + H_3O^+ \rightleftharpoons RC(OH)(NH_2)^+ \rightleftharpoons RC(OH)_2NH_3^+ \rightarrow RCO_2H + NH_4^+ \quad (1)$$



$$RCONH_2 + H_3O^+ \rightleftharpoons RC(=O)NH_3^+ \xrightarrow{H_2O} RCO_2H + NH_4^+ \quad (2)$$

acid [equation (2)]. Opinion has favoured equation (1),[2] based mainly on indirect evidence,[3] but Liler[1a] has recently questioned this conclusion and Bunton and his colleagues[4] have supported concurrent hydrolysis *via* both pathways, at least in concentrated acids, to explain an unexpected acidity dependence. We now have definitive chemical evidence that the hydrolysis of *N*-nitroso-2-pyrrolidone proceeds *via* the *N*-conjugate acid, the less favoured of the two possibilities.

Acid-catalysed decomposition of *N*-nitrosamides has been shown[5] to proceed by two concurrent pathways leading to denitrosation (k^{NO}) and deamination (k^{N_2}), respectively. Kinetic studies of *N*-nitroso-2-pyrrolidone show that



(3)

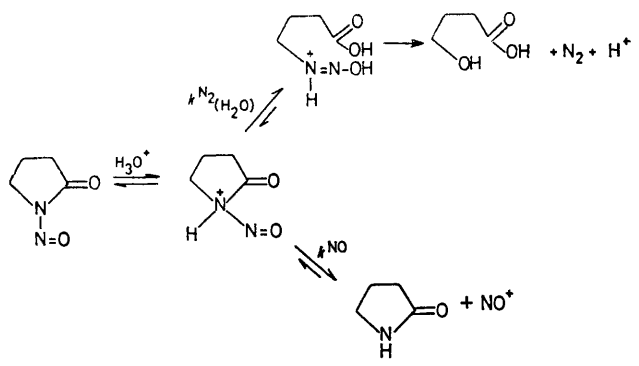
decomposition rates for various acid catalysts are closely similar for both pathways (Table) suggesting a common rate-limiting step. This deduction is confirmed by the

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

Catalyst (HA)	$10^4 k_{HA}^{NO}$/l mol^{-1} s^{-1}	$10^4 k_{HA}^{N_2}$/l mol^{-1} s^{-1}
H_3O^+	2·11	2·03
CF_3CO_2H	1·75	1·58
Cl_2CHCO_2H	0·34	0·32
$ClCH_2CO_2H$	0·035	0·07

closely similar solvent deuterium isotope effects for Cl_2CHCO_2H catalysis ($k_{HA}^{N_2}/k_{DA}^{N_2}$ = 2·82; k_{HA}^{NO}/k_{DA}^{NO} = 2·20) and activation parameters for H_3O^+ catalysis (for denitrosation: $\Delta H^\ddagger$ = 87·8 kJ mol^{-1}, $\Delta S^\ddagger$ = − 50·8 J deg^{-1} mol^{-1}; for deamination: $\Delta H^\ddagger$ = 88·7 kJ mol^{-1}, $\Delta S^\ddagger$ = − 50·2 J deg^{-1} mol^{-1}). Further, the solvent isotope effects show that formation of the common conjugate acid is rate-limiting for both decomposition pathways, as for the denitrosation only of *N*-n-butyl-*N*-nitrosoacetamide.[5]

Whether this conjugate acid intermediate bears the proton on the amido-*N* or *O* atom may be resolved by consideration of the denitrosation pathway. Here, reaction *via* the



SCHEME

O-conjugate acid [equation (3)] would imply (by the principle of microscopic reversibility) that nitrosation of amides proceeds *via* the imido-tautomer, which is, we believe, untenable and contrary to experimental findings.[2a] It follows that both decomposition reactions must proceed through the *N*-conjugate acid (Scheme) with deamination involving hydrolytic cleavage of this species. Other evidence,[6] namely the inability of added nucleophilic species such as Cl^- to effect catalysis, shows that denitrosation of the *N*-conjugate acid is unimolecular. Deamination, however, is very sensitive to the addition of neutral salts, which drastically retard the rate of this reaction.[6] This suggests that deamination involves rate-limiting attack by H_2O on the *N*-conjugate acid, by the bimolecular low energy pathway shown in the Scheme.

It is not clear whether or not hydrolysis *via* the *N*-conjugate acid of *N*-nitroso-2-pyrrolidone is favoured because of its cyclic structure or the presence of the *N*-nitroso group. However, we have deduced previously[5] that hydrolysis of *N*-n-butyl-*N*-nitrosoacetamide involves the *O*-conjugate acid. Comparative data for the acid-catalysed hydrolysis of pyrrolidone, itself, are not available but experiments are in progress to provide this information.

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

[2] For recent reviews see (a) B. C. Challis and J. A. Challis, 'Chemistry of the Amides,' ed. J. Zabicky, Wiley, London, 1970, p. 731; (b) C. J. O'Connor, *Quart. Rev.*, 1970, **24**, 553.

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

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[5] C. N. Berry and B. C. Challis, *J.C.S. Chem. Comm.*, 1972, 627; *J.C.S. Perkin II*, 1974, in the press.

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