

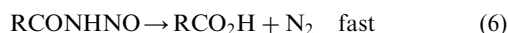
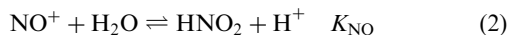
# Kinetics of the Deamination of Amides by Nitrous Acid†

Khawla Al-Mallah and Geoffrey Stedman\*

Chemistry Department, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, UK

The kinetic profile of the rate constant for the nitrous acid–amide reaction in sulfuric acid as a function of acidity for a range of aliphatic and aromatic primary amides has been interpreted in terms of the  $\text{HNO}_2/\text{NO}^+$  and the amide/amide  $\cdot \text{H}^+$  equilibria.

The mechanism of the deamination of primary amides by nitrous acid, eqn. (1), was originally thought<sup>1–3</sup> to involve a rate-determining N-nitrosation reaction, as had been established<sup>4</sup> for primary amines. Primary aliphatic and aromatic amides are much weaker bases than the corresponding primary amines, and in order to get the reaction to proceed at a reasonable rate much higher concentrations of mineral acid are necessary. In these concentrated solutions activity effects are important. Attempts to account quantitatively for the profile of rate constant *versus* acid concentration in terms of a single mechanism<sup>1</sup> were unsuccessful. Subsequent work by a number of groups<sup>5</sup> has established that with the presence of a strongly electron attracting group such as the carbonyl function the initial nitrosation is reversible, and the rate-determining stage involves proton loss. Furthermore the site of the initial nitrosation may be the oxygen of the carbonyl group; this is certainly the site for protonation. The mechanism is summarised in eqns. (2)–(6).



We summarise in this paper the results of kinetic studies on a group of aliphatic and aromatic amides reacting with nitrous acid over the range  $[\text{H}_2\text{SO}_4] = 2.8$  to  $10.5 \text{ mol dm}^{-3}$ , at  $25^\circ\text{C}$ . Reactions were run with a large excess of amide over nitrous acid, and gave good first order plots of  $\ln[\text{nitrite}]$  *versus* time,  $k_1/\text{min}^{-1}$ . Values of  $k_1$  were directly proportional to  $[\text{amide}]$ , yielding second order rate constants  $k_2/\text{dm}^3 \text{ mol}^{-1} \text{ min}^{-1}$  in terms of stoichiometric concentrations.

$$-d[\text{nitrite}]/dt = k_2[\text{amide}][\text{nitrite}] \quad (7)$$

All amides studied showed a similar dependence of  $k_2$  on  $[\text{H}_2\text{SO}_4]$ ;  $k_2$  increased with acidity and passed through a sharp maximum close to  $8 \text{ mol dm}^{-3}$  sulfuric acid, and then decreased sharply. A typical plot is shown in Fig. 1. The decrease in  $k_2$  at higher acidities was always markedly steeper than the increase at lower acid concentrations. In order to check that there was no difference in mechanism for reaction at acidities on each side of the rate maximum, Arrhenius activation energies were measured on each side of the maximum for two of the aliphatic amides, giving

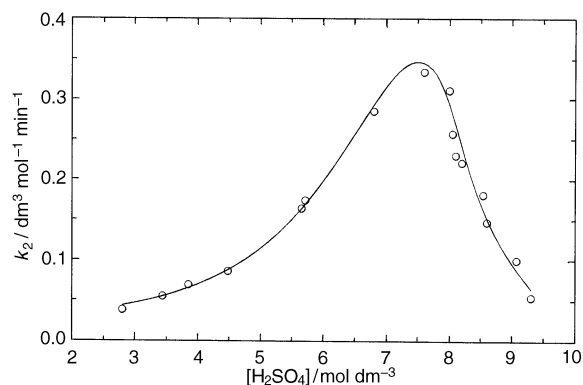


Fig. 1 Variation of  $k_2$  with sulfuric acid concentration for trimethylacetamide at  $0^\circ\text{C}$

the following results at the molar concentrations of sulfuric acid specified in parentheses,  $E/\text{kJ mol}^{-1}$ :  $\text{R} = (\text{CH}_3)_3\text{C}$ ,  $74.2 \pm 1.4$  (4.5);  $76.9 \pm 4.8$  (9.3);  $\text{R} = \text{CNCH}_2$ ,  $60.1 \pm 4.4$  (6.8),  $64.0 \pm 2.4$  (8.0). The activation energies are constant to within one standard deviation. The results for trimethylacetamide were used to correct the rate profile data measured at  $0$  to  $25^\circ\text{C}$ , in order to compare the results with those for the other amides studied. The rate maximum is due to the opposing effects of acidity on equilibria (2) and (3), combined with the effect of sulfuric acid concentration on  $K_{\text{E}}$  and  $k_3$ . Equilibrium (2) is described formally by the  $H_{\text{R}}$  acidity function for which  $\Delta H_{\text{R}}/\Delta[\text{H}_2\text{SO}_4]$  is on average *ca.*  $-1.05 \text{ dm}^3 \text{ mol}^{-1}$ . The  $\text{p}K_{\text{NO}}$  for (2) determined spectrophotometrically using the  $H_{\text{R}}$  function is  $-8.11$ . At  $[\text{H}_2\text{SO}_4] = 8 \text{ mol dm}^{-3}$   $H_{\text{R}} = -7.59$ , and thus at higher acidities conversion of nitrite into  $\text{NO}^+$  is virtually complete. Equilibrium (3) is described by the  $H_{\text{A}}$  acidity function for which  $\Delta H_{\text{A}}/\Delta[\text{H}_2\text{SO}_4]$  is only *ca.*  $-0.28 \text{ dm}^3 \text{ mol}^{-1}$ . Thus at lower acidities the increase in  $[\text{NO}^+]$  dominates over the decrease in  $[\text{RCONH}_2]$ , while as we approach the conditions where  $H_{\text{R}}$  becomes close to  $\text{p}K_{\text{NO}}$  the fraction of  $\text{NO}^+$ ,  $h_{\text{R}}/(K_{\text{NO}} + h_{\text{R}})$ , levels off and tends to 1, while the fraction of free amide,  $K_{\text{A}}/(K_{\text{A}} + h_{\text{A}})$ , continues to decrease. However the decrease in  $k_2$  is very much faster than the decrease in  $1/h_{\text{A}}$  and the rate of proton loss is a sensitive function of sulfuric acid concentration. This is presumably because of variation in the activity of the various proton acceptors such as  $\text{SO}_4^{2-}$ ,  $\text{H}_2\text{O}$  and possibly  $\text{HSO}_4^-$ . In seeking for an empirical measure of this effect we used the  $H_0$  acidity function, with the idea that as the proton donating power measured by  $h_0$  increased so the ability of the medium to remove a proton would decrease. The mechanism in eqns. (2)–(6) requires the rate law (8).

$$\text{rate} = k_3 K_{\text{E}} [\text{NO}^+] [\text{RCONH}_2] \quad (8)$$

To relate this to eqn. (2) we write  $\alpha$  = the fraction of nitrite present as  $\text{NO}^+$ , and  $\beta$  = the fraction of amide present as  $\text{RCONH}_2$ , where  $\alpha$  and  $\beta$  have been defined in

\*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

**Table 1** Parameters used for plots of eqn. (9)

R	Slope	Intercept	[H <sub>2</sub> SO <sub>4</sub> ]/ mol dm <sup>-3</sup>	pK <sub>A</sub>
(CH <sub>3</sub> ) <sub>3</sub> C*	1.21 ± 0.02	7.22 ± 0.08	2.8 to 9.3	-1.40
ClCH <sub>2</sub>	1.01 ± 0.03	5.84 ± 0.12	2.8 to 9.3	-2.74
CNCH <sub>2</sub>	0.92 ± 0.04	5.21 ± 0.16	3.4 to 9.1	-3.73
Cl <sub>2</sub> CH	1.03 ± 0.06	5.12 ± 0.23	2.8 to 9.3	-4.18
<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	1.22 ± 0.04	7.40 ± 0.16	5.5 to 10.4	-1.67
<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	1.29 ± 0.07	7.47 ± 0.27	5.5 to 10.5	-2.02
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	1.32 ± 0.04	7.54 ± 0.13	3.2 to 10.5	-1.97
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	1.28 ± 0.02	7.90 ± 0.07	3.1 to 9.1	-1.54
<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1.25 ± 0.05	6.99 ± 0.19	5.5 to 10.2	-2.70

\*Corrected from 0 to 25 °C.

terms of  $K_{\text{NO}}$ ,  $h_{\text{R}}$ ,  $K_{\text{A}}$  and  $h_{\text{A}}$  in the previous paragraph. To allow for the variation of  $k_3K_{\text{E}}$  with  $1/h_0$  we write  $k_3K_{\text{E}} = k_4/h_0$ . With these substitutions, and the assumption that there is only a small fraction of the amide present as  $\text{RCONH}_2\text{NO}^+$ , we obtain eqn. (9).

$$\log(k_2/\alpha\beta) = \log k_4 + H_0 \quad (9)$$

Plots of this type yielded good straight lines with slopes between 0.92 and 1.27 over the range of acidities specified in Table 1. Values of  $\text{p}K_{\text{A}}$  for aliphatic amides are due to Liler<sup>6</sup> and for aromatic amides come from the review<sup>7</sup> by Boyd. The value for  $(\text{CH}_3)_3\text{CONH}_2$  comes from our own work<sup>8</sup> based upon NMR measurements, and is very close to Liler's value. Although our model gives a reasonably satisfactory description of the data the choice of  $H_0$  was arbitrary. However most acidity functions vary in an approximately linear manner with  $[\text{H}_2\text{SO}_4]$  in the higher range of acid concentrations, and so the choice of other acidity functions to describe the variation of  $K_{\text{E}}k_3$  would still have yielded linear plots, though with different slopes. Since the use of  $1/h_0$  is a purely empirical measure of the ability of the medium to accept a proton we do not offer any comment on the variation of the slopes. There must be considerable differences in the solvation of the aliphatic amides in view of the differences in R; for the aromatic amides which all have a phenyl ring the slopes are quite similar. An alternative explanation of the dependence of  $k_2/\alpha\beta$  upon  $1/h_0$  would be an acid-base equilibrium for (5) followed by a rate-determining rearrangement as in eqn. (6). However as Williams<sup>5</sup> points out the evidence for a rate-determining loss of a proton is very strong, so we reject this alternative.

Although the present model gives a reasonable description of the data in terms of the generally accepted mechanism, it is important to realise its limitations. One concerns the value used for  $\text{p}K_{\text{NO}}$ . Various values have been suggested,<sup>9,10</sup> and in his interpretation of the kinetics of diazotisation in dilute acid Ridd used<sup>11</sup> a value of *ca.* -6.5, which yields limiting rates in good agreement with the calculated value of the encounter rate between  $\text{NO}^+$  and  $\text{ArNH}_2$ . As we are concerned with data over a wide range of sulfuric acid concentration, using the  $H_{\text{R}}$  data to describe (2) we prefer to use the more negative figure of -8.11 deduced by Deno *et al.*<sup>12</sup> when fitting spectrophotometric estimates of  $[\text{NO}^+]/[\text{HNO}_2]$  to his  $H_{\text{R}}$  data obtained by the ionisation of arylcarbinol indicators. At lower  $[\text{H}_2\text{SO}_4]$  changing the value of  $\text{p}K_{\text{NO}}$  merely displaces the line of  $\log(k_2/\alpha\beta)$  versus  $H_0$  without significantly changing the slope. As  $H_{\text{R}}$  approaches  $\text{p}K_{\text{NO}}$  the choice is more important. We tried using  $\text{p}K_{\text{NO}} = -6.5$ , but found deviations at sulfuric acid concentrations greater than  $6.5 \text{ mol dm}^{-3}$ , whereas with Deno's value linearity was observed up to the specified concentrations shown in Table 1. We have also extended a few measurements to higher acidities,  $[\text{H}_2\text{SO}_4] = 13.1 \text{ mol dm}^{-3}$ ,

and there are deviations from eqn. (9); values of  $\log(k_2/\alpha\beta)$  are greater than predicted from the equations in Table 1 for the aliphatic amides. The measurements for the aromatic amides were not extended to such high acidities. It is possible that an extra pathway comes into play at high acidities.

Finally we turn to a consideration of the differing reactivities of the amides studied. Since there are variations in the slopes of the plots of eqn. (9) it is simplest to make comparisons at a given sulfuric acid concentration by substituting the appropriate value of  $H_0$ . The same reactivity sequence is obtained over our range of acidities. For the aliphatic amides it is  $(\text{CH}_3)_3\text{C} > \text{ClCH}_2 > \text{CNCH}_2 > \text{Cl}_2\text{CH}$ , which is the same as the sequence of  $\text{p}K_{\text{A}}$  values. For the aromatic amides the sequence is  $p\text{-CH}_3\text{O} > p\text{-CH}_3 > p\text{-Br} > p\text{-Cl} > p\text{-NO}_2$ , again the same sequence as the  $\text{p}K_{\text{A}}$  values, except for the interchange of positions of chlorine and bromine which are very close together anyway. Clearly the greater the electron releasing power of R in  $\text{RCONH}_2$  the higher is the reactivity. The addition of  $\text{NO}^+$  to the free amide may be expected to vary with R in the same sense as the addition of  $\text{H}^+$ , and this is undoubtedly favoured by electron release by R. Step (5) however involving proton loss will be reduced in rate by increase in electron release by R. We conclude therefore that the reactivity in the reaction of nitrous acid with primary amides is controlled by the basicity of the amide, by favouring the formation of an amide  $\cdot\text{NO}^+$  species, and that this is more important than the effect on the rate of proton loss.

## Experimental

**Materials.**—The amides used were either commercially available materials (Aldrich, BDH, Koch-Light) or were prepared from the acid chlorides by addition to stirred, ice-cold 0.88 ammonia. In some cases the acid chlorides were prepared by reaction of thionyl chloride with the carboxylic acid. The amides were recrystallised from water to constant melting point.

**Kinetic Methods.**—Some reactions were followed by colorimetric analysis for nitrous acid involving diazotisation of sulfanilic acid and coupling with alkaline 2-hydroxynaphthol-3,6-disulfonic acid. Other reactions were followed by direct UV spectrophotometry at wavelengths where nitrite absorbed. For slow runs a blank experiment was carried out to correct for the self-decomposition of nitrous acid.

Thanks are due to the University of Mosul for study leave (to K. A.-M.)

Received, 17th June 1998; Accepted, 10th July 1998

Paper E/8/04600J

## References

- M. N. Hughes and G. Stedman, *J. Chem. Soc.*, 1964, 5840.
- M. L. Bender and H. Ladenheim, *J. Am. Chem. Soc.*, 1960, **82**, 1895.
- J. Jaz and A. Bruylants, *Bull. Soc. Chim. Belges*, 1961, **70**, 99.
- J. H. Ridd, *Q. Rev. Chem. Soc.*, 1961, **15**, 418.
- D. L. H. Williams, in *Nitrosation*, Cambridge University Press, Cambridge, 1988, p. 101.
- M. Liler, *J. Chem. Soc. B*, 1969, 385.
- J. H. Boyd, in *Solute-Solvent Interactions*, ed. J. F. Coetzee and C. D. Ritchie, Marcel Dekker, New York, 1969, vol. 1, ch. 3, p. 97.
- K. Al-Mallah, Ph.D. Thesis, University of Wales, 1974.
- Stability Constants*, Special Publication No. 17, The Chemical Society, London, 1964, p. 163.
- Stability Constants*, Special Publication No. 25, The Chemical Society, London, 1971, p. 91.
- J. H. Ridd, *Adv. Phys. Org. Chem.*, 1978, **16**, 1.
- N. C. Deno, H. E. Berkheimer, W. L. Evans and H. J. Peterson, *J. Am. Chem. Soc.*, 1959, **81**, 2344.