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Kinetics of the Deamination of Amides by Nitrous Acid†

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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 HNO_2/NO^+ and the amide/amide $\cdot$ H^+ equilibria.

The mechanism of the deamination of primary amides by nitrous acid, eqn. (1), was originally thought[1–3] to involve a rate-determining N-nitrosation reaction, as had been established[4] 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[1] were unsuccessful. Subsequent work by a number of groups[5] 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).

$$\mathrm{RCONH_2 + HNO_2 \rightarrow RCO_2H + N_2 + H_2O} \qquad (1)$$

$$\mathrm{NO^+ + H_2O \rightleftharpoons HNO_2 + H^+} \quad K_{\mathrm{NO}} \qquad (2)$$

$$\mathrm{RCONH_2H^+ \rightleftharpoons RCONH_2 + H^+} \quad K_{\mathrm{A}} \qquad (3)$$

$$\mathrm{RCONH_2 + NO^+ \rightleftharpoons RCONH_2 \cdot NO^+} \quad K_{\mathrm{E}} \qquad (4)$$

$$\mathrm{RCONH_2 \cdot NO^+ + B \rightarrow RCONHNO + BH^+} \quad k_3 \text{ slow} \qquad (5)$$

$$\mathrm{RCONHNO \rightarrow RCO_2H + N_2} \quad \text{fast} \qquad (6)$$

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 $[H_2SO_4] = 2.8$ to $10.5\ \mathrm{mol\ dm^{-3}}$, at 25 °C. Reactions were run with a large excess of amide over nitrous acid, and gave good first order plots of ln[nitrite] *versus* time, $k_1/\mathrm{min^{-1}}$. Values of k_1 were directly proportional to [amide], yielding second order rate constants $k_2/\mathrm{dm^3\ mol^{-1}\ min^{-1}}$ in terms of stoichiometric concentrations.

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

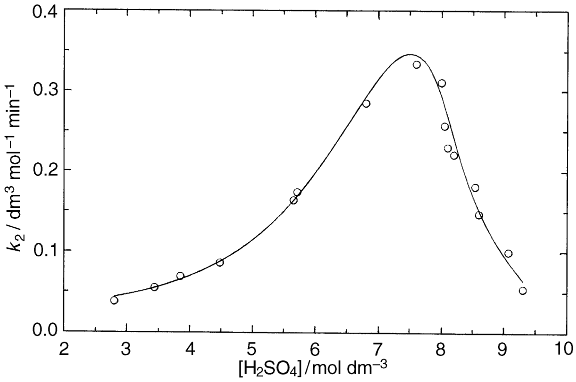

Fig. 1 Variation of k_2 with sulfuric acid concentration for trimethylacetamide at 0 °C

All amides studied showed a similar dependence of k_2 on $[H_2SO_4]$; k_2 increased with acidity and passed through a sharp maximum close to $8\ \mathrm{mol\ dm^{-3}}$ 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 the following results at the molar concentrations of sulfuric acid specified in parentheses, $E/\mathrm{kJ\ mol^{-1}}$: $R = (CH_3)_3C$, 74.2 ± 1.4 (4.5); 76.9 ± 4.8 (9.3); $R = CNCH_2$, 60.1 ± 4.4 (6.8), 64.0 ± 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 °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_E and k_3. Equilibrium (2) is described formally by the H_R acidity function for which $\Delta H_R/\Delta[H_2SO_4]$ is on average *ca.* $-1.05\ \mathrm{dm^3\ mol^{-1}}$. The $\mathrm{p}K_{\mathrm{NO}}$ for (2) determined spectrophotometrically using the H_R function is -8.11. At $[H_2SO_4] = 8\ \mathrm{mol\ dm^{-3}}$ $H_R = -7.59$, and thus at higher acidities conversion of nitrite into NO^+ is virtually complete. Equilibrium (3) is described by the H_A acidity function for which $\Delta H_A/\Delta[H_2SO_4]$ is only *ca.* $-0.28\ \mathrm{dm^3\ mol^{-1}}$. Thus at lower acidities the increase in $[NO^+]$ dominates over the decrease in $[RCONH_2]$, while as we approach the conditions where H_R becomes close to $\mathrm{p}K_{\mathrm{NO}}$ the fraction of NO^+, $h_R/(K_{NO}+h_R)$, levels off and tends to 1, while the fraction of free amide, $K_A/(K_A+h_A)$, continues to decrease. However the decrease in k_2 is very much faster than the decrease in $1/h_A$ 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 SO_4^{2-}, H_2O and possibly 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).

$$\text{rate} = k_3K_E[\mathrm{NO^+}][\mathrm{RCONH_2}] \qquad (8)$$

To relate this to eqn. (2) we write $\alpha =$ the fraction of nitrite present as NO^+, and $\beta =$ the fraction of amide present as $RCONH_2$, where α and β have been defined in

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

R	Slope	Intercept	$[H_2SO_4]$/ mol dm^{-3}	pK_A
$(CH_3)_3C$*	1.21 ± 0.02	7.22 ± 0.08	2.8 to 9.3	−1.40
$ClCH_2$	1.01 ± 0.03	5.84 ± 0.12	2.8 to 9.3	−2.74
$CNCH_2$	0.92 ± 0.04	5.21 ± 0.16	3.4 to 9.1	−3.73
Cl_2CH	1.03 ± 0.06	5.12 ± 0.23	2.8 to 9.3	−4.18
p-MeC_6H_4	1.22 ± 0.04	7.40 ± 0.16	5.5 to 10.4	−1.67
p-BrC_6H_4	1.29 ± 0.07	7.47 ± 0.27	5.5 to 10.5	−2.02
p-ClC_6H_4	1.32 ± 0.04	7.54 ± 0.13	3.2 to 10.5	−1.97
p-$MeOC_6H_4$	1.28 ± 0.02	7.90 ± 0.07	3.1 to 9.1	−1.54
p-$NO_2C_6H_4$	1.25 ± 0.05	6.99 ± 0.19	5.5 to 10.2	−2.70

*Corrected from 0 to 25 °C.

terms of K_{NO}, h_R, K_A and h_A in the previous paragraph. To allow for the variation of k_3K_E with $1/h_0$ we write $k_3K_E = k_4/h_0$. With these substitutions, and the assumption that there is only a small fraction of the amide present as $RCONH_2NO^+$, we obtain eqn. (9).

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

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 pK_A for aliphatic amides are due to Liler[6] and for aromatic amides come from the review[7] by Boyd. The value for $(CH_3)_3CONH_2$ comes from our own work[8] 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 $[H_2SO_4]$ in the higher range of acid concentrations, and so the choice of other acidity functions to describe the variation of K_Ek_3 would still have yielded linear plots, though with different slopes. Since of 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[5] 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 pK_{NO}. Various values have been suggested,[9,10] and in his interpretation of the kinetics of diazotisation in dilute acid Ridd used[11] a value of *ca.* –6.5, which yields limiting rates in good agreement with the calculated value of the encounter rate between NO^+ and $ArNH_2$. As we are concerned with data over a wide range of sulfuric acid concentration, using the H_R data to describe (2) we prefer to use the more negative figure of –8.11 deduced by Deno *et al.*[12] when fitting spectrophotometric estimates of $[NO^+]/[HNO_2]$ to his H_R data obtained by the ionisation of arylcarbinol indicators. At lower $[H_2SO_4]$ changing the value of pK_{NO} merely displaces the line of log $(k_2/\alpha\beta)$ *versus* H_0 without significantly changing the slope. As H_R approaches pK_{NO} the choice is more important. We tried using p$K_{NO} = -6.5$, but found deviations at sulfuric acid concentrations greater than 6.5 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, $[H_2SO_4] = 13.1$ 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 $(CH_3)_3C > ClCH_2 > CNCH_2 > Cl_2CH$, which is the same as the sequence of pK_A values. For the aromatic amides the sequence is p-$CH_3O > p$-$CH_3 > p$-$Br > p$-$Cl > p$-NO_2, again the same sequence as the pK_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 $RCONH_2$ the higher is the reactivity. The addition of NO^+ to the free amide may be expected to vary with R in the same sense as the addition of 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 · 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.

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