

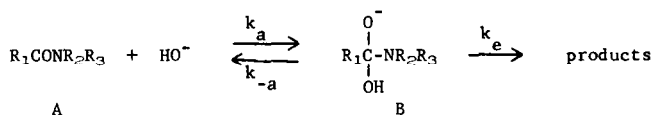
KINETIC EVIDENCE FOR A TWO-STEP MECHANISM
 OF AMIDE HYDROLYSIS¹

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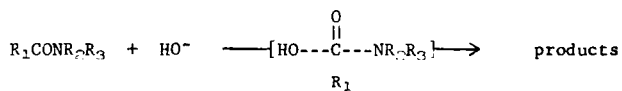
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The previously available evidence on the mechanism of base-catalyzed amide hydrolysis is consistent with the generally accepted,⁴ two-step mechanism I or the one-step, concerted-displacement mechanism II. The

Mechanism I.



Mechanism II.



discovery by Bender and Ginger⁵ that carbonyl-¹⁸O exchange of benzamide in basic solution occurs more rapidly than does hydrolysis, often cited in favor of I, can be reconciled with II by noting that the addition intermediate B should expel the weaker base hydroxide more readily than

amide ($k_{-a} > k_e$). Exchange may then occur by the first step of I and hydrolysis by II in concurrent, independent reactions.⁶

Our recent observation⁷ of superimposed general base catalysis in the hydrolysis of 2,2,2-trifluoro-N-methylacetanilide (A: $R_1 = CF_3$, $R_2 = CH_3$, $R_3 = C_6H_5$) is consistent with I, if the formation or decomposition of B is general-base catalyzed, or with II, if attack of the nucleophilic hydroxide is general-base catalyzed.

We have now extended our measurements to sufficiently high base concentrations to permit a distinction of these possibilities. The data in the first two columns of Table I show the reaction to become first-order in base at high base concentrations, requiring modification of the previous rate law^{7a} to eq. 1, which reduces to eq. 2 in unbuffered solution. The third column of

$$-d[A]/dt = [A] \left\{ k_0 + [HO^-] \frac{k_a(k'_1 + \Sigma k'_i[B_i])}{k_{-a} + k'_1 + \Sigma k'_i[B_i]} \right\} \quad (1)$$

$$k_{obs} = k_0 + [HO^-] \left\{ \frac{k_a(k_1 + k_2[HO^-])}{k_a + k_1 + k_2[HO^-]} \right\} \quad (2)$$

Table I shows values of k_{obs} calculated from eq. 2 with the values of the rate constants given in footnote a of the table. The agreement is good. Eqs. 1 and 2 may be derived from mechanism I (after allowance for the small k_0 term found before^{7b}) by application of steady-state kinetics, with $k_e = k'_1 + \Sigma k'_i[B_i]$ in general and $k_e = k'_1 + k'_2[HO^-]$ in unbuffered solutions. Here $k'_1 = k_{-a}k_1/k_a$. In solutions of low basicity, the base-catalyzed conversion of B to products is rate-determining. At higher basicities, this process exceeds in rate the base-independent reversion of B to reactants and the addition of base to A becomes the rate-determining process.

TABLE I.

Hydrolysis of 2,2,2-Trifluoro-N-methylacetanilide at 25°

| $10^3[\text{HO}^-], \text{M.}$ | $10^4k_{\text{obs}}, \text{sec.}^{-1}$ | $10^4k_{\text{calc}}, \text{sec.}^{-1})^a$ |
|--------------------------------|--|--|
| 1.5 | 0.57 | 0.59 |
| 3.0 | 1.53 | 1.57 |
| 4.5 | 2.75 | 2.78 |
| 6.0 | 4.02 | 4.11 |
| 8.0 | 5.83 | 6.02 |
| 10.5 | 9.2 | 8.5 |
| 12.0 | 9.8 | 10.1 |
| 13.5 | 12.6 | 11.7 |
| 15.0 | 13.5 | 13.3 |
| 20.0 | 17.6 | 18.8 |
| 25.0 | 22.8 | 22.4 |
| 30.0 | 26.8 | 29.9 |
| 35.0 | 34.5 | 35.5 |

a. Calculated from eq. 2 with $k_0 = 5 \times 10^{-5} \text{ sec.}^{-1}$, $k_1 = 2 \text{ M.}^{-1} \text{ sec.}^{-1}$, $k_2 = 2000 \text{ M.}^{-2} \text{ sec.}^{-1}$ and $k_a = 11.5 \text{ M.}^{-1} \text{ sec.}^{-1}$.

These results, by demonstration of a change in rate-determining step, require that 2,2,2-trifluoro-N-methylacetanilide undergo hydrolysis by a two-step mechanism, presumably I. We have presented arguments^{7b} that the mechanistic behavior of this amide may be generalized and we therefore conclude that the basic hydrolysis of amides is a two-step process. This mechanism is in agreement with the more complex kinetic scheme found by Mader⁸ for 2,2,2-trifluoroacetanilide and with the demonstration by Jencks and Gilchrist⁹ of a two-step pathway for the reaction of hydroxylamine with amides.

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