Intramolecular General Base Catalysis of Aminolysis by Ethylenediamine

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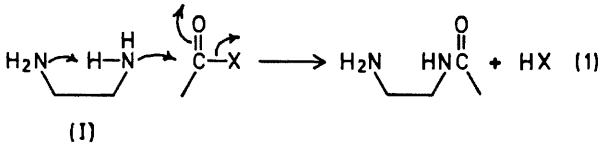
Summary The aminolysis of acetylimidazole by ethylenediamine shows a rate enhancement of more than 10^3 compared to glycine, which is attributed to intramolecular general base catalysis; the reaction with acetylimidazolium ion shows no significant rate enhancement.

SEVERAL previous attempts to demonstrate intramolecular general base catalysis by nucleophilic reagents containing a suitably located basic group, such as ethylenediamine (equation 1), have shown no definite evidence for such catalysis in the aminolysis of acyl compounds with good leaving groups, such as phenyl acetates.[1-4] In the course



(I)

of an examination of the reactivity of a series of nucleophilic reagents with the activated amides acetylimidazole and acetylimidazolium ion[5] we have found an extraordinary enhancement of the rate of reaction of ethylenediamine with acetylimidazole (AcIm). Reactions of amines with free acetylimidazole, which has a poor leaving group of pK 14·2,[6] occur relatively slowly, show a moderate dependence on amine basiciety (β = *ca.* 0·5) and proceed largely by general base catalysis of hydrolysis rather than nucleophilic reaction.[5] The rate constant for the reaction of ethylenediamine is more than 10^3 faster than that for the reaction of simple primary amines of comparable basicity, such as glycine (Table). This rate enhancement is ascribed to intramolecular general base catalysis of the nucleophilic reaction of ethylenediamine by the second amino-group; the actual rate enhancement may be larger than 10^3 since the rate constant for glycine can be determined only as a limit and, in any case, may not represent a nucleophilic reaction.

In contrast, there is little or no rate enhancement (after allowance for a statistical factor of 2) in the reaction of ethylenediamine with acetylimidazolium ion, which has a much better leaving group (pK 7·0). We conclude that such catalysis is important only when it is needed; imidazole and phenolate ion can be expelled by free ethylenediamine (pK 10·4) without significant assistance from an intramolecular or intermolecular general base catalyst. Most physiological substrates of hydrolytic enzymes also have poor leaving groups. Of the several possible mechanisms to account for kinetic general base catalysis we favour one in which the second amine group acts as a true general base as in (I) or in a tetrahedral addition intermediate; the choice of mechanism is simplified for the intramolecular reaction by the fact that the second amine group is sterically unable to catalyze proton transfer to the distal nitrogen atom of the leaving imidazole.

Reactions of primary amines with acetylimidazole[a]

	pK_a[b]	k_{AcIm} ($M^{-1}min^{-1}$)	k_{AcImH^+} ($M^{-1}min.^{-1}$)
$H_2N{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$	10·36	4200	$8{\cdot}3 \times 10^6$
$^-O_2{\cdot}C{\cdot}CH_2{\cdot}NH_2$	10·25	2 ± 2	$1{\cdot}3 \times 10^6$

[a] Ionic strength 1·0 maintained with Me_4NCl, 25°, followed at 245 nm. Rate constants were measured at 3 to 6 amine concentrations in ethylenediamine buffers at 5, 10, 20, 30, 40, 50, 70, and 95% monocation (pH 6·2—8·6) and with glycine at 0·1, 1% (in imidazole buffer), 10, 20, and 40% base. The observed second-order rate constants were extrapolated to zero buffer concentration to correct for third order catalytic terms. The rate law for the second-order term is $v = k_{AcIm}[RNH_2][AcIm] + k_{AcImH^+}[RNH_2][AcImH^+]$, where the second term = $k'[RNH_3^+][AcIm]$.

[b] Statistically corrected.

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