On the Search for Bifunctional Catalysis of Esterolytic Reactions

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IT has been reported[1] that the monocation of 4-(2-diethylaminoethyl)imidazole (I) is thirty-six times more effective as a catalyst for the hydrolysis of 4-nitrophenyl acetate than imidazole. No experimental details were published. The enhanced activity of the monocation (I H^+) compared with imidazole was attributed to a bifunctional mode of reaction: the nucleophilic addition of the imidazolyl moiety to the ester carbonyl was assisted by the protonated amino-group acting as a general acid. This result has been quoted[2] as an example of bifunctional catalysis. However, Bruice and Schmir[3] have shown that the monocations of histamine and histidine methyl ester are no better as catalysts for the hydrolysis of 4-nitrophenyl acetate than would be expected for any 4-substituted imidazole of comparable basicity.

We have determined the second-order rate constants for the hydrolysis of 4-nitrophenyl acetate catalysed by (I) and by 4-diethylaminomethylimidazole (II): the results, together with the rate constants obtained for catalysis by imidazole, are set out in Table 1. It can be seen that the monocations of (I) and (II) are in fact less effective as catalysts for the hydrolysis of 4-nitrophenyl acetate than is imidazole. Comparison of our results with those of Bruice and Schmir[3] shows that the catalytic activities of (I H^+) and (II H^+) are just as one would expect from their basicities. The measurements have been repeated using the acyl-activated ester 3-nitrophenyl chloroacetate as the substrate. The second-order rate constants for imidazole (I H^+), and (II H^+) were 242 (pH 5·5), 31·1 (pH 7·0), and 2·18 M^{-1} $min.^{-1}$ (pH 6·0) respectively. Again there is no indication of enhanced catalytic activity for (I H^+) or (II H^+).

TABLE 1

Spectrometric second-order rate constants for the reaction of 4-nitrophenyl acetate with imidazole, (I H+), *and* (II H+) *in* aqueous solution (9% methanol), $\mu = 0{\cdot}2$ (adjusted with KCl), 25°

Nucleophile	pK_{a_1}*	pK_{a_2}*	pH	k† (M^{-1} $min.^{-1}$)
Imidazole	7·10	—	7·0	14·2
			9·1	22·0
(I H+)	6·04	9·88	7·1	2·22
			9·1	4·68‡
(II H+)	4·25	9·68	4·9	0·054
			7·1	0·70‡

* The dissociation constants were obtained from titration curves.

† k is the slope of the plots of the observed pseudo-first-order rate constants against the concentrations of free imidazole, (I H+) or (II H+).

‡ Nucleophilic attack by the diethylamino-groups of (I) and (II) may be neglected since triethylamine itself has an insignificant effect on the hydrolysis of 4-nitrophenyl acetate.

Bruice and Willis[4] have suggested that the hydrazinolysis of phenyl acetate by 3-dimethylaminopropylhydrazine is assisted by the amino-group acting as a general base. Jencks and Gilchrist[5] have pointed out that this conclusion has a very tenuous basis. Further, polymethylene diamines do not aminolyse phenyl acetate at a significantly greater rate than monoamines.[4] In our hands, 1,3-diamino-2,2-dimethylpropane (the methyls should tend to keep the amino-groups in a favourable orientation[6]) aminolysed phenyl acetate at about the same rate as n-butylamine. 4,4′(5,5′)-Bisimidazolylmethane is no more reactive than imidazole towards 4-nitrophenyl acetate.[7] We have measured the rates of reaction of imidazole (I), and (II), with phenyl acetate at pH 11·0 (0·02-M-triethylamine buffer, $\mu = 0{\cdot}2$, 25°). The apparent second-order rate constants (1·13, 1·07, and 1·22 M^{-1} $min.^{-1}$ respectively) are similar and provide no evidence for nucleophilicity being enhanced by the presence of a base within the nucleophile.

Despite the evidence accumulated in support of intermolecular general acid- and base-catalyses of the aminolysis of esters,[8] there has been no demonstration of nucleophilic attack being assisted by the presence of acidic or basic functions on the nucleophile. The apparent intermolecular catalysis of ester aminolysis has been observed only for substrates possessing rather poor leaving groups (*e.g.* 4-methylphenyl acetate), for which collapse of the tetrahedral intermediate to products is expected to be rate-determining in uncatalysed aminolysis. Consequently, for carboxylic derivatives with poor leaving groups, catalysis of nucleophilic addition to the carbonyl group cannot increase the rate of the overall reaction. It is conceivable that the elimination of the leaving group from the tetrahedral intermediate could be catalysed by an acidic group on the nucleophilic portion of the intermediate. However, for most of the nucleophilic-acidic bifunctional reagents that have been used, it seems likely that elimination of the nucleophile would be catalysed to a much greater degree than the elimination of the leaving group because proton donation to the leaving group requires the greater degree of organization of the tetrahedral intermediate.

In the reactions of acyl halides with nucleophiles the formation of the tetrahedral intermediate should be the rate-determining step. It follows that catalysis of nucleophilic addition to the carbonyl group may be more manifest in the reactions of acyl halides than in the reactions of esters. (It is recognized, however, that the more reactive substrates may have a low susceptibility towards general acid- or base-catalysis of their reactions with nucleophiles since the catalysed reaction may be less sensitive than the uncatalysed reactions towards substrate reactivity.[9]) The rate constants for the reactions of ethyl chloroformate with a variety of potentially bifunctional reagents are presented in Table 2 together with the rate constants obtained for reactions with nucleophiles

TABLE 2

Titrimetric second-order rate constants for the reaction of ethyl chloroformate with nucleophiles in aqueous solution (1% acetonitrile), pH 7·0, $\mu = 0{\cdot}2$ (adjusted with KCl), 25°

Nucleophile	pK_{a_1}	pK_{a_2}	k (M^{-1} $min.^{-1}$)
Phenoxide ion	9·8	—	1540
Hydroquinone mono-anion ..	9·9	—	3700
Catechol mono-anion ..	9·4	—	3240
Imidazole	7·1	—	366
(I H+)	6·0	9·9	84
Benzimidazole	5·8	—	130
4-Benzimidazolecarboxylate	3·0	5·2	41
4-Aminobenzoate	2·8	4·7	192
2-Aminobenzoate	2·7	4·8	408

which have similar basicities and functional groups but which cannot act in a bifunctional manner. These measurements lend no support to the concept of bifunctional catalysis.

The examination of the reactions of the nucleophiles with a number of esters differing widely in the natures of their leaving groups and in their degrees of acyl activation has shown that no profound rate enhancements can be expected from the use of a nucleophile selected only because its functional groups are favourably disposed for simultaneous participation in the transition state.

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