Nucleophilic and General Base Catalysis by Acetate Ion in the Hydrolysis of Aryl Acetates: Substituent Effects, Solvent Isotope Effects, and Entropies of Activation

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THE relative rates of nucleophilic and general base catalysis are an important problem in hydrolysis reactions, particularly in relation to enzymes and enzyme model systems.[1]

Nucleophilic catalysis in the acetate-catalysed hydrolysis of aryl acetates leads to the formation of acetic anhydride as intermediate:

$$\mathrm{ArOAc} + \mathrm{OAc}^- \rightarrow \mathrm{ArO}^- + \mathrm{Ac_2O}$$

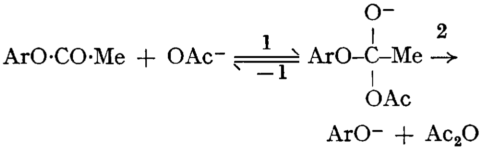
Although acetic anhydride is much more rapidly hydrolysed than the esters, its transient presence can be detected by trapping with aniline,[2] since even at low concentrations of aniline in aqueous solution the predominant reaction is the formation of acetanilide.

This test, using an improved technique to that previously described,[2] has now been systematically applied to ten aryl acetates at 25°, in aqueous acetate buffers at pH 5·00 and ionic strength 0·50 (added sodium chloride).

Having thus established the relative importance of nucleophilic and general base catalysis for different acetate esters, we measured the effect of substituents, the deuterium solvent isotope effect, and the heats and entropies of activation from the catalytic coefficients of the acetate ion in reactions of different mechanism. The results provide a guide to the relative usefulness of different indications of mechanism.[3]

Nucleophilic catalysis was found to predominate in acetate esters of phenols having a pK-value less than *ca.* 5, whereas no nucleophilic catalysis was detected for esters of more feebly acidic (p$K > 8$) phenols, and the catalysis for these esters is described as general base catalysis. The acetate-catalysed hydrolysis of esters in the intermediate range proceeds by the two simultaneous paths.

This change of mechanism with pK-value is intelligible if nucleophilic catalysis involves the sequence of steps:—



$$\mathrm{ArO{\cdot}CO{\cdot}Me} + \mathrm{OAc}^- \underset{-1}{\overset{1}{\rightleftharpoons}} \mathrm{ArO{-}}\overset{\displaystyle \mathrm{O}^-}{\underset{\displaystyle \mathrm{OAc}}{\mathrm{C}}}\mathrm{{-}Me} \xrightarrow{2} \mathrm{ArO}^- + \mathrm{Ac_2O}$$

If $k_{-1} \gg k_2$, these reactions do not contribute to catalysis of the hydrolysis. To the extent that k_2/k_{-1} is governed by the stability of the ArO^- ion, one would then expect the nucleophilic path to gain in importance as the acidity of the phenol ArOH, and hence the stability of ArO^-, is increased.

The ratio of the observed catalytic coefficient of acetate ion (k_{OAc}) to the rate constant of "spontaneous" hydrolysis (k_0) appears to follow a pattern the establishment of which could provide mechanistic interpretation. The dependence of the catalytic coefficient on the pK-value of the phenolic component of the ester is fairly regular over the whole series of compounds, but dissection of catalytic coefficients into contributions due to nucleophilic and general base catalysis suggests that reaction by the nucleophilic mechanism is more susceptible to polar substituent effects than the general base-catalysed reaction.

The change in solvent isotope effect on the catalytic coefficient $[k_{\mathrm{OAc}}(\mathrm{H_2O})/k_{\mathrm{OAc}}(\mathrm{D_2O})]$ with mechanism is in the expected direction, but the differences are not large enough for an isotope effect to provide, by itself, a clear indication of mechanism.

The difference in entropy of activation ($\Delta S^{\ddagger}$) between the two mechanisms (*ca.* 20 e.u.) seems to be more promising from this point of view, particularly since it corresponds quite closely to the value of 18 e.u. which is the expected entropy loss resulting from the inclusion of a water molecule in the transition state of the general base-catalysed reaction.[4]

TABLE

Substituents in aryl group	pK of phenol	%N*	$10^8 k_{OAc}$ (sec.$^{-1}$M^{-1})	k_{OAc}/k_0 (M^{-1})	$\frac{k_{OAc}(H_2O)}{k_{OAc}(D_2O)}$	$\Delta S^{\ddagger}$ (e.u.)
2,6-Dinitro	3·71	100	125,000	88	—	—
2,4-Dinitro	4·11	100(96†)	54,600	46	1·8	—
2,3-Dinitro	4·96	100	25,600	49	—	—
3,4-Dinitro	5·42	79	10,200	22	—	−10
4-Nitro	7·15	56(58†)	566	6·7	1·9**	(††)
2-Nitro	7·21	45	413	5·4	—	—
3-Nitro	8·40	0	336	11·2	—	—
4-Chloro	9·38	0	90	14·5	—	—
—	10·00	0	38	5·8	—	−31·2***
4-Methyl	10·26	0	26	6·7	2·4	−32

* Percentage of catalysed reaction proceeding by nucleophilic mechanism.

† Using *m*-toluidine instead of aniline for trapping the anhydride.

** Overall value (nucleophilic mechanism, 1·4; general base catalysis, 4).

†† Nucleophilic mechanism, −16 e.u.; general base catalysis, −39 e.u. Overall value, −24 e.u. (*cf.* Bender and Neveu's value[5] of −28·7 e.u.)

*** Result due to Bender and Neveu. (reference 5).

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