Control of the ' Extended ' *E*1cB Mechanism of Acyl Group Transfer in Activated Esters of Acrylic Acids

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Aminolysis and alkaline hydrolysis of aryl propenoates are shown to proceed *via* a normal nucleophilic substitution mechanism. The ' extended ' *E*1cB mechanism of hydrolysis involving attack of hydroxide ion at the β carbon followed by expulsion of the phenolate ion from the resulting carbanion is shown not to occur with the parent propenoate. The ' extended ' *E*1cB mechanism is taken by the hydrolysis of 2-cyano-3-(4-methoxyphenyl)propenoate esters due to the stabilising effect of the cyano-group on the intermediate carbanion.

Inoue and Bruice [1] recently demonstrated that the hydrolysis of 4-nitrophenyl 2-cyano-3-(4-methoxyphenyl)propenoate provides 4-nitrophenol, 4-methoxybenzaldehyde, and cyanoacetic acid. The initial reaction was shown to involve hydroxide ion attack at the β-position to give a 3-hydroxy-2-cyanoketen [equation (1)]. Subsequent addition of water to the keten and a retro-Knoevenagel reaction yields 4-methoxybenzaldehyde and cyanoacetic acid.

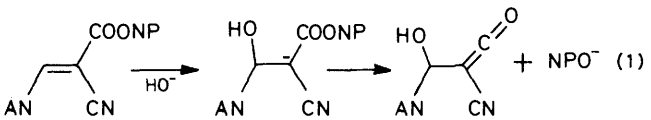
We were interested in the possibility of a similar ' extended ' *E*1cB mechanism [equation (1)] in the transfer of the parent propenoyl group from active esters to amine or water. We are prompted to report our data on this mechanism as it complements the findings of Inoue and Bruice and points to factors controlling the ' extended ' *E*1cB pathway in relation to the normal substitution process.

Precedent for simple β-addition (without leaving group expulsion) is widespread in reactions of propenoate esters with carbon nucleophiles.[2] Hydrazinolysis of aryl propenoates occurs at the β-position [3] as does aminolysis with ethanolamine [4] and hydroxylamine.[5] Blocking of the β-position of propenoic acid with a phenyl group diverts ammonolysis to the carbonyl function but the products of ethylaminolysis are from both β- and carbonyl attack.[6] Hydrogensulphite ion attacks the β-carbon of cinnamic acid and aldehyde [7] and reaction of cysteamine with methyl propenoate is initially with sulphur at the β-atom followed by ring closure through nitrogen and carbonyl group; [8] cysteamine also attacks 3-indolylpropenoylimidazole at the β-carbon atom.[9] Although the alkaline hydrolysis of several propenoate ester series has been discussed [10-21] the existence of the ' extended ' *E*1cB mechanism has never been demonstrated prior to the work of Inoue and Bruice; [1] the mechanism was advanced by Douglas in his doctoral thesis.[22]

The present kinetic and product analysis study is of the aminolysis and hydrolysis in aqueous solution of activated esters of propenoic acid. In contrast to the findings of Inoue and Bruice for the 2-cyano-3-(4-methoxyphenyl)propenoate [1] we observe a normal $B_{Ac}2$ process for the parent ester. We discuss the factors controlling the ' extended ' *E*1cB mechanism.

Experimental

Materials.—Propenoate esters were prepared from the acid chloride and the appropriate phenol in dichloromethane in the presence of an equimolar proportion of triethylamine. The liquid esters were purified by fractional distillation from quinol. Substrates were characterised by i.r. (Perkin-Elmer 237 or 257 instruments) and n.m.r. (Perkin-Elmer R10 machine) spectroscopy and their physical and analytical properties are recorded in Table 1.



AN = 4-methoxyphenyl NPO⁻= 4-nitrophenoxide ion

NP = 4-nitrophenyl

Other materials were of analytical reagent grade and water, doubly distilled from glass, was used throughout.

Methods.—Kinetics of phenol release were followed by adding a portion of substrate (50 μl of an acetonitrile stock solution of the ester) to buffer (hydroxide or glycinate) (2.5 ml) in a silica cell in the thermostatted cell compartment of a Unicam SP 800 spectrophotometer, from the flattened tip of a glass rod. Repetitive spectral scans were carried out to identify the best wavelength for the kinetic study and this was employed in the detailed kinetics. Pseudo-first-order rate constants were determined from linear plots of $A_\infty - A_t$ *versus* time using semi-logarithmic graph paper.

Product analysis was carried out by comparing the u.v. spectrum of the products with that of the appropriate phenol. Identification of the acidic portion of the molecule was made through n.m.r. spectroscopic analysis of the products of experiments carried out on a preparative, but otherwise similar, scale to the kinetic runs.

Results

Product Analysis.—Spectroscopic analysis of the products of the hydrolysis of 4-nitrophenyl propenoate indicated 4-nitrophenol and propenoic acid; no evidence was seen of n.m.r. signals from 3-hydroxypropionic acid, formaldehyde, or acetic acid. Moreover the propenoic acid and 4-nitrophenol were estimated to be formed in approximately equimolar quantities with an overall theoretical yield. Reaction of the 4-nitrophenyl ester with glycinate buffers was shown to yield the corresponding propenamide by the n.m.r. method.

Kinetics.—The esters solvolysed in alkali and glycine buffers yielding sharp u.v. isosbestic wavelengths consistent with a simple A to B stoicheiometry. The rates of reaction were strictly pseudo-first-order in the substrate (*ca.* 10^{-3}M) and rate constants were proportional to the concentration of hydroxide ion and to the free base form of the glycine buffer. The derived second-order rate constants for hydroxide ion (k_{HO^-}) and glycine (k_{gly}) are recorded in Table 2.

Table 1. Analytical and physical data for aryl propenoates [e]

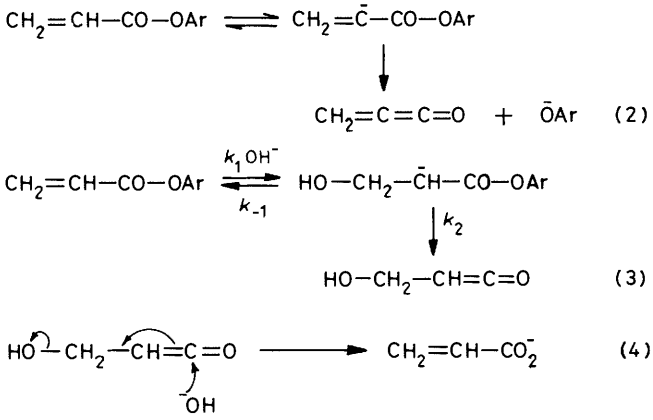
Aryl substituent	M.p. (b.p.) T/°C	Found (%) C	H	N	Formula	Calculated (%) C	H	N
4-Nitro	61—64 [d]	55.9	3.6	7.3	$C_9H_7NO_4$	56.0	3.6	7.3
3-Nitro	34—35 [c]	55.8	3.6	7.3	$C_9H_7NO_4$	56.0	3.6	7.3
4-Acetyl	72—73	69.7	5.3		$C_{11}H_{10}O_3$	69.5	5.3	
4-Chloro	(88—89 at 0.4 Torr) [a]	58.9	4.0		$C_9H_7ClO_2$	59.2	3.8	
H	(72 at 0.4 Torr) [b]	72.7	5.4		$C_9H_8O_2$	73.0	5.4	

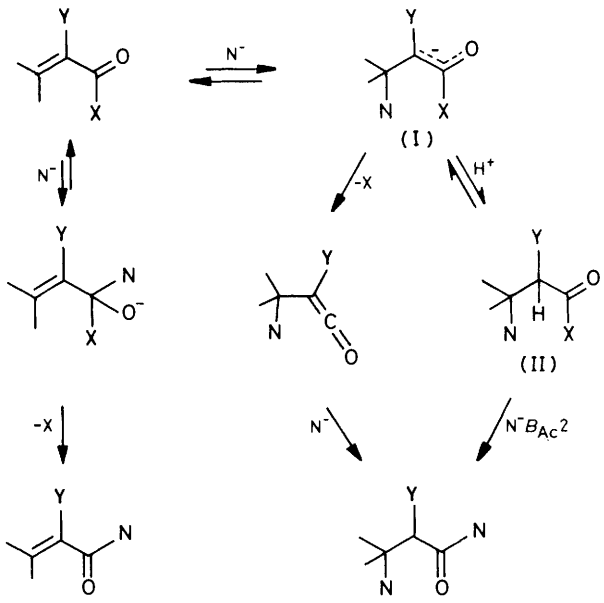
[a] Lit. b.p. 70 °C at 1 Torr; found: n_D^{20} 1.5363 (lit. 1.5356) (E. M. Filachione and C. H. Fisher, U.S.P. 2 477 293/1949; *Chem. Abstr.*, 1950, **44**, 2027e). [b] Lit. b.p. 65 °C at 1.0 Torr; found: n_D^{20} 1.5191 (lit. 1.5210) (A. H. Albrecht and D. W. Codding, *J. Am. Chem. Soc.*, 1953, **75**, 984). [c] Lit. m.p. 34—35 °C (N. N. Lebedev and L. V. Andrianova, *J. Gen. Chem. U.S.S.R.*, 1955, **25**, 193; *Chem. Abstr.*, 1956, **50**, 1676c). [d] Lit. m.p. 59—60 °C. Reference in footnote *c*. [e] M.p.s were determined using a Kofler Thermospan instrument and are corrected. Microanalyses were performed by Mr. G. M. Powell and Miss L. Tidy using a Hewlett-Packard model 185 CHN analyser.

Table 2. Rate constants for hydrolysis and glycinolysis of aryl propenoates [a]

Aryl substituent	k_{HO^-}/ l mol^{-1} s^{-1} [b]	k_{HO^-}/ l mol^{-1} s^{-1} [c]	k_{Gly}/ l mol^{-1} s^{-1} [c]	λ_{kin}/nm
4-Nitro	8.65	12.5	28.5	400
3-Nitro	5.61	8.97		300
4-Acetyl	3.58	3.48	4.95	330
4-Chloro	1.61	1.36	1.08	300
Parent	0.750	0.512	0.350	290
ρ	1.29	1.75	2.45	
Correlation coefficient	0.996	0.999	0.999	

[a] 25 °C, 0.1M ionic strength. [b] 20% Dioxan–water (v/v). [c] 50% Ethanol–water (v/v).





Scheme

Discussion

Hydrolysis of aryl propenoates by formation of the propenoyl anion followed by subsequent decomposition to cumuloketen [equation (2)] is unlikely because the rate constant for exchange of the α-hydrogen is too low [23] to account for the hydrolysis. Moreover, the good correlation of k_{HO^-} with Hammett's σ constants (r 0.996) and the low ρ values preclude equation (2) as well as the synchronous or stepwise displacement of phenolate ion by the mechanism of equation (1). The present data for hydroxide ion attack on aryl propenoates could be consistent with equation (1) provided the addition step were rate limiting [equation (3) $k_{-1} < k_2$]. Since the product is propenoic acid and not 3-hydroxypropionic acid the keten of equation (3) would need to be hydrated with expulsion of the hydroxide ion [equation (4)] by a mechanism essentially the reverse of that for formation of the keten and not across the 1,2-ene position as is normal.[24] Such a process is scarcely conceivable with the hydrolysis reaction but is most unlikely when the leaving group is an amine as in the glycinolysis reaction.

The fit of k_{Gly} to a Hammett σ dependence and a ρ value of 2.45 for glycinolysis is typical of nucleophilic displacements by amines at aromatic esters.[25]

Although the 3-position in 2-cyano-3-(4-methoxyphenyl)-propenoates is hindered by the aromatic substituent, β-attack by the hydroxide ion still occurs to yield the 3-hydroxyketen.[1] Control of the *E*1cB mechanism in acyl group transfers involves the acidity of the α-hydrogen, leaving group ability, stability of the heterocumulene intermediate, the nucleophile, and the internal nucleophilicity of the conjugate base.[26] These factors apply to the 'extended' *E*1cB mechanism of Inoue and Bruice because the conjugate base is formed in this mechanism but by a different route. We can delineate the major paths available for the acyl group transfer in the Scheme. If the acidity of the species (II) to yield (I) is sufficiently high the intermediate (I) will be present in significant proportions, sufficient to support a reaction flux to the keten. Holmquist and Bruice [27] have already shown that compounds of the type (II) with Y = CN transfer the acyl function through the keten intermediate rather than through the $B_{Ac}2$

pathway. Thus when (I) is formed (Y = CN) it will naturally proceed *via* keten to products.

It is known [26a,28] that compounds of the type (II) where Y = H do not undergo acyl group transfer through the *E*1cB path. We may therefore apply the above argument to the hydrolysis and aminolysis of the parent propenoates and this indicates that the keten path should *not* be traversed. An argument against the *E*1cB mechanism for hydrolysis of 4-nitrophenyl acetate [26a] is that deprotonation of the acetate [analogous to (II; Y = H)] to give the carbanion is too slow to account for the observed rate *via* the carbanion [analogous to (I; Y = H)]. The 'extended' *E*1cB path provides an easier route to the carbanion and it might be expected that the keten path should then be taken by propenoate hydrolysis as the carbanion would be very basic and exert a very powerful internal nucleophilicity.[26] However (I) will also protonate from water at a diffusion-controlled rate and even if formation of keten is at the diffusion limit the 55M concentration of water will ensure diversion of (I) to (II). Approximate calculations indicate that the formation of keten from the carbanion (I; Y = H) is indeed at a diffusion-controlled rate.

Reduction of the reactivity at the carbonyl centre can divert attack of nucleophiles to the β-position. Johnson and his coworkers [29] found that ethoxide ion preferentially attacks at the β-carbon in propenoylanilides. The initially formed carbanion (I) will clearly prefer protonation to give (II) because the formation of keten from acid compounds with poor leaving groups is very inefficient.[26]

In the case of the present propenoates the mechanism involving expulsion of the leaving group concerted with hydroxide ion addition is still not favourable enough to compete with the $B_{Ac}2$ process even though the full expression of the unstable carbanion is suppressed.

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