Alkaline Hydrolysis of Aryl Phenylacetates and Aryl 4-Nitrophenylacetates. Evidence consistent with an Elimination–Addition Mechanism

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Hydrolysis of the substituted phenyl esters of phenylacetic acid is found to be first order each in the ester and hydroxide ion. Hydrolysis is catalysed by general bases and the catalytic coefficients for the substituted phenoxides obey the Brønsted relation with β +0.49. The rate of hydrolysis of the esters of 4-nitrophenylacetic acid is independent of [hydroxide] in the range employed. Both series of reactions exhibit low solvent isotope effect and high sensitivity to substituents in the leaving group [ρ 1.40 for the esters of phenylacetic acid and 3.4 for the esters of 4-nitrophenylacetic acid in 80% DMSO–20% water (v/v)]. These data suggest an *E*1cB mechanism for the hydrolysis. The keten intermediate envisaged for such a mechanism has been trapped as the anilide when the reactions are conducted in aniline buffers, without any effect on the rate of hydrolysis for variations in [aniline]. An increase in the DMSO content in the solvent decreases the rate of hydrolysis of the esters of 4-nitrophenylacetic acid, which is explained by an $(E1cB)_{anion}$ mechanism for the hydrolysis. Transfer to aqueous DMSO results in rate accelerations for the esters of phenylacetic acid which can be accounted for by either an $(E1cB)B_{ion\ pair}$ or $(E1cB)_{reversible}$ mechanism for the hydrolysis.

The *E*1cB mechanism has been established as an alternative mode of acyl transfer from substrates containing acidic α-hydrogens.[1] Esters of acetic acid with electron-withdrawing substituents on the α-carbon which could promote the acidity of the α-carbon are systems wherein the *E*1cB mechanism may prevail over the $B_{Ac}2$ mechanism. An incursion of the *E*1cB mechanism has resulted upon introduction of groups such as acetyl,[2a] ethoxycarbonyl,[2b] and cyano [2c] on the α-carbon of acetic acid esters. The question of whether a phenyl group on the α-carbon could also bring about such a change in mechanism from $B_{Ac}2$ to *E*1cB is quite open. Bruice and Holmquist [2c] have presented evidence in favour of a $B_{Ac}2$ mechanism for the 2-nitrophenyl ester of phenylacetic acid. But for a system structurally similar to phenylacetic acid, *viz.*, aryl α-phenylmethanesulphonates, hydrolysis has been shown to proceed by an *E*1cB mechanism.[3] In view of their structural similarity and comparable acidities,[4] the operation of an *E*1cB mechanism may be considered as an interesting alternative possibility. It was, therefore, considered worthwhile to investigate the hydrolysis of esters of phenylacetic acid with variations in the leaving group so that structure–activity correlations might be attempted. But unambiguous assignment of the hydrolytic pathway is made difficult by the high pK_a of these esters. The introduction of a nitro-group in the acyl part reduces the pK_a of the ester and promotes the *E*1cB process. This is borne out by the observed *E*1cB mechanisms for the elimination reactions of β-(4-nitrophenyl)ethyl derivatives,[5] while the β-phenylethyl derivatives react by an *E*2 process.[6] Also the ease of formation of the carbanion from the esters of nitrophenylacetic acid may be expected to be high, judged from the equilibrium formation of deeply coloured anions of 5-nitrocoumaranone.[7] This lactone has been shown to hydrolyse by an addition–elimination pathway and not by an elimination–addition mechanism, as inferred from the solvent isotope effect values.[7] The absence of an *E*1cB process has been explained [8] as due to the intramolecular trapping of the keten intermediate by the *o*-hydroxy-function rather than by an external nucleophile. If this was true, the acyclic esters of nitrophenylacetic acid should be expected to hydrolyse by an *E*1cB mechanism. The present paper details the results of a kinetic investigation on the alkaline hydrolysis of the esters of phenylacetic acid and 4-nitrophenylacetic acid, which indicate the operation of the predicted *E*1cB mechanism.

Table 1. M.p.s and rate constants for the hydrolysis of aryl phenylacetates [a]

$Ph{\cdot}CH_2{\cdot}COO{\cdot}C_6H_4X$ X	M.p.[b] (°C)	λ_k[c]/nm	λ_i[d]/nm	k_2 in H_2O/ l mol^{-1} s^{-1}	k_2 in D_2O/ l mol^{-1} s^{-1}
H	40.5	290	255	4.53	3.96
4-Methyl	76	290	255	3.20	2.98
4-Carboxy	160	295	250	4.60	5.61
4-Chloro	39	290	245	9.20	9.41
4-Bromo	52	300	250	8.92	9.36
4-Methoxycarbonyl	81	295	255	19.0	18.9
3-Nitro	62	390	320	48.7	52.1
4-Nitro	62.6	400	320	52.3	57.2

[a] 30 °C, aqueous medium with 1.67% acetonitrile, [OH^-] 0.005–0.08M; [ester] 2×10^{-4}M. [b] M.p.s measured on a Toshniwal instrument and are uncorrected. [c] Kinetic wavelength. [d] Isosbestic wavelength.

Experimental

Materials.—The esters of phenylacetic acid were prepared by refluxing equimolar quantities of phenylacetyl chloride, b.p. 94—95 °C at 12 mmHg, and the required phenol with catalytic amounts of pyridine for 4 h in chloroform. The solution was washed successively with dilute HCl, water, dilute hydrogencarbonate, and water. The organic layer was dried (Na_2SO_4) and the solvent evaporated to give the crude ester which was recrystallised from chloroform–hexane mixtures.

The substituted phenyl esters of 4-nitrophenylacetic acid were prepared by treating 4-nitrophenylacetyl chloride (1 g, 5 mmol) with 1 mol equiv. of the appropriate sodium phenoxide in dry benzene (10 ml). The precipitated sodium chloride was filtered off and evaporation of benzene afforded the crude ester which was repeatedly recrystallised from chloroform–hexane to constant m.p. The purity of the esters were checked by t.l.c. and by measuring the absorbance of the phenol released on complete hydrolysis. The compounds were characterised by their m.p. and analysis (Tables 1 and 2) and by i.r. spectroscopy. Acetonitrile was purified by distillation over P_2O_5. Dimethyl sulphoxide was purified by distil-

Table 2. M.p.s and analytical data for the esters of 4-nitrophenylacetic acid [a]

p-$O_2NC_6H_4CH_2COOX$ X	M.p. (°C)	Found (%) C	Found (%) H	Formula	Calculated (%) C	Calculated (%) H
Ethyl	62 (63) [b]					
4-Methoxyphenyl	85	62.65	4.65	$C_{15}H_{13}NO_5$	62.7	4.5
4-Methylphenyl	83	66.7	5.1	$C_{15}H_{13}NO_4$	66.4	4.85
Phenyl	93	65.0	4.4	$C_{14}H_{11}NO_4$	65.35	4.3
4-Bromophenyl	124—125	49.7	3.25	$C_{14}H_{10}BrNO_4$	50.0	3.0
3-Nitrophenyl	108—109	53.75	3.45	$C_{14}H_{10}N_2O_6$	55.65	3.35
4-Nitrophenyl	120	55.4	3.6	$C_{14}H_{10}N_2O_6$	55.65	3.35

[a] Analysis by Ciba-Geigy Research Centre, Bombay by courtesy of Dr. K. Nagarajan. M.p.s measured on a Toshniwal instrument are uncorrected. [b] H. Cook and E. R. H. Jones, 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1959, vol. 3.

Table 3. Rate data for the hydrolysis of aryl 4-nitrophenylacetates [a]

p-$O_2NC_6H_4CH_2COOX$ X	λ_k [b]/nm	λ_i [c]/nm	$10^3 k_{obs}/s^{-1}$	pK_a [d]
Ethyl	510	328	0.338	
4-Methoxyphenyl	510	380	0.840	13.3
4-Methylphenyl	510	380	1.32	13.2
Phenyl	520	350	5.65	13.0
4-Bromophenyl	520	340	36.5	12.1
3-Nitrophenyl	520	*e*	1 850	10.6

[a] 30 °C, 80% DMSO–20% H_2O (v/v), [hydroxide] 0.005—0.08M, [ester] 2×10^{-5} to 2×10^{-4}M. [b] Kinetic wavelength. [c] Isobestic wavelength. [d] pK_a of the leaving phenol in 80% DMSO–20% H_2O, calculated from M. M. Kreevoy and E. H. Baughman, *J. Am. Chem. Soc.*, 1973, **95**, 8178. [e] Too fast to allow repetitive scanning.

Table 4. Rate dependence on the concentration of hydroxide ion for the hydrolysis of phenyl phenylacetate [a]

10^2[hydroxide]/M	$10^3 k_{obs}/s^{-1}$	k_2/l mol^{-1} s^{-1}
0.5	2.28	4.56
1.0	4.52	4.52
2.0	9.24	4.62
3.0	13.8	4.60
4.0	18.1	4.52

[a] 30 °C, aqueous medium with 1.67% acetonitrile. [ester] 1×10^{-4}M.

lation under reduced pressure. Absolute ethanol was prepared from commercial rectified spirits by the method of Vogel.[9] Water twice distilled from all-glass apparatus was boiled before use. The buffer solutions were made from reagent grade chemicals, Tris, borax, and disodium hydrogenphosphate. A solution of the required pH was prepared by titrating a solution of the buffer agent of known concentration against standard hydrochloric acid or sodium hydroxide, pH being measured with a digital pH meter (±0.01 accuracy; Bhagyanagar Instruments, India). The phenols used as catalysts were either recrystallised or distilled before use. A 0.01M solution of phenol in freshly boiled water was titrated against 0.1M-hydroxide to the required pH. These buffers were diluted with 1.0M-KCl solution whenever required. The pH was checked for any change upon dilution.

Methods.—The hydrolysis of the esters was followed initially at constant pH by repetitively scanning the u.v. spectrum using a Pye–Unicam SP 800 spectrophotometer provided with a SP820B programmer. Scanning experiments showed the best wavelength for kinetic study and also indicated the stoicheiometry of the reactions. The rates of hydrolysis was measured spectrophotometrically using a Carl Zeiss VSU2P spectrophotometer equipped with a Carl Zeiss recorder. The cell compartments was thermostatted (±0.05 °C) with water. Quartz or glass cells of 1 cm pathlength were used. In a typical run, the ester (50 μl) of appropriate concentration in acetonitrile as solvent was injected into the buffer (2.95 ml) kept thermostatted in the cell compartment. The solution was shaken to ensure proper mixing. The changes in absorbance at suitable wavelength (Table 3) were then recorded at regular time intervals, till 80% completion. Each reaction was repeated twice and the average of the rate coefficients were taken. Some of the fast reactions were followed by the stopped flow method using an Aminco Morrow stopped flow instrument with a Beckman spectrophotometer and a Dektronix-D11 storage oscilloscope. The pseudo-first-order rate coefficients were evaluated by a least square analysis of log $(A_\infty - A_t)$ or log $(A_t - A_\infty)$ *versus* time as the case may be, using a Hindustan Micro 2200 programmable calculator. The rate data are reproducible to within a ±3% error.

Trapping Experiments.—To the buffer (100 ml; pH 9.0; 20% acetonitrile) was added aniline (1 ml, 0.01M) followed by the ester (2 ml, 0.01M). After nearly two half-lives of the reaction, the solution was extracted with ether, dried (Na_2SO_4), and the ether evaporated to get the product. Formation of the anilide was inferred from the m.p., t.l.c. with an authentic sample, and the i.r. spectra.

Results

The stoicheiometry of the hydrolytic reactions was determined by spectrophotometric procedures.[10] The observation of perfect isosbestic wavelength between the reactants and products is proof of a simple 1 : 1 stoicheiometry (Tables 2 and 3). The rate of release of the phenoxide in the hydrolysis of the esters of phenylacetic acid and the rate of decay of the carbanion in the hydrolysis of the esters of 4-nitrophenylacetic acid is exponential giving linear plots of log $(A_\infty - A_t)$ or log $(A_t - A_\infty)$ *versus* time, as the case may be. The rate of hydrolysis of aryl phenylacetates is first order in [hydroxide] in the range of concentration employed (0.005—0.04M) (Table 4). The rate of hydrolysis of the esters of 4-nitrophenylacetic acid, however, is not affected by changes in the range of [hydroxide] employed (Table 5). The rates of hydrolysis of these esters are not appreciably affected by change of solvent to D_2O (Tables 1 and 6). The rate data for both systems fit the Hammett equation when the σ values are used (Figure 1, ρ 1.4, *r* 0.99 for the phenylacetic acid esters; Figure 2, ρ 3.4, *r* 0.99 for 4-nitrophenylacetic acid esters). The rate data also fitted the Brønsted relationship when the pK_a of the leaving phenols are used (Figure 1, β −0.65, *r* 0.98 for the esters of phenylacetic acid; Figure 2, β −1.25, *r* 0.98 for the esters of 4-nitrophenylacetic acid). The hydrolysis

Table 5. Rate dependence on the concentration of hydroxide ion for the hydrolysis of aryl 4-nitrophenylacetates [a]

p-$O_2NC_6H_4$-CH_2COOX X	$10^3 k_{obs}/s^{-1}$					
$10^2[OH^-]$/M	Ethyl	4-Methoxyphenyl	4-Methylphenyl	Phenyl	4-Bromophenyl	3-Nitrophenyl
0.5	0.336	0.840	1.31	5.64	36.2	1 850
1.0	0.339	0.848	1.34	5.63	36.3	1 810
2.0	0.334	0.842	1.29	5.61	36.7	1 870
4.0	0.341	0.836	1.30	5.70	36.5	1 860
8.0	0.332	0.844	1.32	5.66	36.1	

[a] 30 °C, 80% DMSO–20% H_2O (v/v). [ester] = 1×10^{-4}M.

Table 6. Solvent isotope effect in the hydrolysis of ethyl 4-nitrophenylacetate [a]

Solvent	$10^2[OH^-]$/ M	$10^2[OD^-]$/ M	$10^3 k_{obs}/s^{-1}$	k_{H_2O}/k_{D_2O}
H_2O	2.0		11.1	
	4.0		11.9	
	6.0		11.5	
	8.0		10.9	
		1.0	9.25	1.22
D_2O		2.0	9.10	
		4.0	9.04	
		8.0	9.07	

[a] 30 °C, 60% DMSO–40% water (v/v), [ester] 1×10^{-4}M.

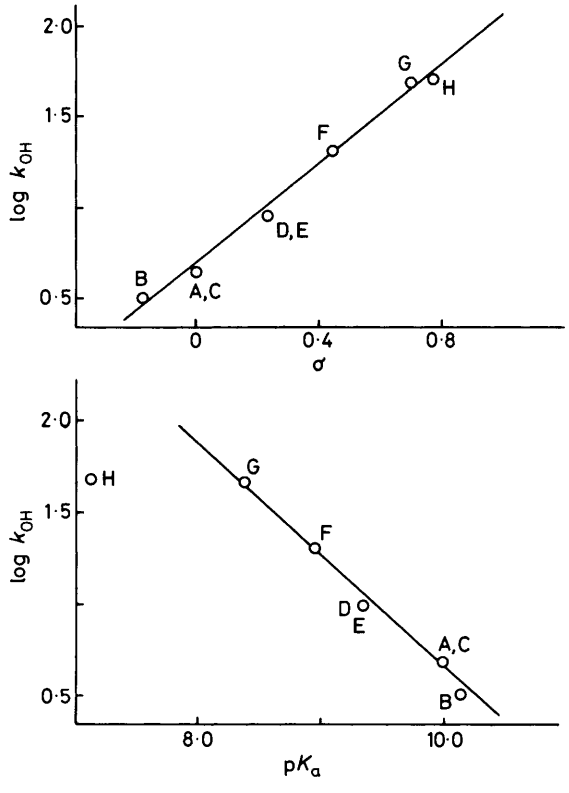


Figure 1. Hydrolysis of the substituted phenyl esters of phenylacetic acid. Hammett and Brønsted plots. A Phenyl; B, 4-methylphenyl; C, 4-carboxyphenyl; D, 4-chlorophenyl; E, 4-bromophenyl; F, 4-carboxymethylphenyl; G, 3-nitrophenyl; H, 4-nitrophenyl (ρ 1.4, r 0.99; β −0.65, r 0.98)

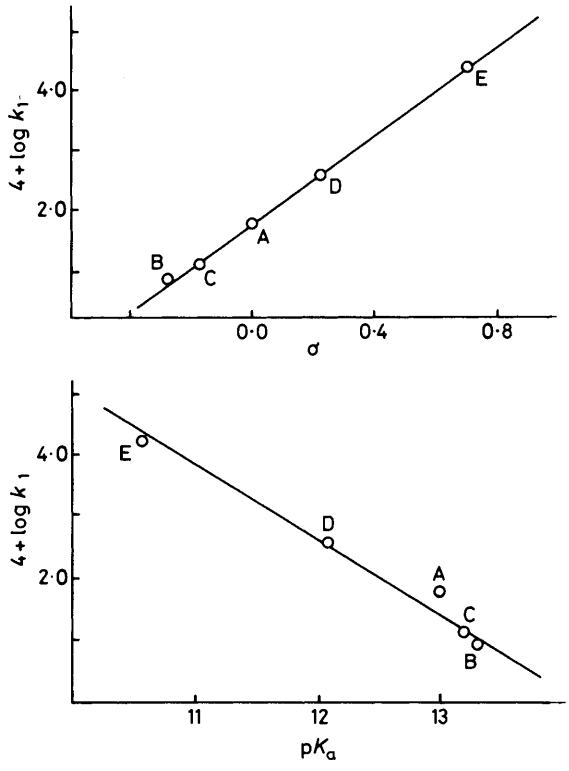


Figure 2. Hydrolysis of substituted phenyl esters of 4-nitrophenyl acetic acid, in 80% DMSO–20% water (v/v) medium at 30 °C. Hammett and Brønsted plots of log rate constants *versus* σ values of the substituents in the leaving group or the pK_a of the leaving phenol. A, Phenyl; B, 4-methoxyphenyl; C, 4-methylphenyl; D, 4-bromophenyl; E, 3-nitrophenyl (ρ 3.4, r 0.99; β −1.25, r 0.98)

of the esters of phenylacetic acid is catalysed by general bases. Substituted phenoxides were used as general bases and the catalytic coefficients evaluated from the rate data for variations in [phenoxide] (Table 7). In spite of the fact that phenoxide ions are products and are also general base catalysts, no autocatalysis was observed. This could be due to the very low concentration of the ester (10^{-4}—10^{-5}M) which make contribution from catalysis by products negligible (for example at pH 11.0, $[OH^-]$ 10^{-3}M and with k_2 52.3 l mol^{-1} s^{-1}, k_1 5.23×10^{-2} s^{-1}, [product phenoxide] *ca.* 10^{-5}M, k_2 *ca.* 0.5 l mol^{-1} s^{-1}, k_1 5.0×10^{-6} s^{-1}). The catalytic coefficients are related to their pK_a by the Brønsted equation with β +0.49 (Figure 3, r 0.98). For the esters of phenylacetic acid, transfer to aqueous ethanol leads to rate increase for esters with good leaving groups (Table 9). A change of solvent to aqueous

Table 7. Catalysis of hydrolysis 4-nitrophenyl phenylacetate [a]

Catalyst	pK_a [b]	k_{cat}/l mol^{-1} s^{-1}
Phenoxide	10.0	4.60
4-Methylphenoxide	10.14	8.01
2-Chlorophenoxide	8.58	0.90
4-Bromophenoxide	9.36	1.90

[a] 30 °C, in aqueous medium containing 1.67% acetonitrile, k_{cat} evaluated by regression analysis of rate *versus* [phenoxide]. [b] pK_a values from A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Methuen, London, 1962.

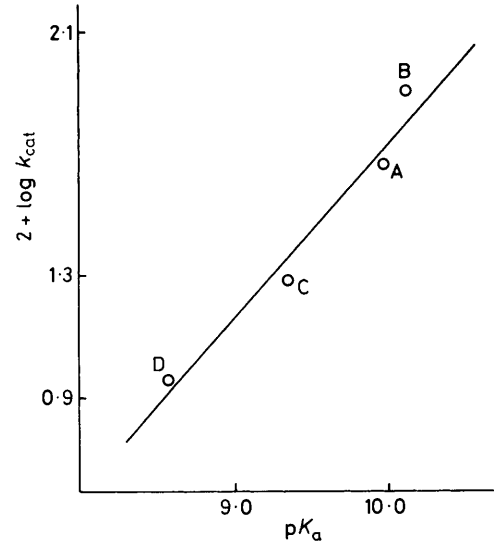


Figure 3. Catalysis by substituted phenoxides in the hydrolysis of 4-nitrophenyl phenylacetate at 30 °C. Brønsted plot of log (catalytic coefficients) *versus* the pK_a of the phenoxide. A, Phenoxide; B, 4-methylphenoxide; C, 4-bromophenoxide; D, 2-chlorophenoxide (β +0.49, r 0.98)

Table 8. Effect of varying the concentration of aniline in the buffer

10^3 [aniline]/M	10^3 k_{obs} [a]/s^{-1}	k_{obs} [b]/s^{-1}
2.0	2.98	3.95
4.0	3.00	4.20
6.0		4.17
8.0	2.89	4.23
16.0	3.02	

[a] For the 4-nitrophenyl phenylacetate, [ester] 2 × 10^{-5}M, pH 10.0, 30 °C, aqueous medium containing 1.67% acetonitrile. [b] For the 3-nitrophenyl 4-nitrophenylacetate, [ester] 2 × 10^{-5}M, pH 10.0, 30 °C, aqueous medium containing 3.5% DMSO.

DMSO results in an initial rate decrease up to 40% DMSO and then a rate increase for the esters of phenylacetic acid (Table 10) while for the esters of 4-nitrophenylacetic acid there is a pronounced rate retardation upon increasing the DMSO content in the solvent medium (Table 11).

Discussion

Generally, for aryl acetates only the addition–elimination mechanism can be expected to operate, yet for the hydrolysis of the esters of phenylacetic acid and 4-nitrophenylacetic acid other mechanisms are possible (Scheme 1).

For the hydrolysis of esters of phenylacetic acid, the rate law observed will be consistent with the mechanisms given above. The attack of water molecule on the carbonyl of the ester anion (k_3) involves a water molecule in the transition state and would, therefore, demand a considerable solvent isotope effect for reactions conducted in D_2O. The absence of any such isotope effect for all the esters (Table 1) studied, point out to the absence of such a pathway. Also the rate constant k_3 may be calculated from the pK_a of the ester [4] and the autoprotolysis constant using equation (1). Phenyl

$$k_3 = k_{OH}k_w/K_a \quad (1)$$

phenylacetate has pK_a *ca.* 20 and with k_{OH} 4.56 l mol^{-1} s^{-1}, k_3 will have a value of 4.56 × 10^6 l mol^{-1} s^{-1}. This would lead to an estimate of the rate constant at pH 8.0 as 2.54 × 10^8 s^{-1}. The observed rate is 4.36 × 10^{-6} s^{-1} and hence this mechanism can be ruled out.

An *E*2 reaction involves the scission of a C–H bond in the rate-determining step. For such a reaction a primary kinetic isotope effect of 6 and a considerable solvent isotope effect is

Table 9. Effect of varying the ethanol content in the solvent system in the hydrolysis of aryl phenylacetates [a]

Ph·CH_2·COOX X	k_2/l mol^{-1} s^{-1}				
	40 [b]	50 [b]	60 [b]	70 [b]	80 [b]
H	3.55	2.78	3.29	3.91	3.76
4-Methyl	2.38	2.45	2.60	3.10	3.63
4-Carboxy	3.30	2.29	3.66	4.06	4.56
4-Chloro	10.2	9.90	12.5	13.1	13.9
4-Methoxycarbonyl	19.3	22.8	23.1	32.1	41.6
4-Bromo	10.3	10.3	14.1	15.9	17.1
3-Nitro	60.6	75.4	17.6		
4-Nitro	67.0	81.1	114		

[a] 30 °C, aqueous ethanol (v/v). [b] % ethanol in the medium.

Table 10. Effect of varying DMSO content in the solvent medium in the hydrolysis of aryl phenylacetates [a]

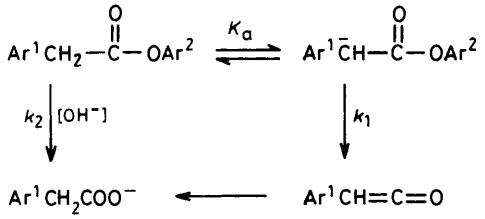
$PhCH_2COOC_6H_4X$ X	k_2/l mol^{-1} s^{-1}				
	40 [b]	50 [b]	60 [b]	70 [b]	80 [b]
H	3.95	4.67	11.1	42.8	91.8
4-Methyl	2.58	3.93	9.05	20.1	38.3
4-Carboxy	5.01	5.69	16.9	50.4	86.7
4-Chloro	6.36	9.98	38.6	89.4	
4-Bromo	6.78	12.2	42.2	81.3	
4-Methoxycarbonyl	27.6	58.3			

[a] 30 °C, aqueous DMSO (v/v). [b] % DMSO in the solvent medium.

Table 11. Effect of varying the DMSO content in the solvent medium in the hydrolysis of aryl 4-nitrophenylacetates [a]

p-$O_2NC_6H_4CH_2COOX$ X	10^2 k_1/s^{-1}			
	60 [b]	70 [b]	80 [b]	90 [b]
Ethyl	1.12	0.230	0.0338	
4-Methoxyphenyl	3.15	0.553	0.0840	0.006 35
4-Methylphenyl	3.66	0.691	0.132	0.0114
Phenyl	4.00	1.60	0.565	0.0557
4-Bromophenyl		14.5	3.65	0.800
3-Nitrophenyl			185	

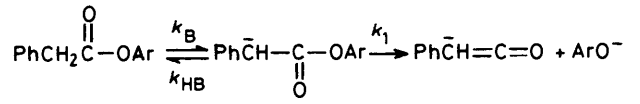
[a] 30 °C, aqueous DMSO (v/v). [b] % DMSO in the solvent medium.



Scheme 1

to be expected. The near insensitivity of the rate to exchange of solvent with D_2O for all the esters thus rules out this mechanism. The choice is between a $B_{Ac}2$ process (k_2) and an $E1cB$ mechanism (k_1). The $B_{Ac}2$ reaction proceeds *via* a tetrahedral intermediate while the $E1cB$ mechanism involves the formation of a keten intermediate. Keten if formed can be trapped by nucleophiles. In the present study the hydrolysis of the 4-nitrophenyl ester when conducted in buffers containing aniline leads to the formation of phenylacetanilide, which has been isolated and identified by t.l.c. with an authentic sample of the anilide and by the i.r. spectrum. The possibility of direct nucleophilic attack by aniline on the carbonyl of the ester, which could also lead to the same product, may be easily ruled out on the following grounds. The hydrolysis of the 4-nitrophenyl ester is catalysed by general bases and a plot of log k_{cat} *versus* the pK_a of the attacking base is linear (Figure 3) with β 0.49. Such a low value of β is indicative of general base catalysis and nucleophilic attack would result in a Brønsted slope of *ca.* 0.8.[11] Also, when the pK_a of the leaving group is very close to or less than that of the attacking base, nucleophilic attack may be expected. If however, the nucleophile is several times more basic than the leaving group, general base catalysis is observed.[12] Aniline, with a pK_a of *ca.* 5 may be expected to act only as a general base and not as a nucleophilic catalyst. The nucleophilic reactivity of aniline will be very low compared with that of hydroxide ion.[13] This may also be seen by the calculation of k_{cat} for aniline and hydroxide ion for a nucleophilic reaction for which the Brønsted slope is 0.8. For a pK_a difference of 9 log units the difference in reactivity should be $0.8 \times 9 = 7.2$ long units. Aniline is 10^7 times less reactive than hydroxide and cannot be an effective competitor at pH 9.0 as a nucleophile. In fact for reactions conducted at pH 10.0 with varying concentrations of aniline in the buffer there is a negligible effect on the rate for variations in [aniline] (Table 8). The formation of the anilide without a rate dependence on [aniline] can be explained only by invoking rate-determining formation of a keten intermediate which in a fast step would form the anilide.

Leaving Group Effects.—The Hammett reaction constant for variations in the leaving group can be used to distinguish between $B_{Ac}2$ and $E1cB$ pathways. The transition state for a $B_{Ac}2$ process involves little cleavage of the C–OAr bond and hence the rate of hydrolysis will not be subject to appreciable change on varying the leaving group. For example, the hydrolysis of aryl acetates exhibit a Hammett ρ value of +0.8 for the σ substituent constants.[14] The rate-determining step for the $E1cB$ reaction is the unimolecular expulsion of the aryloxy group with the concomitant formation of the C=C double bond. The transition state for such a process would have extensive C–OAr bond cleavage and hence substituents on the leaving group can effectively interact with the reaction centre and contribute to rate changes in large measure. For arylphenyl acetates there is a good correlation of rate with the σ values (Figure 1, r 0.99) giving ρ +1.4. This rather high value is more in agreement with the $E1cB$ than with the $B_{Ac}2$ mechanism.



Scheme 2

Solvent Isotope Effects.—It has been shown [7] that for ionized substrates k_{H_2O}/k_{D_2O} has values around unity for an $E1cB$ process and 1.5 for a $B_{Ac}2$ reaction. Although for the esters of phenylacetic acid, complete ionization of the substrate does not take place under experimental conditions, one is justified in assigning values of k_{H_2O}/k_{D_2O} of *ca.* 1 as indicative of an $E1cB$ process since the alternative $B_{Ac}2$ process would definitely demand values exceeding 1.5.

Buffer Catalysis.—Buffer catalysis has been used to decide mechanisms of acyl transfer. Esters with good leaving groups which hydrolyse by the $B_{Ac}2$ mechanism undergo nucleophilic catalysis by the general bases present in the buffer system.[15] In such systems the Brønsted β value for variations in the nucleophile is *ca.* 0.8. But esters which hydrolyse by the $E1cB$ mechanism do not show any buffer catalysis if their pK_a is within the water scale. If the pK_a is greater than 14, there is buffer catalysis but of a smaller magnitude. The hydrolysis of 4-nitrophenyl phenylacetate is found to be catalysed by phenoxide ions as general bases with a Brønsted exponent of +0.49. This low value of β is indicative of general base catalysis, possibly of the proton removal from the carbon acid (Scheme 2). According to Scheme 2, the reaction would be expected to show saturation kinetics with respect to the buffer agent at high buffer concentrations. This, however, has not been realised in the present investigation.

Mechanism of Hydrolysis of Aryl 4-Nitrophenylacetates.—The instantaneous formation of the carbanion and its rate-determining decomposition are indicative of an $E1cB$ process, although other mechanisms may also at times lead to such a rate picture [7] (Scheme 1). The pH of the medium being much higher (>11) than the pK_a of the ester which may be *ca.* 9.5,* the ester would have completely ionised to give the carbanion. This is checked by following the absorbance at 510 nm for the addition of increasing concentrations of hydroxide ion. The initial increase in absorbance due to the carbanion soon tapers off to the maximum value corresponding to the complete ionization of the ester. A bimolecular attack of hydroxide ion on the un-ionised ester (k_2) and its kinetically equivalent bimolecular attack of water on the ester anion (k_3) may be ruled out on the basis of solvent isotope effect. For a $B_{Ac}2$ mechanism, the ratio k_{H_2O}/k_{D_2O} would have values >1.5 while for an $E1cB$ reaction it would be around unity. The observed solvent isotope effect value is suggestive of the operation of an $E1cB$ mechanism.

The hydrolysis reactions exhibit high ρ values (2.6 in 70% DMSO, 3.4 in 80% DMSO, and 4.1 in 90% DMSO–water mixtures). Such high sensitivity to the variation in the leaving group is typical of $E1cB$ reactions.[1a] The high value of the reaction constant indicates extensive C–OAr bond cleavage, and the accumulation of negative charge on the phenolate oxygen in the transition state. For such reactions the correlation of the rate data would be more satisfactory with σ^- values for substituents which mesomerically interact with the reaction centre. The hydrolysis of the 4-nitrophenyl ester

* The pK_a of 5-nitrocoumaranone, the cyclic analogue of the 4-nitrophenyl ester of 3-nitrophenylacetic acid has been shown [7] to be 9.8.

which could test this proposition could not be followed since the ester is unstable in aqueous solution.

The high negative β value [−1.25 in 80% DMSO–20% water (v/v)] is characteristic of an *E*1cB reaction and has been explained [16] as arising out of a twin process of bond formation (HC–C=O) and bond cleavage (–C–OAr) since β_{lg} is numerically equal to the ratio of the reaction constants for the hydrolysis reaction and the protonation equilibrium of the leaving group ($\beta_{lg} = \rho_{hydrolysis}/\rho_{ionization}$). β Values greater than unity may be considered as indicative of the greater charge accumulation on the phenolate oxygen in the transition state for the hydrolysis reaction compared to the ionisation of phenols. This also explains the greater dependence of $\rho_{hydrolysis}$ on the solvent medium for an *E*1cB rather than for $B_{Ac}2$ process for which the β value is low (*ca.* 0.3). Since both $\rho_{hydrolysis}$ and $\rho_{ionisation}$ change in the same direction, there would be little change in β_{lg} for reactions in different solvents. This could not be verified for lack of pK_a values for the leaving phenols at other solvent compositions.

The results of the hydrolysis experiments conducted in the presence of aniline provide added proof for the elimination–addition mechanism. At pH 9.0, the rate of hydrolysis is independent of the concentration of aniline employed and yet the product is 4-nitrophenylacetanilide. This clearly indicates that the expulsion of phenoxide from the carbanion and product formation are two different steps, thus involving an intermediate. This intermediate, most logically, is the transient keten.

Solvent Effects.—The differential effects of protic and dipolar aprotic solvents have been effectively used as a mechanistic criterion to elucidate the mechanisms of acyl transfer. Change of solvent from water to aqueous ethanol retards the rate of hydrolysis by a $B_{Ac}2$ mechanism,[17] while accelerating it for reactions by an *E*1cB mechanism.[18] This is only to be expected, for in the transition state for a $B_{Ac}2$ process, there is a transfer of charge to the non-electrolyte ester molecule without dispersal.[19] For an *E*1cB reaction the ground state is the anion and there is dispersal of charge in going to the transition state. The *E*1cB mechanism proposed for the hydrolysis of aryl phenylacetates derives support from the acceleration observed particularly for esters with good leaving groups (Table 9).

Transfer to dipolar aprotic solvents such as DMSO ordinarily results in rate accelerations for hydrolysis by a $B_{Ac}2$ mechanism.[19] This is due to the desolvation of the reactant hydroxide ion and the relative stabilization of the transition state by solvent DMSO. But in hydrolysis by an *E*1cB mechanism, the reactant anion, which is charge extended and polarisable, is effectively solvated by DMSO and such a solvation of the ground state would result in rate retardation. Indeed, pronounced rate retardation has been observed in the hydrolysis of acetoacetates,[18a] indole-2-carboxylates,[18b] aryl 4-nitrophenylmethanesulphonates,[18c] phenylsulphonyl acetates,[18c] benzoyl acetates,[18c] ethyl fluorene-9-carboxylate,[20] and aryl *NN'*-diphenylphosphorodiamidates,[20] all of which hydrolyse by the *E*1cB mechanism. In the case of aryl 4-nitrophenylacetates, there is substantial retardation of the rate upon increasing the DMSO content in the medium (Table 11), thus indicating an $(E1cB)_{anion}$ mechanism for the hydrolysis.

The hydrolysis of aryl phenylacetates is however, accelerated by transfer to solvent DMSO (Table 10). This clearly indicates that the hydrolysis of these esters does not proceed by the same $(E1cB)_{anion}$ mechanism as do the esters of 4-nitrophenylacetic acid. An *E*1cB reaction could proceed through any among various pathways such as $(E1cB)_{anion}$, $(E1cB)_{reversible}$, $(E1cB)_{ion\text{-}pair}$, $(E1cB)_{irreversible}$, depending on the extent of C–H bond dissociation in the transition state.[21] The $(E1cB)_{irreversible}$ mechanism would demand a high value for solvent isotope effect and be relatively less sensitive to changes in the leaving group.[21] The observed low solvent isotope effect and high ρ value rule out the operation of this mechanism. This leaves $(E1cB)_{ion\text{-}pair}$ and $(E1cB)_{reversible}$ mechanisms for consideration. Both these are subject to considerable leaving group effects and are not subject to solvent isotope effects.[21,22] $(E1cB)_{reversible}$ would lead to the rate law $k_{obs} = k_a \cdot k_1[OH^-]/k_w$. Since hydroxide ion is involved in the rate expression, transfer to solvent DMSO would lead to rate acceleration because of the desolvation of the hydroxide ion by DMSO. For an $(E1cB)_{ion\ pair}$ mechanism also, the desolvation of the hydroxide ion in aqueous DMSO will facilitate the reaction. Further, the transition state will have considerable charge dispersal and, therefore will be solvated by DMSO leading to rate accelerations. Such an ion-pair mechanism has been earlier identified to operate in the hydrolysis of aryl α-phenylmethanesulphonates.[20] However, discrimination may not be possible between $(E1cB)_{reversible}$ and $(E1cB)_{ion\text{-}pair}$ mechanisms with the data available for the hydrolysis of the esters of phenylacetic acid. The difference in the reactivity of the two systems is perhaps a reflection of the inherent instability of the benzyl carbanion compared to its 4-nitro analogue.[23]

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