Nucleophilic displacement at the benzoyl centre: a study of the change in geometry at the carbonyl carbon atom

Matthew J. Colthurst and Andrew Williams *

Department of Chemistry, University of Kent, Canterbury, Kent, UK CT2 7NH

The second-order rate constants for the reaction between hydroxide ion and phenoxide ion with 4-nitrophenyl esters of substituted benzoic acids in 10% acetonitrile–water (v/v) solution obey Hammett σ correlations. The values of the Hammett ρ of 1.67 (k_{ArO}) and 2.14 (k_{OH}) are consistent with a large change in hybridization at the central carbon by comparison with the ρ value for a standard reaction where a full sp^2 to sp^3 change occurs. The transition state for the concerted reaction thus has a substantially tetrahedral geometry. The observation of the *anti*-Hammond effect whereby the ρ value for the hydroxide ion exceeds that of the less reactive phenoxide ion is consistent with a concerted, A_ND_N, mechanism for these reactions. A stepwise mechanism, $A_N + D_N$, is unlikely to yield a measurable break in the Hammett correlation for a change in the benzoyl substituent if the partitioning of the putative tetrahedral intermediate involves forward and reverse reactions with Hammett correlations possessing similar ρ values.

Introduction

There is substantial evidence from both substituent effect[1] and isotope effect[2] studies that carbonyl acyl group transfer reactions have a concerted A_ND_N mechanism when the nucleophile and leaving group are only weakly basic. The results of thermodynamic studies[3] on the stability of putative tetrahedral intermediates are also consistent with this mechanism and ligands which have been demonstrated to confer concertedness include the phenolate and pyridine nucleophiles and leaving groups.[1–3] Acyl functions with very good leaving groups and possessing features stabilising the acylium ion favour stepwise displacement reactions with $D_N + A_N$ mechanisms[4] whereas poor leaving groups confer $A_N + D_N$ mechanisms.[5] There are some displacement reactions where pyridine and phenolate ion ligands do not confer concertedness[6] and this indicates that reactions with these ligands probably occupy a borderline region between A_ND_N and $A_N + D_N$ processes.

While direct probes of the geometry at the carbon in the transition state for substitution reactions at the carbonyl centre are not known it may be inferred from secondary isotope effects on adjacent atoms.[7a,b] The geometry of the transition state for concerted identity displacements at carbonyl can also be inferred from the location (τ) of the transition state on the tightness diagonal[7c] of a More O'Ferrall–Jencks diagram obtained from Brønsted or Hammett data for nucleophile and leaving group variation. The position of the transition state on the tightness diagonal for an identity reaction is an indication of whether the transition state is tetrahedral ($\tau = 2$) or linear (where bonding of carbonyl to leaving atom and attacking atom is zero; $\tau = 0$). Intermediate τ values cannot be assumed to be linear functions of geometry; at low values of τ the geometry must be planar but as τ increases the transition state structure will approach that of a tetrahedral intermediate. The Hammett substituent effect of substituents on the acyl function is an indirect probe of the transition state geometry of a concerted displacement reaction at the acyl group. Byers[8,9] has studied the addition of nucleophiles to aldehydes as a model of the first step in an $A_N + D_N$ acyl group transfer process. The addition of water to substituted benzaldehydes is associated with a Hammett ρ_{eq} value of 1.71[10] and refers to the change from sp^2 to sp^3 geometry without development of formal negative charge. When a formal charge develops on the oxygen from the carbonyl group the ρ value is substantially larger and hydroxide ion addition has a ρ_{eq} of 2.76.[11] The present study is of the reactions of phenoxide ion and hydroxide ion with 4-nitrophenyl benzoate esters [eqns. (1) and (2); 4NP = 4-nitrophenyl]

$$\mathrm{PhO^- + ArCO\text{-}O\text{-}4NP} \xrightarrow{k_{ArO}} \mathrm{ArCO\text{-}OPh + 4NP\text{-}O^-} \quad (1)$$

$$\mathrm{HO^- + ArCO\text{-}O\text{-}4NP} \xrightarrow{k_{OH}} \mathrm{ArCO\text{-}O^- + 4NP\text{-}O^-} \quad (2)$$

where the variation of the substituent on the benzoyl function will affect the stability of charge and hybridisation developing at the carbonyl centre.

Experimental

Materials

Most of the esters were prepared by reaction of the appropriate acid chloride with 4-nitrophenol[12a] with a base catalyst such as pyridine solvent. The acid chloride was either used as supplied (method A, Table 1) or prepared *in situ* (method B) from the corresponding acid. The 4-nitrophenyl 2,4-dinitrobenzoate and 3,5-dinitrobenzoate were prepared from the acids and 4-nitrophenol by use of dicyclohexylcarbodiimide (method C). All esters were recrystallised from suitable solvents and their physical characteristics are listed in Table 1. The esters were identified by comparing their melting points with literature values[12] and where these are not known they were characterised by elemental analysis and by IR and ^{1}H NMR spectroscopy. The following preparative procedures are typical.

4-Nitrophenyl 3-trifluoromethylbenzoate

3-Trifluoromethylbenzoyl chloride (2.5 ml) was added to a stirred solution of 4-nitrophenol (2 g) in pyridine. After a few minutes, the reaction mixture was diluted with water and extracted twice with toluene. The combined organic extracts were washed with dilute HCl, sodium carbonate solution and water, dried with magnesium sulfate, filtered and evaporated to give crude solid; this was recrystallised from ethanol to give a white crystalline solid.

4-Nitrophenyl 3-cyanobenzoate

Thionyl chloride (1 ml) was slowly added to a cold, stirred solution of 3-cyanobenzoic acid (1.5 g) in tetrahydrofuran (THF). This mixture was slowly added to a solution of 4-

Table 1 Physical characteristics of substituted 4-nitrophenyl benzoates prepared for this work

Benzoate ester[a]	Mp/°C (lit.)	Formula	(%) Found[b] C	H	N
Parent(B)	142–143 (143)[12b]	$C_{13}H_9NO_4$	64.4 (64.2)	3.6 (3.7)	5.7 (5.75)
3-CN(B)	177–178	$C_{14}H_8N_2O_4$	62.6 (62.7)	2.65 (3.0)	10.3 (10.45)
3-Cl(B)	132–133 (132.5–133)[12c]	$C_{13}H_8ClNO_4$	56.1 (56.2)	2.75 (2.9)	5.1 (5.0)
4-Cl(A)	135–137 (138)[12d]	$C_{13}H_8ClNO_4$	56.2 (56.2)	2.8 (2.9)	4.75 (5.0)
4-Me(B)	121–122 (120–121)[12a]	$C_{14}H_{11}NO_4$	65.2 (65.4)	4.1 (4.3)	5.4 (5.4)
4-NO_2(B)	158–159 (158–159)[12d]	$C_{13}H_8N_2O_6$	54.2 (54.2)	2.6 (2.8)	9.7 (9.7)
4-Cl-3-NO_2(B)	163–164	$C_{13}H_7ClN_2O_6$	47.9 (48.4)	2.2 (2.2)	8.7 (8.7)
3-NO_2(B)	142–143 (135.5)[12e]	$C_{13}H_8N_2O_6$	53.9 (54.2)	2.6 (2.8)	9.6 (9.7)
3-CF_3(A)	94–95 (82.0–82.5)[12c]	$C_{14}H_8F_3NO_4$	54.1 (54.0)	2.5 (2.6)	4.5 (4.5)
3,5-$(NO_2)_2$(C)	192–193 (190)[12f]	$C_{13}H_7N_3O_8$	46.8 (46.9)	2.0 (2.1)	12.7 (12.6)
2,4-$(NO_2)_2$(C)	167–168	$C_{13}H_7N_3O_8$	46.7 (46.9)	2.0 (2.1)	12.5 (12.6)

[a] Method of preparation A: from acid chloride; B: from acid *via* the acid chloride *in situ*; C: from acid using dicyclohexylcarbodiimide. [b] The calculated values are given in parentheses.

Table 2 Kinetic data for the reaction of 4-nitrophenyl X-substituted benzoates with the phenolate ion[a]

X	σ[b]	k_{OH}[c,d]/$dm^3 mol^{-1} s^{-1}$	k_{ArO}[c,e]/$dm^3 mol^{-1} s^{-1}$	pH[f]	N[g]	[PhOH][h]/mM	$k_{obs}/10^{-3} s^{-1}$[i]
H	0	2.01 (0.19)	0.232 (0.01)	10.97 and 10.00	20	6.5–32	3.2–9.0
4-NO_2	0.78	77.6 (20.2)	6.15 (0.229)	9.99	9	4.8–24	7.1–86
4-Me	−0.17	2.02 (0.24)	0.064 (0.03)	9.96	6	23–115	1.1–4.1
3-NO_2	0.71	49.0 (3.84)	3.72 (0.034)	9.95	13	6.5–33	17–65
4-Cl	0.23	7.69 (0.32)	0.458 (0.005)	9.98	5	9.5–48	3.4–13
3-Cl	0.37	15.2 (0.51)	0.911 (0.028)	9.97	5	13–62	8.5–31
3-CF_3	0.47	19.8 (5.74)	0.995 (0.037)	9.99	11	9.6–48	1.3–26
3-CN	0.61	37.9 (14.9)	2.34 (0.084)	9.97	5	9.8–49	14–62
4-Cl-3-NO_2	0.94	190 (6.15)	6.71 (0.243)	9.96	10	2.6–13	26–61
3,5-$(NO_2)_2$	1.42	3700 (320)	36.0 (3.3)	8.01[j]	5	3.9–38.6	5–18
2,4-$(NO_2)_2$	1.10	456 (35)	11.7 (0.91)	7.97[j]	5	3.4–34.3	2–5

[a] General conditions: wavelength 400 nm, 25 °C, 25 mM $KHCO_3$ buffer, 0.1 M ionic strength maintained with KCl. Solvent: 10% v/v MeCN–water. [b] All values are from ref. 21. [c] The standard errors are given in parentheses. [d] Calculated using measured pH values and assuming $pK_w = 14$. [e] Calculated using a fraction of base derived from measured pH values and assuming the pK_a of phenol to be 9.95. [f] pH of the aqueous stock buffered solutions. [g] Number of data points not including duplicates. [h] Concentration range of phenol. [i] Range of pseudo-first-order rate constants observed. [j] The buffer employed here was tris(hydroxymethyl)aminomethane at 25 mM.

nitrophenol (1.4 g) in pyridine, decolourising the solution and precipitating a solid. After stirring the mixture for a few minutes the precipitate was isolated by filtration and the filtrate evaporated to give a solid. The combined solids were taken up in dichloromethane, washed with dilute HCl, aqueous Na_2CO_3, and water, and then dried (magnesium sulfate), filtered and evaporated to give crude solid; this was recrystallised from ethyl acetate to yield a white crystalline solid.

4-Nitrophenyl 2,4-dinitrobenzoate

Dicyclohexylcarbodiimide (4.12 g) was added to a solution of 4-nitrophenol (2.78 g) and 2,4-dinitrobenzoic acid (4.24 g) in pyridine (30 ml). The mixture was stirred overnight at room temp. and then filtered to yield 6.66 g of dicyclohexylurea. The residue from the evaporated filtrate was recrystallised from butan-1-ol to yield needles.

Methods

Melting points were determined using a Kofler Thermospan instrument and elemental analyses were carried out with a Carlo Erba C,H,N analyser. IR spectra were obtained from Nujol mulls recorded on a Perkin-Elmer 683 spectrometer and ^1H NMR spectra were recorded at 100 MHz with a JEOL JNM-PS-100 instrument.

Kinetics

All solutions were prepared with water that was double distilled from glass and degassed before use. Buffer materials were either of AR grade or purified before use. The solutions for studies of rates at different phenolate ion concentrations were prepared by dilution of a stock solution containing the phenolate ion with a stock solution without phenol (but identical in respect of buffer component concentration, pH and ionic strength) to give a series of buffered solutions with different phenolate ion concentrations. Acetonitrile was added (to give 10% v/v) to counter solubility problems of the ester substrates. See footnotes to Table 2 for identities of components.

The fraction of phenolate ion (FB) in the phenol buffers in the aqueous–organic solvent was calculated from the pH of the aqueous stock solution. Dilution with organic solvent will change the pK_a of the phenol but this will be counterbalanced by a change in the pH. In the present case the increase in acetonitrile to 10% concentration (v/v) causes an average increase in the pH-meter reading (glass electrode) of 0.14. The hydroxide ion concentration in aqueous solvent was calculated from the pH of the aqueous solution and includes a correction for dilution by the organic solvent.

Reactions were initiated by the addition of an aliquot (0.01 to 0.05 ml) of a solution of the substrate (in acetonitrile) on the tip of a glass rod to 2.5 ml of buffered solution, contained in a 1 cm path-length silica cuvette in the thermostatted cell compartment of either a Pye Unicam SP 800 or a Perkin-Elmer Lambda 5 UV–VIS spectrophotometer. A few vertical strokes of the glass rod effected mixing and the reaction was followed by monitoring the change in absorbance with time at 400 nm, the optimal wavelength for analysis of the 4-nitrophenolate ion product. The pH of the solutions were measured before and after each kinetic run using a Radiometer PHM62 meter with a Russell CMAWL combined electrode, calibrated with BDH buffers; data for experiments where the pH changed by more than 0.1 units were discarded.

Pseudo-first-order rate constants were obtained from linear plots of $\log(A_\infty - A_t)$ *vs.* t where A_t is the absorbance of the solution at the given wavelength at time t. The rate constants were also obtained by fitting the value of A_t (which increases with time in these cases) to the equation $A_t = A_\infty - (A_\infty - A_0)e^{-kt}$. Ester concentrations employed in the kinetics were 50–100 μM; at the upper limit of concentration some of the esters still exhibited solubility problems and for these esters the lower limit was employed.

Data were fitted to theoretical equations by use of programs operating on an Opus IV or V PC or by use of 'grid-search' programs written in BASIC and employing a BBC Master 128 computer.

Results

The reactions of 4-nitrophenyl esters of substituted benzoic acids with phenol exhibited good first-order kinetics over at least 90% of the total reaction. The reactions followed the rate law of eqn. (3) with good linear correlations of k_{obs} against total

$$k_{obs} = k_{ArO}[ArO^-] + k_{OH}[OH^-] \qquad (3)$$

phenol concentration; examples of the plots of values of k_{obs} against phenol concentration are shown in Fig. 1. The absence of a background buffer effect is deduced from the lack of a significant difference in the rate constants obtained for the phenolysis of 4-nitrophenyl 3-chlorobenzoate at different buffer concentrations and constant pH (Fig. 2). The second-order rate constants for phenolysis, k_{ArO}, were obtained using eqn. (4)

$$k_{ArO} = (dk_{obs}/d[ArO^-])/FB \qquad (4)$$

(where FB is the fraction of total phenol present as the ion).

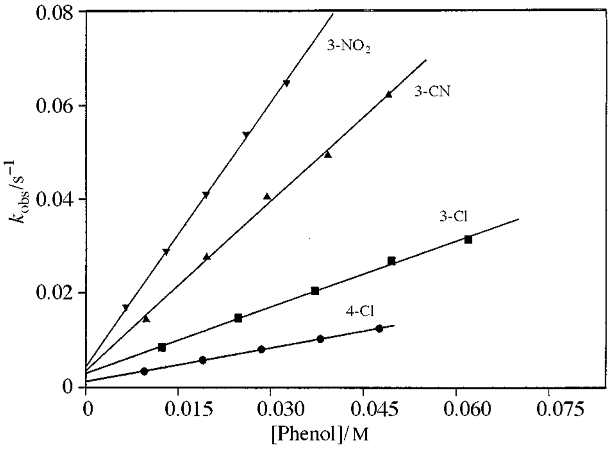


Fig. 1 Dependence of k_{obs} on phenol concentration for the phenolysis of 4-nitrophenyl esters of substituted benzoic acids. The conditions of measurement are given in Table 2 and the substituents are as labelled.

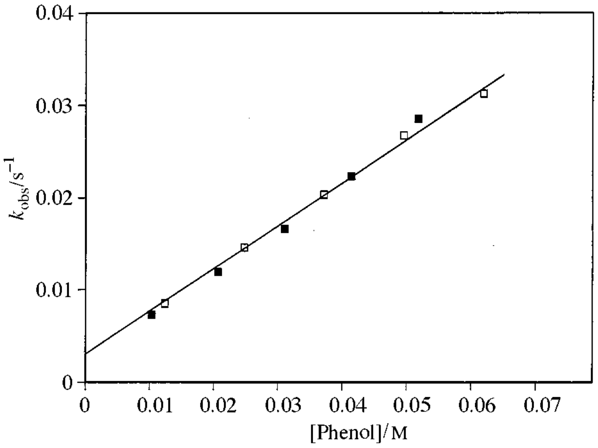


Fig. 2 The absence of background buffer catalysis in the phenolysis of 4-nitrophenyl 3-chlorobenzoate in different $KHCO_3$–K_2CO_3 buffer concentrations (■ 50 mM, □ 25 mM) that demonstrates the lack of buffer catalysis. Other conditions are as listed in Table 2.

Eqn. (4) was checked for the reaction of phenolate ion with 4-nitrophenyl benzoate at two pH (Table 2). The second-order rate constants for hydrolysis (k_{OH}, listed in Table 2) were calculated from observed rate constants at zero phenol concentration which agreed with the extrapolated values. No correction was made for the effect of buffer concentration as this had already been shown to be negligible at the concentrations of buffer employed (Fig. 2). The second-order rate constants for hydrolysis are similar to those previously reported under different solvent conditions.[12a,13] The rate constants for the reaction of phenolate ion with 4-nitrophenyl benzoates are also similar to those recently reported for the reaction in 20% dimethyl sulfoxide–water (v/v) and in ethanol.

The second-order rate constants, k_{ArO} and k_{OH}, for the reaction of substituted 4-nitrophenyl benzoates with phenolate and hydroxide ions both exhibit Hammett σ dependences [eqn. (5) and (6)] depicted in Fig. 3. The values for ρ for

$$\log k_{ArO} = 1.67 \pm 0.08\sigma - 0.716 \pm 0.060 \qquad (n = 11, r = 0.9900) \quad (5)$$

$$\log k_{OH} = 2.14 \pm 0.07\sigma + 0.314 \pm 0.052 \qquad (n = 11, r = 0.9952) \quad (6)$$

hydrolysis may be compared with those previously determined with values ranging from $\rho = 1.86$ in water[13b] to $\rho = 2.04$ and $\rho = 2.01$ in 33% acetonitrile–water.[12a,13a]

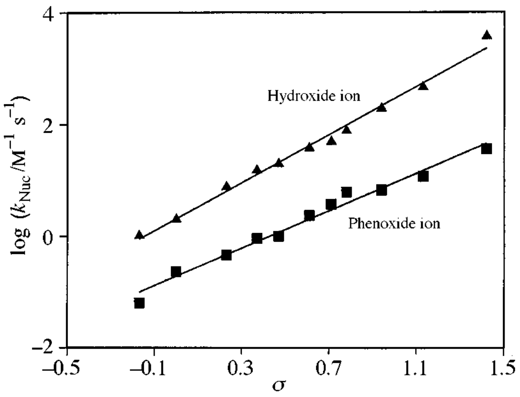


Fig. 3 The Hammett dependence of the phenolysis (■) and hydrolysis (▲) of 4-nitrophenyl esters of substituted benzoic acids. The substituents and conditions used are given in Table 2.

The value of σ for the 2,4-dinitro array of substituents is composed of the sum of that for the 4-nitro and the 2-nitro groups. The σ value for the 2-nitro group is estimated accounting for the steric hindrance of the substituent, from the hydroxide ion rate constant for attack on the ethyl 2-nitrobenzoate utilising a Hammett equation derived from data from Tommila and Hinshelwood's work for hydrolysis of substituted ethyl benzoates.[14] The data yield a value of 0.33 for the σ value of the *ortho* substituent and the value for the 2,4-dinitro array is thus 1.10. This value is employed for both hydroxide ion and phenoxide ion attack on the 4-nitrophenyl substituted benzoate ester. The fit to the linear regression is good in both cases and the inclusion of the *ortho* substituent is not critical to the final σ values.

Discussion

Evidence for concertedness

By analogy with similar systems[1a,b,e] it would seem reasonable to suppose that reactions of 4-nitrophenyl benzoates with phenolate ions possess concerted mechanisms.

The value of Leffler's α for the hydroxide ion (0.78, obtained by use of $\beta_{eq} = 2.76$[11]) is larger than that for the phenoxide ion attack (0.61) consistent with an *anti*-Hammond effect. The sensitivity to σ of the 4-nitrophenyl substituted benzoates also increases with increasing reactivity of the nucleophile in the series −2.17, −2.61 and −2.80 for 4-cyano-, unsubstituted and 4-methoxy-phenolate ion nucleophiles respectively for reactions in 20% dimethyl sulfoxide–water.[15] The values of β_{nuc} for attack of substituted phenoxide ion on 4-nitrophenyl benzoates in 20% dimethyl sulfoxide–water are respectively 1.18, 1.04 and 0.98 for the 4-nitrophenyl esters of the 4-nitro-, parent and 4-methoxy-benzoates[15] and the trend in selectivity can be explained by the effect of the substituents in the benzoate on the stability of the acylium ion corner of the More O'Ferrall–Jencks diagram (analogous to Fig. 4). The ρ values for attack of phenolate ion, ethoxide ion and acetophenone oximate ion on substituted benzoate esters of 4-nitrophenol in ethanol increase with reactivity.[16] The *anti*-Hammond effects are consistent with the concerted process but cannot readily be explained by an $A_N + D_N$ mechanism with rate-limiting addition.

Geometry of the transition state

The hybridization change from sp^2 to either sp (for acylium ion formation) or sp^3 (for tetrahedral intermediate) would give ρ values with respectively positive and negative values.

The polar effect of substituents in the benzaldehyde nucleus of 1.71[10] for the addition of water is due to the change of hybridization from sp^2 to sp^3. The ionisation of the hydrated species gives an extra contribution to ρ of 1.05 (the ρ value for addition of the hydroxide ion is 2.76). Change in hybridization from sp^2 to sp as in the formation of an acylium ion would give a negative ρ which would be modified by a further negative component due to the formation of positive charge. The observed values of ρ for the various displacements all lie in the positive region and are consistent with hybridization of the central carbon tending towards sp^3.

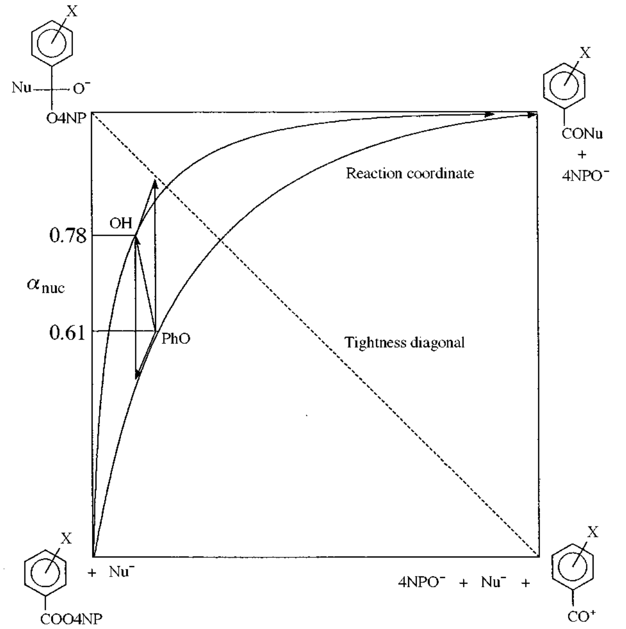


Fig. 4 More O'Ferrall–Jencks diagram for the displacement of 4-nitrophenolate ion from substituted 4-nitrophenyl benzoate esters by nucleophiles. The movement of the transition state consequent on the change in stabilities of the four corners is the resultant of motion parallel to the reaction coordinate towards the least stable corner and motion perpendicular to the reaction coordinate towards the most stable corners.

Prediction of breakpoint position and 'sharpness'

The Brønsted correlation for a two-step mechanism [$A_N + D_N$; eqn. (7*a*)] including a breakpoint is described by eqn. (7*b*).[17]

$$\text{RCO-Lg} + \text{Nu}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Intermediate} \xrightarrow{k_2} \text{RCO-Nu} + \text{Lg}^- \qquad (7a)$$

$$\log k_{Nuc} = \log(10^{\beta 1.\mathrm{p}K+C}) - \log(1 + 10^{(\beta\text{-}1-\beta 2)(\mathrm{p}K-\mathrm{p}K_o)}) \qquad (7b)$$

The 'sharpness' of the break is related to the difference, $\Delta\beta$, between β_{-1} and β_2, the Brønsted selectivities for k_{-1} and k_2 respectively. A similar equation governs the correlation if Hammett methodology is used.

The value of $\Delta\beta$ can be estimated for the putative stepwise mechanism for the reaction of substituted phenolate ions with a phenyl ester such as 4-nitrophenyl acetate [eqn. (8)] because there are a considerable number of known values of β_{eq}[7d] and good estimates of β for rate constants which might be expected for formation and decomposition of tetrahedral intermediates. The β value for k_2 (structure **1**) is likely to be slightly more positive than zero because the effect of electron donating substituents is to assist the departure of negative charge but is only felt through two atoms by the bond undergoing fission. The value of β_{-1} will be substantially negative because of the proximity of the substituent of the bond undergoing fission; the β_{lg} is estimated from β values for fission of alcoholate and phenolate ions from tetrahedral intermediates (−0.63[18a] and −0.9[18b]) and an average value of −0.76 is chosen for β_{lg}. The value of −0.76 is probably an *upper limit* for $\Delta\beta$ and this means that there should be a substantial break in the free energy correlation. Fig. 5 illustrates the phenolysis of 4-nitrophenyl acetate[1a] where the data are fitted to eqn. (7) with $\Delta\beta$ and the pK_a of the phenol at the breakpoint (pK_o) fixed at −0.76 and 7.14 respectively and β_1

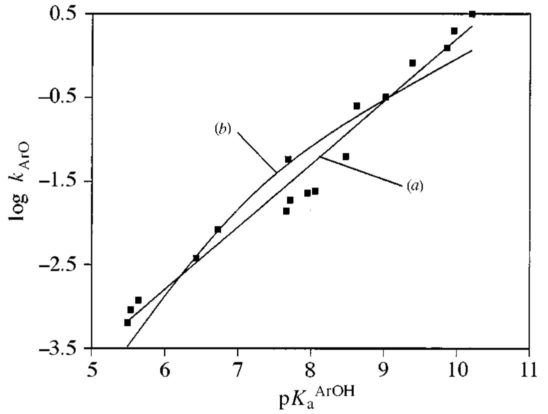
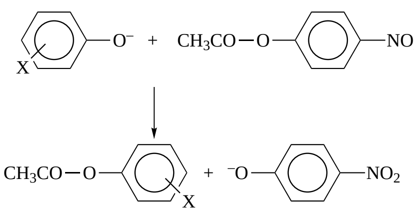
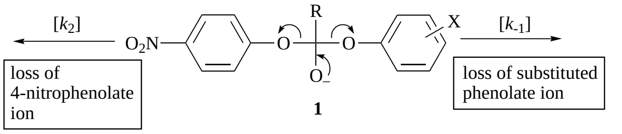


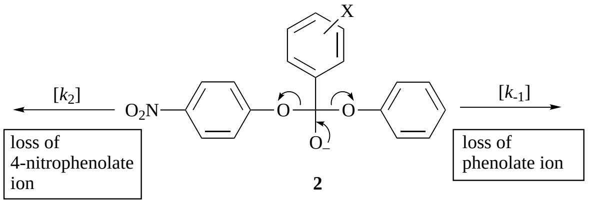
Fig. 5 Brønsted type dependence for the displacement of 4-nitrophenolate ion from 4-nitrophenyl acetate by substituted phenolate ions. The data and the linear correlation (*a*) are from Ba-Saif, Luthra and Williams;[1a] the line (*b*) is calculated from eqn. (7) assuming that pK_o is 7.14 and that $\Delta\beta = -0.76$ (see text). The correlation coefficients for the fit to the lines are: *A*, 0.9860;[1a] *B*, 0.9527.



(8)



1



2

and C are variant. The predicted fit for the stepwise mechanism correlates poorly compared with that of the linear Brønsted equation.

The position of a break (pK_o) on the pK_a or σ axis for reaction of phenolate ions with substituted benzoates is not predictable from a mechanism involving a putative tetrahedral intermediate (structure **2**) unlike the situation where the substituent change is on either leaving group or nucleophile. Data were reported[15] for the reaction of three phenolate ions with substituted phenyl benzoates which were interpreted by the intervention of breaks in the Hammett plots at pK_o *ca.* 3.5 corresponding to σ values of between 0.5 and 0.6. Increased electron withdrawing ability of the acyl function was claimed to cause a change in rate-limiting step because the leaving group departure (k_2) becomes reduced as k_1 increases with increasing σ. The criterion for a change in rate-limiting step is the ratio k_{-1}/k_2 (see structure **2**) and thus any change in rate-limiting step must be caused by a difference in selectivity of k_{-1} and k_2 and not that between k_1 and k_2. The ρ value for k_{-1} would be relatively small and approximately equal to that for k_2 as both reactions are essentially similar; the value of $\Delta\rho$, a measure of the sharpness of the breakpoint, would thus be close to zero.

Sharp breaks are possible for the Hammett plot for a putative stepwise process when the Hammett ρ values for k_{-1} and k_2 are expected to be substantially different. Such effects are observed in the formation of semicarbazones from benzaldehydes[19,20] because the ρ value for the forward, acid catalysed, dehydration step has a relatively large negative ρ value in contrast to the small negative ρ value expected for the expulsion of the hydrazine from the carbinolamine intermediate. The reverse step will have a ρ value only slightly more negative than zero because it is expected that the transition state for addition is close to the structure of the tetrahedral adduct.

References

1 (*a*) S. Ba-Saif, A. K. Luthra and A. Williams, *J. Am. Chem. Soc.*, 1987, **109**, 6362; (*b*) S. Ba-Saif, A. K. Luthra and A. Williams, *J. Am. Chem. Soc.*, 1989, **111**, 2647; (*c*) S. Ba-Saif, M. Colthurst, M. A. Waring and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1901; (*d*) A. Williams, *Acc. Chem. Res.*, 1989, **22**, 387; (*e*) M. J. Colthurst, M. Nanni and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1996, 2285.

2 A. C. Hengge, *J. Am. Chem. Soc.*, 1992, **114**, 6575; (*b*) A. C. Hengge and R. A. Hess, *J. Am. Chem. Soc.*, 1992, **114**, 11256; (*c*) W. W. Cleland and A. C. Hengge, *FASEB J.*, 1995, **9**, 1585.

3 P. J. Guthrie, *J. Am. Chem. Soc.*, 1991, **113**, 3941.

4 A. Williams and K. T. Douglas, *Chem. Rev.*, 1975, **75**, 627.

5 M. L. Bender, *Chem. Rev.*, 1960, **60**, 53; S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.

6 (*a*) E. A. Castro, M. T. Borquez and P. M. Parada, *J. Org. Chem.*, 1986, **51**, 5072; (*b*) M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 6963, 6970; (*c*) E. A. Castro and F. J. Gil, *J. Am. Chem. Soc.*, 1977, **99**, 7611; (*d*) E. A. Castro, F. Ibanez, S. Lagos, M. Schick and J. G. Santos, *J. Org. Chem.*, 1992, **57**, 2691.

7 (*a*) L. do Amaral, M. P. Bastos, H. G. Bull, J. J. Ortiz and E. H. Cordes, *J. Am. Chem. Soc.*, 1979, **101**, 169; (*b*) Z. Bilkadi, R. deLorimer and J. F. Kirsch, *J. Am. Chem. Soc.*, 1975, **97**, 4317; (*c*) M. M. Kreevoy and I. S. H. Lee, *J. Am. Chem. Soc.*, 1984, **106**, 2550; (*d*) A. Williams, *Adv. Phys. Org. Chem.*, 1992, **27**, 1.

8 S. L. Shames and L. D. Byers, *J. Am. Chem. Soc.*, 1981, **103**, 6170.

9 M. S. Kanchuger and L. D. Byers, *J. Am. Chem. Soc.*, 1979, **101**, 3005.

10 R. A. McClelland and M. Coe, *J. Am. Chem. Soc.*, 1983, **105**, 2178.

11 W. J. Bover and P. Zuman, *J. Chem. Soc., Perkin Trans.* 2, 1973, 786.

12 (*a*) J. F. Kirsch, W. Clewell and A. Simon, *J. Org. Chem.*, 1968, **33**, 127; (*b*) M. J. Collins and D. R. Goddard, *J. Chem. Soc.*, 1958, 1952; (*c*) C. D. Hubbard and J. F. Kirsch, *Biochemistry*, 1972, **11**, 2483; (*d*) T. Matsukawa, S. Ban and T. Imada, *J. Pharm. Soc. Jpn.*, 1951, **71**, 477 (*Chem. Abstr.*, **46**, 454); (*e*) G. Neumann, *Chem. Ber.*, 1886, **19**, 2018; (*f*) Y. Akahori, *Chem. Pharm. Bull.*, 1965, **13**, 368 (*Chem. Abstr.*, 1965, **61**, 550b).

13 (*a*) M. Caplow and W. P. Jencks, *Biochemistry*, 1962, **1**, 883; (*b*) V. R. Correia, I. M. Cuccovia and H. Chaimovich, *J. Phys. Org. Chem.*, 1991, **4**, 13.

14 (*a*) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1938, 1801; (*b*) E. Tommila, *Ann. Acad. Sci. Fenn., Ser. A57*, 1941, 3.

15 I.-H. Um. J.-S. Min, J.-S. Jeon and D.-S. Kwon, *Bull. Korean Chem. Soc.*, 1995, **16**, 569.

16 I.-H. Um. S.-J. Oh and D.-S. Kwon, *Bull. Korean Chem. Soc.*, 1996, **17**, 802.

17 (*a*) E. A. Castro and R. B. Moodie, *J. Chem. Soc., Chem. Commun.*, 1973, 828; (*b*) P. M. Bond, E. A. Castro and R. B. Moodie, *J. Chem. Soc., Perkin Trans. 2*, 1976, 68.

18 (*a*) C. F. Bernasconi and G. D. Leonarduzzi, *J. Am. Chem. Soc.*, 1982, **104**, 5133; (*b*) N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 507.

19 B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, 1960, **82**, 1773.

20 D. S. Noyce, A. T. Bottini and S. G. Smith, *J. Org. Chem.*, 1958, **23**, 752.

21 D. D. Perrin, B. Dempsey and E. P. Serjeant, *pK$_a$ Prediction for Organic Acids and Bases*, Chapman and Hall, London and New York, 1981.

Paper 7/00686A
Received 30*th January* 1997
Accepted 24*th March* 1997