Transfer of a positively charged acyl group between substituted phenolate ion nucleophiles: the Brønsted β for the calibrating equilibrium for *N*-methylisonicotinyl (4-carbonyl-*N*-methylpyridinium) transfer

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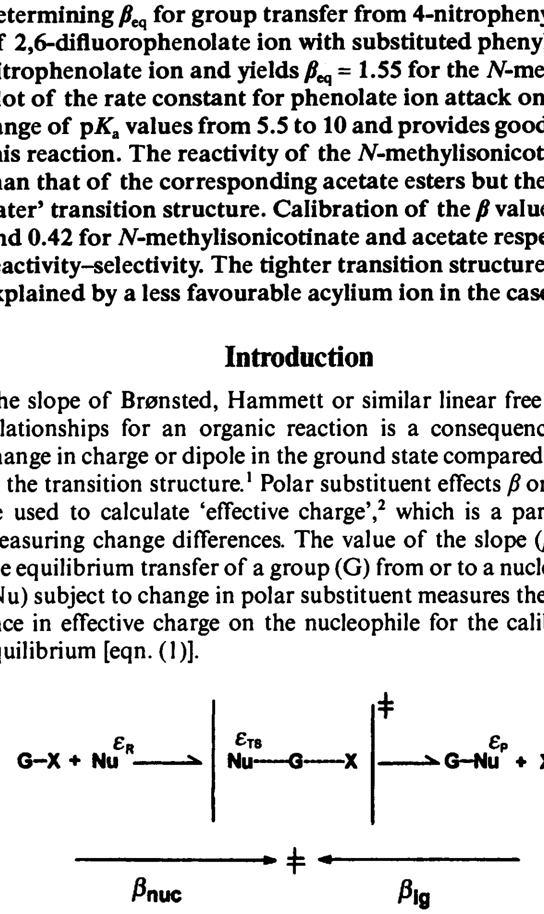
Rate constants have been measured for the reaction of substituted phenolate ions with aryl acetate esters and with aryl *N*-methylisonicotinate esters† in aqueous solution. A new method is demonstrated for determining β_{eq} for group transfer from 4-nitrophenyl esters; it employs the rate constant for the reaction of 2,6-difluorophenolate ion with substituted phenyl ester as a surrogate for the reactivity of the 4-nitrophenolate ion and yields $\beta_{eq} = 1.55$ for the *N*-methylisonicotinyl transfer reaction. The Brønsted-type plot of the rate constant for phenolate ion attack on 4-nitrophenyl *N*-methylisonicotinate is linear over a range of pK_a values from 5.5 to 10 and provides good evidence for a concerted displacement mechanism for this reaction. The reactivity of the *N*-methylisonicotinate esters to phenolate ions is some 300 times larger than that of the corresponding acetate esters but the larger β_{nuc} value (0.90 compared with 0.74) suggests a 'later' transition structure. Calibration of the β values with the corresponding β_{eq} gives a Leffler $\alpha_{nuc} = 0.58$ and 0.42 for *N*-methylisonicotinate and acetate respectively, which contrasts with the order expected from reactivity–selectivity. The tighter transition structure indicated by comparison of these α values is explained by a less favourable acylium ion in the case of the *N*-methylisonicotinyl transfer reaction.

Introduction

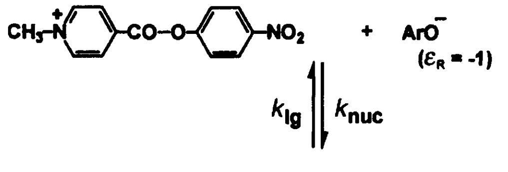
The slope of Brønsted, Hammett or similar linear free energy relationships for an organic reaction is a consequence of a change in charge or dipole in the ground state compared to that in the transition structure.[1] Polar substituent effects β or ρ may be used to calculate 'effective charge',[2] which is a parameter measuring change differences. The value of the slope (β_{eq}) for the equilibrium transfer of a group (G) from or to a nucleophile (Nu) subject to change in polar substituent measures the difference in effective charge on the nucleophile for the calibrating equilibrium [eqn. (1)].



(1)

Calibrating Equilibrium

The Hammett or Brønsted slope for the calibrating equilibrium is important because it measures the change in effective charge for complete bond fission or formation and permits the use of the Leffler parameter ($\alpha = \beta/\beta_{eq}$) which is related to the fraction of bond fission or formation in a reaction.[3] A substantial number of β_{eq} values have been obtained for calibrating equilibria where the acceptor nucleophiles (wherein lies the polar substituent effect) are variously phenolate ions, pyridines, amines, alcohols or thiolate ions.[2,3,4] Values of β_{eq} are restricted to these structural types because they have the possibility of smoothly varying the strength of the polar substituent. The effective charge is defined as residing on the atom forming part of the bond to the transferring group. The transferring groups for which β_{eq} values have been measured have a large range of structural types and examples are alkyl, aryl, sulfonyl, phosphoryl, acyl and glycosyl functions.[2,3,4] The values of β_{eq} range from *ca.* −0.4 up to +2.4. The introduction of a negative charge into the acyl group reduces the effective change on the alkyl oxygen from +0.7 in the acetate ester (MeCO–OR)[5] to +0.4 on the carbonate half ester (OCO–OR)[6] and the ionisation of the monophosphate ester $(HO)_2PO$–OR progressively reduces the effective charge on the ether oxygen from +0.83 through +0.74 to +0.36.[7] Ionisation of the NH group of aryl carbamate esters reduces the effective charge on the aryl oxygen from +0.8 to +0.3.[8] This paper addresses for the first time the measurement of the effective charge induced on the aryl oxygen in aryl esters of positively charged acyl groups; we employ as a charged group the *N*-methylisonicotinyl function (with toluene-*p*-sulfonate counter ions) and study the forward and reverse rate constants of the reaction of eqn. (2).



(2)

The value of β_{lg} for the rate constant for attack of 4-nitrophenolate anion on the aryl esters is, in principle, obtained from measurements of the rate constant (k_{lg}). These rate constants are not easily measured directly because of the strong absorbance of the 4-nitrophenolate ion and the consequent requirement to employ low concentrations of this species. This study investigates the use of 2,6-difluorophenolate ion as a nucleophile in place of the 4-nitrophenolate ion so that k_{lg} may be estimated and the equilibrium constant and β_{eq} for eqn. (2) therefore readily determined.

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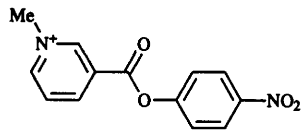
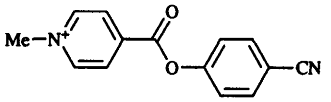
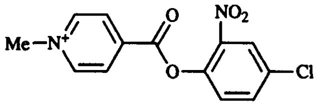
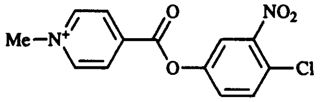
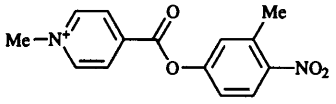
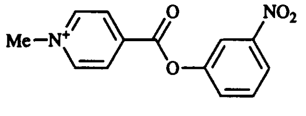
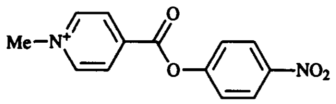
† IUPAC name: 4-aryloxycarbonyl-*N*-methylpyridinium toluene-*p*-sulfonate. *N*-methylisonicotinate nomenclature is used for simplicity, and the presence of the sulfonate counter ion is assumed.

Table 1 Physical characteristics of substituted phenyl esters

Toluene-*p*-sulfonate salt	Mp/°C (Literature)	Formula	Elemental analysis (%)[a] C	H	N
	194–196	$CH_{20}H_{18}N_2O_7S$	53.9 (55.8)	4.4 (4.2)	6.4 (6.5)
	219–221	$C_{21}H_{18}N_2O_5S$	61.1 (61.45)	4.0 (4.4)	6.7 (6.8)
	147–150(dec)	$C_{20}H_{17}ClN_2O_7S$	50.8 (52.9)	3.6 (3.6)	5.9 (5.9)
	174–177	$C_{20}H_{17}ClN_2O_7S$	51.55 (52.9)	3.5 (3.6)	6.0 (5.9)
	186–188.5	$C_{21}H_{20}N_2O_7S$	55.6 (56.7)	4.9 (4.5)	6.0 (6.3)
	185–187	$C_{20}H_{18}N_2O_7S$	55.8 (55.8)	4.1 (4.2)	6.6 (6.5)
	205–207	$C_{20}H_{18}N_2O_7S$	56.0 (55.8)	4.2 (4.2)	6.6) (6.5)

[a] The calculated values are given in parentheses.

Experimental

Materials

The materials were either commercially available and purified where necessary, or prepared as described below. 4-Nitrophenyl picolinate,‡ nicotinate and isonicotinate esters were prepared by the method of Hassner and Alexanian[9a] from 4-nitrophenol and the respective pyridinecarboxylic acid; 4-nitrophenyl picolinate had mp 146–148 °C (lit.,[9b] 144–146 °C), 4-nitrophenyl nicotinate had mp 172–173 °C (lit.,[9c] 172–173 °C and 4-nitrophenyl isonicotinate had mp 146–148 °C (lit.,[10a] 144–146 °C). Other isonicotinate esters were prepared by the methods of either Hassner and Alexanian or Ljungqvist and Folkers,[10a] and, following recrystallisation, identification and analysis by IR and NMR spectroscopy, were methylated with methyl toluene-*p*-sulfonate without further characterisation.

4-Carboxy-*N*-methylpyridinium toluene-*p*-sulfonate was prepared as follows. A solution of isonicotinic acid (10 g) and methyl toluene-*p*-sulfonate (16 g) in DMF was stirred at about 100 °C overnight. On cooling the reaction mixture to room temperature a solid precipitated which was isolated by filtration, washed with DMF and acetonitrile and recrystallised from DMF to give a white crystalline solid, mp 214–217 °C (Found: C, 54.5; H, 4.7; N, 4.5. $C_{14}H_{15}NO_5S$ requires C, 54.35; H, 4.9; N, 4.5%).

N-Methylation of substituted phenyl isonicotinate esters was carried out by the following general procedure for the preparation of 4-(4-nitrophenoxycarbonyl)-*N*-methylpyridinium toluene-*p*-sulfonate. A solution of 4-nitrophenyl isonicotinate (0.5 g) and excess methyl toluene-*p*-sulfonate in dry acetonitrile was stirred under reflux overnight. A solid precipitated from the hot reaction mixture which, after cooling to room temperature, was isolated by filtration *in vacuo* and recrystallised from dry DMF to give a white crystalline solid which was subjected to characterisation by melting point, TLC, IR and ^1H NMR spectroscopy and by elemental analysis. The ester substrates had melting points and elemental analyses given in Table 1 and had IR and ^1H NMR spectra consistent with the proposed structures. TLC indicated that all the substrates were single compounds. In cases where the C,H,N analysis of the salts does not conform to the expected values, there was no improvement from further recrystallisation and, because the IR, ^1H NMR and ^{13}C NMR spectra and the TLC indicated single species, the compounds were considered satisfactory for kinetic study.

Methods

The melting points were determined using a Kofler Thermospan instrument and are uncorrected. Elemental analyses were carried out using a Carlo Erba C,H,N analyser. Infrared spectra were obtained from either Nujol mulls or, with liquid samples, thin films and recorded on a Perkin-Elmer 683 spectrometer. ^1H NMR spectra were recorded on a JEOL JNM-PS-100 MHz instrument.

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‡ IUPAC recommended name: 4-nitrophenyl 2-pyridinecarboxylate.

Kinetics

All solutions were prepared with water that was double distilled from glass and degassed before use and chemicals that were either of AR grade or purified before use. The sample solutions for studies of rates at different nucleophile concentrations were prepared from paired stock solutions of identical buffer concentration, ionic strength and solvent composition, only one of which contained the nucleophile. They were adjusted to constant pH by the addition of either dilute hydrochloric acid or potassium hydroxide solution. The sample solutions were prepared by dilution of the stock solution containing the nucleophile with the other stock solution to give a series of solutions with different nucleophile concentrations with other parameters remaining constant.

The sample solutions for pH–rate studies were prepared from stock solutions of identical buffer concentration, ionic strength, solvent composition and, where present, nucleophile concentration. These were adjusted by the addition of either dilute hydrochloric acid or potassium hydroxide to give a series of solutions differing only in their pH.

Reactions were initiated by the addition of an aliquot (0.01 to 0.05 ml) of a solution of the substrate (in either acetonitrile or DMSO) on the tip of a glass rod to 2.5 ml of sample 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–visible 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 the optimal wavelength, determined by preliminary experiments involving repetitive scanning of the spectrum of a solution undergoing reaction. The pH values 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.

The pK_a values were determined by measuring the UV absorbance of buffered solutions of the phenol at a single wavelength over a range of pH values. The absorbance data (A_{pH}) against the pH were analysed by regression analysis on a microcomputer employing eqn. (3). A_{low} and A_{high} are disposable

$$A_{pH} = A_{low}/(1 + 10^{pH-pK}) + A_{high}/(1 + 10^{pK-pH}) \qquad (3)$$

parameters representing absorbance of the acid and base forms of the phenol. A potentiometric titration method was also employed to determine pK_a values whereby a solution of the phenol was adjusted to a pH of about 3 and then titrated with KOH solution using a titration rig comprising a Radiometer ABU11 autoburette, TTT60 titrator, REC61 servograph and PHM62 pH meter equipped with a Russell CMAWL combination glass electrode. The data of volume added against pH were fitted to eqn. (4), where *a*, *b*, *c* and *d* are disposable

$$\text{volume} = a(10^{pH-pK_w}) + b/(1 + 10^{pK_a-pH}) + c/(1 + 10^{d-pH}) \qquad (4)$$

parameters relating to the cell volume, concentration of titrant and concentration of phenol.

Pseudo-first-order rate constants were obtained from linear plots of $\log(A_\infty - A_t)$ *vs.* time 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 $A_t = A_\infty - (A_\infty - A_0)\exp^{-kt}$. Ester concentrations employed in the kinetics were between 0.1 mM and 1 mM.

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

Reactions of the esters in buffer solutions obeyed good first-order kinetics up to at least 90% of the total reaction. According to the change in absorbance and the extinction coefficients measured at the wavelengths in question, there is full release of phenols in the reactions studied here and there is no evidence for substitution at the aromatic nucleus. The pseudo-first-order rate constants were dependent on the concentration of buffer components and on the hydroxide ion concentration according to eqn. (5), where k_{OH} is the second-order rate constant for

$$k_{obs} = k_{OH}[OH] + k_{Nu}[Nu] \qquad (5)$$

hydroxide ion attack and Nu is the basic form of the buffer component.

In the case of the reactions in the *absence* of phenolate ion nucleophiles, data were fitted to the pH-profile using eqn. (6),

$$k_{obs} = k_{OH}10^{pH-pK_w} + k_{Nu}[Nu_{total}]/(1 + 10^{pK_a-pH}) \qquad (6)$$

derived from eqn. (5) where pK_a is that of the buffer component acting in its base form and pK_w is for the ionic product of water under the conditions of the experiments.

Fig. 1(*a*) illustrates the pH dependence of the reaction of 4-nitrophenyl nicotinate in buffers containing TRIS [tris(hydroxymethyl)aminomethane] at constant concentration. Kinetic parameters for reaction of the various esters in the *absence* of phenolate ion nucleophiles are collected in Table 2 together

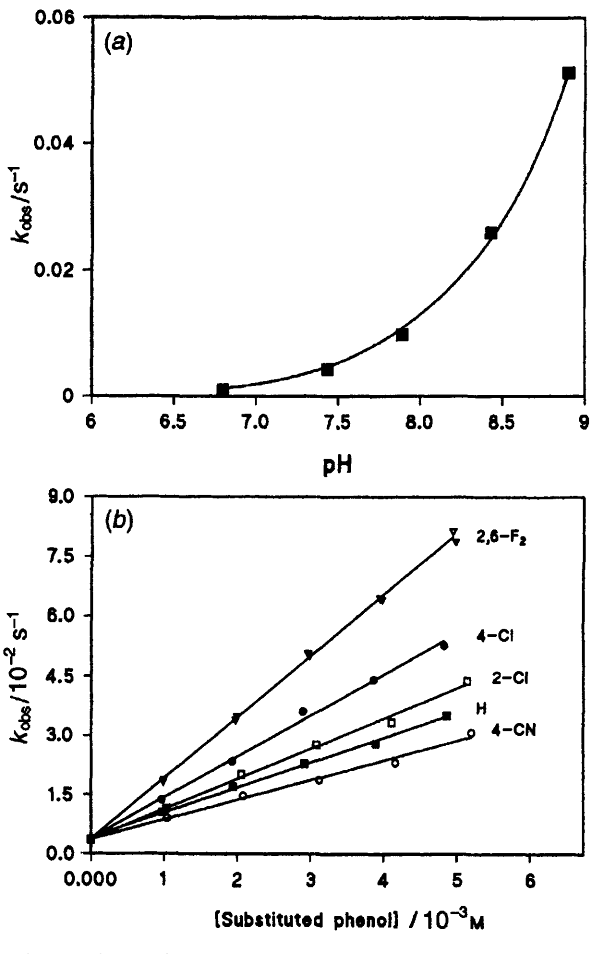

Fig. 1 (*a*) The pH dependence of the reaction of 4-nitrophenyl nicotinate in TRIS buffers; line is calculated from eqn. (6) from parameters given in Table 2. (*b*) Reaction of substituted phenoxide ions with 4-nitrophenyl acetate; open and closed triangles (for the 2,6-difluoro species) represent reaction in the absence and presence of 2,6-lutidine buffer (at 25 mM concentration) respectively.

Table 2 Hydrolysis and aminolysis of 4-nitrophenyl esters of pyridinecarboxylic acid derivatives[a]

Ester	pH range	N^b	$\Delta k_{obs}/10^{-3}\ s^{-1c}$	TRIS/M	$k_{OH}/M^{-1}\ s^{-1}$	$k_{TRIS}/M^{-1}\ s^{-1}$
Picolinate	7.35–8.97	4	0.4–4.0	0.1	242 ± 3	0.188 ± 0.001
Nicotinate	7.9–9.2	4	0.1–1.2	0.1	48.5 ± 4	(4.25 ± 0.05) × 10^{-3}
Isonicotinate	7.3–9.2	5	0.3–7.0	0.1	303 ± 34	0.024 ± 0.004
N-Methylnicotinate	6.8–8.9	9	0.1–5.2	0.1	4 370 ± 250	0.195 ± 0.018
N-Methylisonicotinate	6.9–8.4	26	0.7–16	0.025–0.1	30 600 ± 2 000	0.69 ± 0.09

[a] General conditions: wavelength 400 nm, 25 °C, 0.1 M ionic strength maintained with KCl. Solvent: water. [b] Number of data points not including duplicates. [c] Range of pseudo-first-order rate constants observed.

Table 3 Kinetic data for the reaction of phenyl acetates with substituted phenolate ions[a]

Acetate	Phenolate	$pK_a{}^b$	$k_{Nu}{}^c/M^{-1}\ s^{-1}$	pH^d	N^e	$[Phenol]^f/mM$	$k_{obs}{}^g/10^{-3}\ s^{-1}$
$4\text{-}O_2NC_6H_4OAc$	$3\text{-}NCC_6H_4O^-$	8.61	0.175	8.99	5	12–61	2.0–8.2
$4\text{-}O_2NC_6H_4OAc$	$C_6H_5O^-$	9.96	1.12^h	8.99	5	16–78	2.2–9.1
$4\text{-}O_2NC_6H_4OAc$	$2\text{-}FC_6H_4O^-$	8.82	0.243	8.99	6	8.1–40	0.21–6.1
$4\text{-}O_2NC_6H_4OAc$	$2,6\text{-}F_2C_6H_3O^-$	7.21	0.020 0	9.02, 8.61	11	4.0–40	0.25–10
$4\text{-}O_2NC_6H_4OAc$	$2,6\text{-}F_2C_6H_4O^-$	7.14	0.020 0	data as given in line 4 above			
$4\text{-}Cl,3\text{-}O_2NC_6H_4OAc$	$2,6\text{-}F_2C_6H_4O^-$	7.75	0.001 63	8.70	5	8–40	0.027–0.074
$2\text{-}Cl,4\text{-}O_2NC_6H_4OAc$	$2,6\text{-}F_2C_6H_4O^-$	5.45	0.59	8.80	5	8–40	7.8–23
$3\text{-}O_2NC_6H_4OAc$	$2,6\text{-}F_2C_6H_4O^-$	8.35	8.23×10^{-4}	8.74	5	8–40	0.008 68–0.034

[a] General conditions: wavelength 400 nm, 25 °C, 0.1 M TRIS buffer, 0.1 M ionic strength maintained with KCl. Solvent: water. [b] pK_a values determined by potentiometric titration. [c] Error range not more than 10% of the quoted figure. [d] Average pH for all the runs. [e] Number of data points not included duplicates. [f] Concentration range of phenol. [g] Range of pseudo-first order rate constants observed. [h] Previous values obtained for this system under slightly different conditions are 1.24 (ref. 11) and 0.97 (ref. 21).

Table 4 Kinetic data for the reaction of 4-(4-nitrophenoxycarbonyl)-*N*-methylpyridinium toluene-*p*-sulfonate with X-substituted phenolate ions[a]

X	$pK_a{}^b$	$k_{Nu}/M^{-1}\ s^{-1}$	pH^c	N^d	$[ArOH]^e/mM$	$k_{obs}/10^{-3}\ s^{-1}$
H	9.96	5770 ± 130	6.99	6	0.97–4.9	3.7–35
4-Cl	9.37	2550 ± 80	6.99	6	0.97–4.8	3.5–53
2-F	8.82	1070 ± 40	6.98	8	1.1–5.4	4.0–93
2-Cl	8.46	279 ± 9	6.93	6	1.0–5.1	3.6–43
4-Ac	8.03	59.0 ± 8	7.00	6	1.0–5.2	3.8–29
4-CN	7.97	50.7 ± 2	6.99	6	1.0–5.2	3.6–31
$2,6\text{-}F_2$	7.21	39.5 ± 0.4	7.03	6	0.99–4.9	3.7–81
$2,4,5\text{-}Cl_3$	6.72	12.0 ± 0.4	7.90	6	1.5–7.6	36–120
$2,3,5\text{-}Cl_3$	6.43	4.61 ± 0.2	7.91	6	1.5–7.4	36–120
$2,3,5,6\text{-}F_4$	5.53	0.587 ± 0.03	6.99	6	1.9–9.4	3.8–9.2
$2,6\text{-}Me_2$	10.61	510 ± 20	6.98	5	5–25	3.6–6.0
$2,6\text{-}Cl_2$	6.75	4.0 ± 0.1	6.99	5	10–50	15–126

[a] General conditions: $\lambda = 400$ nm, 25 °C, 25 mM 2,6-lutidine ($pH \approx 7$) or 25 mM tris ($pH \approx 8$) buffer, 0.1 M ionic strength maintained with KCl. Solvent: water. [b] Determined by potentiometric or spectrophotometric titration. [c] Average measured pH for all runs. [d] Number of data points not including duplicates. [e] Concentration range of substituted phenol. [f] Range of pseudo-first-order rate constants observed.

with the overall conditions including ranges of concentration of TRIS, pH and observed rate constants. Where comparison is possible the data for the 4-nitrophenyl esters are in good agreement with those obtained by other workers.[10b–d]

The reaction of phenolate ions with the aryl esters was followed at constant pH with varying total phenol concentration. The differential of eqn. (6) $\{dk_{obs}/d[Nu_{total}] = k_{Nu}/(1 + 10^{pK_a - pH})\}$ was employed to determine the second-order rate constant (k_{Nu}) for phenolate ion utilising plots of k_{obs} against total phenol concentration. Fig. 1(*b*) illustrates the data for the reaction of phenolate ions with 4-nitrophenyl *N*-methylisonicotinate and the parameters and conditions are collected in Tables 3, 4 and 5.

The second-order rate constants for phenolate ion attack on the aryl esters obey Brønsted-type free energy relationships [eqns. (7)–(10)].

Aryloxide ions on 4-*nitrophenyl acetate* (Table 3):

$$\log k_{Nu} = 0.74 \pm 0.033pK_a - 7.24 \pm 0.26\ (n = 20, r = 0.9832) \quad (7)$$

2,6-*Difluorophenoxide ion on substituted phenyl acetates* (Table 3):

$$\log k_{Nu} = -1.02 \pm 0.11pK_2 + 5.38 \pm 0.81\ (n = 4, r = 0.9883) \quad (8)$$

Aryloxide ions on 4-(4-*nitrophenoxycarbonyl*)-1-*methylpyridinium toluene*-p-*sulfonate* (Table 4):

$$\log k_{Nu} = 0.896 \pm 0.052\ pK_a - 5.11 \pm 0.42\ (n = 10, r = 0.987) \quad (9)$$

2,6-*Difluorophenoxide ion on* 4-(*substituted phenoxycarbonyl*)-1-*methylpyridinium toluene*-p-*sulfonates* (Table 5):

$$\log k_{Nu} = -0.653 \pm 0.175\ pK_a + 6.45 \pm 1.31\ (n = 6, r = 0.882) \quad (10)$$

The fits to the equations are illustrated in Figs. 2 and 3

Table 5 Kinetic data for the reaction of 4-(X-phenoxycarbonyl)-*N*-methylpyridinium toluene-*p*-sulfonate with 2,6-difluorophenlate ions[a]

X	pK_a[b]	$k_{Nu}/M^{-1}\,s^{-1}$	pH[c]	*N*[d]	[ArOH][e]/mM	k_{obs}[f]$/10^{-3}\,s^{-1}$	λ[g]/nm
3-NO_2	8.35	13.0 ± 0.8	8.00	6	0.82–4.1	0.72–2.4	340
4-CN	7.97	14.6 ± 0.8	7.96	6	0.50–2.5	3.2–64	254
4-Cl,3-NO_2	7.75	40.7 ± 1.5	6.97	7	1.3–6.7	47–100	360
3-Me,4-NO_2	7.26	24.2 ± 1.6	6.00	5	1.3–6.6	2.5–9.6	340
4-NO_2	7.14	39.5 ± 0.42	7.03				
4-Cl,2-NO_2	6.46	302 ± 20	5.95	9	1.2–6.2	0.02–0.11	370

[a] General conditions: 25 °C, 25 mM 2,6-lutidine (pH ≈ 6 and 7) or TRIS (pH ≈ 8) buffer, 0.1 M ionic strength maintained with KCl. Solvent: H_2O. [b] Determined by potentiometric or spectrophotometric titration. [c] Average measured pH for all runs. [d] Number of data points not including duplicate. [e] Concentration range of substituted phenol. [f] Range of pseudo-first-order rate constants observed. [g] Wavelength of kinetic study.

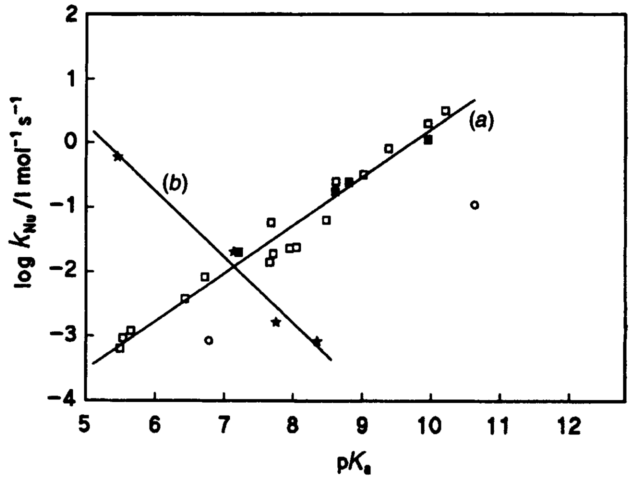

Fig. 2 Brønsted dependence of the reaction of (*a*) substituted phenolate ions with 4-nitrophenyl acetate and (*b*) 2,6-difluorophenolate ions with substituted phenyl acetate; lines are calculated from eqns. (7) and (8) and the closed squares and stars represent data obtained in this work (Table 3). The open squares are from Basaif, Luthra and Williams (ref. 11), and the open circles represent 2,6-dichloro- and 2,6-dimethylphenol. In order of increasing pK_a the phenolate ions given by the squares are: pentafluoro-, 2,3,5,6-tetrafluoro-, 2,3,4,5-tetrafluoro-, 2,3,5-trichloro-, 2,4,5-trichloro-, 2,6-difluoro-, 4-formyl-, 3,4,5-trichloro-, 2,3-dichloro-, 4-cyano-, 4-acetyl-, 2-chloro-, 3-cyano-, 3,4-dichloro-, 2-fluoro-, 3-chloro-, 4-chloro-, parent, 4-fluoro- and 4-methyl-phenolate. In order of increasing pK_a the leaving phenolate ions (stars) are: 2-chloro-4-nitro-, 4-nitro-, 4-chloro-3-nitro- and 3-nitrophenolate.

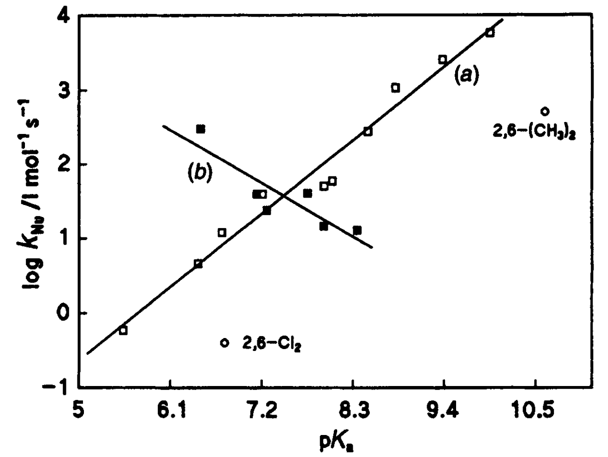

Fig. 3 Brønsted dependence of the reaction of (*a*) phenolate ions with 4-nitrophenyl *N*-methylisonicotinate and (*b*) 2,6-difluorophenoxide ion with substituted phenyl *N*-methylisonicotinate esters. Lines are calculated from eqns. (9) and (10) and the data and identities of the points are from Tables 4 and 5. The open circles are for the reaction of 2,6-dichlorophenolate ion and 2,6-dimethylphenolate ion with the ester.

respectively; the data for eqn. (7) incorporate parameters obtained in previous work,[11] but the value of β_{nuc} is not altered significantly from that obtained earlier ($\beta_{nuc} = 0.75 \pm 0.04$) by the inclusion of *ortho*-fluoro substituents (2-fluoro, 2,6-difluoro, 2,3,4,5,6-pentafluoro and 2,3,5,6-tetrafluoro).

Reactions with the aryl *N*-methylisonicotinate esters were carried out using 2,6-lutidine buffers and the rate constants were insensitive to this buffering species. Fig. 1(*b*) indicates that under these conditions 2,6-lutidine never accelerates the rate constant by more than 0.002 s^{-1} in an overall rate constant of 0.09 s^{-1} and this gives rise to a rate constant $k_{2,6\text{-lutidine}} < 0.08$ l mol^{-1} s^{-1}.

Discussion

Nucleophilic reaction with phenolate ions

The values of k_{Nu} for the 2,6-dimethyl- and 2,6-dichlorophenolate anions are substantially below the regression line consistent with the phenolate ions acting as nucleophiles. Studies with the acetate series indicated nucleophilic reaction rather than general base expulsion of the leaving phenolate from the ester, although it is possible that the *hindered* phenolate ions react *via* a general base process with the *N*-methylisonicotinate esters. The upper limit for the reaction of 2,6-lutidine with the 4-nitrophenyl *N*-methylisonicotinate (0.08 l mol^{-1} s^{-1}) is some 100 times smaller than that of a phenolate ion with similar pK_a (6.77). A general base mechanism is excluded for phenolate ion attack because such a process should yield similar rate constants for both base species.

The relative values of the rate constants for attack of hydroxide ion on the various neutral and charged esters (Table 2) are in agreement with what are expected by extrapolation from data already known.[12,13] The position of the formal charge on the pyridinium species makes little difference to the reactivity at the carbonyl centre so far as the 2- and 4-positions are concerned. Since the *N*-methyl derivatives of the isonicotinate esters are more readily synthesised than are those of the picolinates they are the substrates of choice to study the effect of positive charge on β_{eq}.

The measurement of β_{eq}

The value of β_{eq} for a calibrating equilibrium is formally obtained by determination of the polar substituent effect for the equilibrium constant, however, it is usually obtained from an equation such as eqn. (11),[4] which is the difference between β values for the rate constants for forward and reverse reactions.

$$\beta_{eq} = \beta_{nuc} - \beta_{lg} \qquad (11)$$

The requirements for the use of eqn. (11) are that the two parameters β_{lg} and β_{nuc} refer to the Brønsted correlations for reactions that are the exact microscopic reverse of each other and that they therefore refer to the same rate determining step.[14] The method has been applied successfully to the transfer of the diethoxyphosphoryl[6] and acetyl[5] groups between imidazole and phenolate anions. There are difficulties in the use of this method for measuring β_{eq} for certain systems, such as the transfer of the diphenylphosphinate group (Ph_2PO) between 4-nitrophenolate ion and phenolate ions[14] because, although the expulsion of 4-nitrophenolate ion from the ester to give β_{nuc} is easily measured, the 4-nitrophenolate ion is a weak nucleophile and strongly absorbs in the UV–visible region, thus complicating the measurement of the reverse rate constant. The value of β_{lg} may be measured for other phenolate nucleophiles under favourable conditions and that for 4-nitrophenolate attack may be extrapolated from the correlation of β_{lg} with the pK_a of the nucleophile. The extrapolation to obtain β_{lg} for nitrophenolate must be minimal to ensure exact microscopic reversibility in β_{nuc} and β_{lg}. Unfortunately, the accuracy with which β_{lg} can be obtained is not very high and, for example, the β_{lg} for attack of 4-nitrophenolate ion on aryl acetates is estimated to be -0.66 ± 0.44,[15] which gives rise to a β_{eq} of 1.41 ± 0.48. Such a procedure gives substantial uncertainty and is therefore not preferred, making the search for a 4-nitrophenolate ion surrogate of great importance. The basicity of 2,6-difluorophenol (pK_a = 7.21) is similar to that of 4-nitrophenol (pK_a = 7.14) and the nucleophilic reactivity, as measured by the Brønsted dependence of the second order rate constants for attack upon 4-nitrophenyl acetate (Fig. 2), is that expected for a nucleophile of this basicity. 4-Nitrophenol and 2,6-difluorophenol, therefore, possess similar steric and electronic properties, and the latter phenolate ion, which does not exhibit the strong UV–visible absorbance of the former, can therefore be used to determine β_{lg}, while using the 4-nitrophenyl ester to determine β_{nuc}. In any case, single *ortho* substituents do not have a substantial effect on reactivity to attack by phenolate ions on esters[16] and this is another case where fluorine and hydrogen have similar steric requirements.

A value of β_{eq} (1.76 ± 0.14) for acetyl transfer was determined by the method employing 2,6-difluorophenol and is, within the error limits, the same as the literature value (1.70). The result is better than that obtained by extrapolation. Application of eqn. (11) to the *N*-methylisonicotinate case employs β_{lg} for the 2,6-difluorophenolate ion attack and β_{nuc} for the 4-nitrophenyl esters and gives a value of β_{eq} of 1.55 ± 0.23.

Concerted process

Fig. 3 indicates that over the pK_a range 5.5 to 10 there is no break in the Brønsted-type plot for reactivity of phenolate ion nucleophiles with 4-nitrophenyl *N*-methylisonicotinate in aqueous solution. This is good evidence of a concerted mechanism of displacement of the 4-nitrophenolate ion from the ester and this result is consistent with previous work on attack at phenyl esters.[17,18]

The arrangement of the transition structure for the displacement mechanism may be deduced from the value of α_{nuc} derived from β_{nuc} and β_{eq} determined above. The value of α_{nuc} (0.58 ± 0.05) is larger than that for the attack of phenolate ion nucleophiles on 4-nitrophenyl acetate (0.42 ± 0.01) suggesting a 'later' transition structure for the *N*-methylisonicotinyl transfer. This is in opposition to the reactivity selectivity 'principle'[19] because the acetate is *less* reactive than the *N*-methylisonicotinate. In the more reactive *N*-methylisonicotinate series bond fission, as judged from the value of β_{lg}, is less advanced compared with that for the acetate; this result is consistent with the reactivity selectivity 'principle'. The origin of the 'anomaly' may be understood in terms of a Jencks–More–O'Ferrall diagram (Fig. 4) where the tightness parameter τ (given by $2\alpha_{nuc}$)[20] of 1.16 for the *N*-methylisonicotinyl transfer between 4-nitrophenolate ions is larger than that (0.82) for acetyl transfer. This implies that the transition structure of the identity reaction has more tetrahedral quality than the acylium ion (the transition structure lies closer to the top left corner on the tightness diagonal of the Jencks–More–O'Farrell diagram) and this agrees with the expected relative instability of the acylium ion from the *N*-methylisonicotinyl group compared to that of the acetyl group.

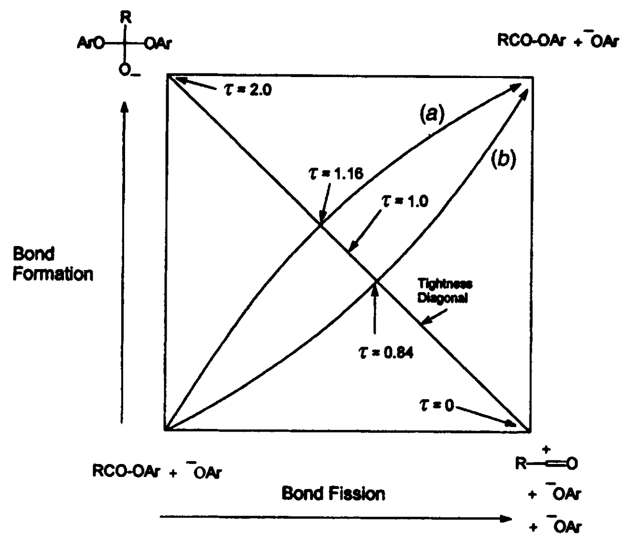

Fig. 4 Jencks–More–O'Ferrall diagram for the concerted nucleophilic displacement reaction between phenolate ions and phenyl esters. For an identity reaction the transition structure of the concerted process lies on the tightness diagonal.[20] Line (*a*) is for the *N*-methylisonicotinate ester and line (*b*) is for acetate; the lines refer to the identity displacements of the 4-nitrophenyl esters.

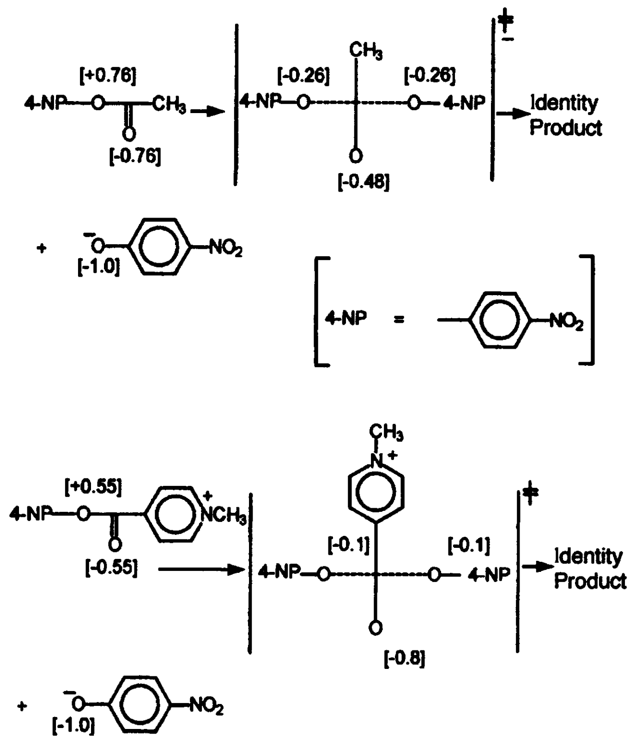

Fig. 5 Effective charge maps for the identity reactions of 4-nitrophenolate ion with 4-nitrophenyl esters. The effective changes on the various atoms are given in parentheses.

It is instructive to compare the effective charge maps for the identity reactions of 4-nitrophenolate ion on the 4-nitrophenyl esters (Fig. 5). These may be constructed using the effective charge distribution in the ester obtained from β_{eq} and the value of β_{nuc} for the attack of substituted phenyl esters. The effective charge on the carbonyl oxygen in the transition structure is obtained by assuming conservation[2,3] of effective charge in the system. Since the reaction is an identity reaction[20] and concerted the transition structure is symmetrical with regard to the bonding between the central carbon and the leaving and entering oxygens. The effective charge on the carbonyl oxygen is substantially more negative in the case of the *N*-methylisonicotinyl transfer than it is in the acetyl transfer, consistent with a structure more like a tetrahedral intermediate.

Prediction of β_{eq}

A large number of β_{eq} values have been obtained and these have been collected in various articles.[2,3,4] It is remarkable that β_{eq} for reactions in aqueous solution does not vary substantially; for a sample of 35 values there are only two extreme values (+2.4 and +0.6) and an average β_{eq} of 1.42 ± 0.36 may be obtained. To a first approximation it would not make a large difference if the β_{eq} were assumed to be unity; in other words the absolute magnitude of either β_{nuc} or β_{lg} is a useful measure of the transition structure relative to the difference between reactant and product states. The value of β_{eq} to be employed can be improved for individual cases and is in general closer to unity if the transfer group is an alkyl moiety. Sulfonyl and acyl functions usually have a slightly higher value of β_{eq} (1.5–1.8). However, the β_{eq} values known at the present time[2,3,4] enable reasonably good estimates to be made of Leffler's α given experimental values of β_{nuc} or β_{lg}. The present study is a case in point for the necessity to possess β_{eq} values otherwise it would be impossible to interpret the differences in β_{nuc} with confidence.

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