Nucleophilicity of Phenolates in the Reaction with *p*-Nitrophenyl Acetate in Ethanol

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The rate of release of *p*-nitrophenol in the reaction of nine substituted phenolates with *p*-nitrophenyl acetate has been determined by spectrophotometric measurements in absolute ethanol at 22°. The phenolate anion is the reactive species and competes with ethoxide anion, arising from solvolysis of the phenolate, for nucleophilic attack on the ester carbonyl carbon atoms. From the observed reaction rates the solvolysis constants and the pK_a values of the phenols were obtained. The second-order rate constants for phenoxide anions were correlated with the pK_a values of the corresponding phenols giving a Brönsted β value of 0.57. A comparison with the nucleophilic reactivity of arenethiolates towards the same substrate in ethanol has been made. The rate-determining step is probably the expulsion of the leaving group in the reaction of arenethiolates, whereas it is the nucleophile attack in the reaction of phenoxides.

STUDIES on the nucleophilicity of hydroxy- and mercapto-compounds towards ester sp^2 carbon atoms are important because they can help to clarify some facets of acyl-transfer reactions, whose significance in the biological area is well known.

Recently, we reported a kinetic study on the nucleophilicity of substituted arenethiols in reaction with *p*-nitrophenyl acetate (*p*-NPA) in 95% aqueous ethanol at 22°.[1] A Brönsted β value of 0.61 was found and we noted that it was higher than the β value of 0.38 for the reaction of alkanethiols with *p*-NPA in aqueous solution reported by Ogilvie *et al.*,[2] but lower than that obtained by Bruice and Lapinsky[3] for a series of oxygen bases towards *p*-NPA (β 0.8). However, this β value for oxygen bases was obtained in 28.5% aqueous ethanol at 30° and with only four experimental points corresponding to phenol, *p*-chlorophenol, *p*-hydroxybenzaldehyde, and acetate ion.

Therefore, in an attempt to obtain more significant data on acyl-transfer to oxyanions, and thus to achieve a more stringent comparison between the nucleophilic reactivities of thiol anions and oxyanions towards the ester carbonyl carbon atom, we decided to investigate in greater detail the effect of substituents in the aromatic ring of the phenol on the reaction with *p*-NPA in ethanol.

While this work was in progress, Hupe and Jencks[4] reported an extensive study on the reactivity of thiol anions and oxyanions with thiol and oxygen esters in water. Some of their results are in good agreement with some of our data, obtained in ethanol, reported in the present work.

RESULTS AND DISCUSSION

The reaction of phenoxide ion with *p*-NPA in absolute ethanol is complicated by the well known[5] solvolysis reaction [equation (1)] due to the low acidity of phenol.

$$\mathrm{PhO^- + EtOH \rightleftharpoons PhOH + EtO^-} \qquad (1)$$

Both the ionic species, phenoxide and ethoxide, react with *p*-NPA [equations (2) and (3)] with rate constants k_1 and k_2, respectively. Under the experimental conditions used, the release of *p*-nitrophenolate ion, spectrophotometrically monitored at 400 nm, follows first-order kinetics [equation (4)]. If $K_s = [\mathrm{PhOH}][\mathrm{EtO^-}]/[\mathrm{PhO^-}]$

$$\mathrm{CH_3CO_2C_6H_4NO_2}\text{-}p + \mathrm{PhO^-} \xrightarrow{k_1} p\text{-}\mathrm{NO_2C_6H_4O^-} + \mathrm{CH_3CO_2Ph} \qquad (2)$$

$$\mathrm{CH_3CO_2C_6H_4NO_2}\text{-}p + \mathrm{EtO^-} \xrightarrow{k_2} p\text{-}\mathrm{NO_2C_6H_4O^-} + \mathrm{CH_3CO_2Et} \qquad (3)$$

$$\mathrm{d}[p\text{-nitrophenol}]/\mathrm{d}t = k_{\mathrm{obs}}[p\text{-NPA}] \qquad (4)$$

is the solvolysis constant of phenoxide ion in ethanol, [base] is the overall base concentration (phenoxide plus ethoxide) and [PhOH] is the concentration of free phenol, k_{obs} is given[5c] by equation (5) which reduces

$$k_{\mathrm{obs}} = [\mathrm{base}]\,\frac{k_1 + k_2K_s/[\mathrm{PhOH}]}{1 + K_s/[\mathrm{PhOH}]} \qquad (5)$$

to equation (6) when $K_s/[\mathrm{PhOH}]$ is much smaller than unity.

$$k_{\mathrm{obs}}/[\mathrm{base}] = k_1 + k_2K_s/[\mathrm{PhOH}] \qquad (6)$$

Typical plots of $k_{\mathrm{obs}}/[\mathrm{base}]$ *versus* $[\mathrm{ArOH}]^{-1}$ at [base] *ca.* 10^{-2}M are shown in Figure 1. Good straight lines were generally obtained in all cases when the concentration of free phenol was in the range 10^{-2}—10^{-1}M and, from the slope and intercept, k_1 and k_2K_s were obtained. Since it is possible to measure k_2 independently, the value of K_s can also be obtained and, from the equation pK_a = pK_{auto} − pK_s, where K_{auto} is the ionic product of the solvent, the pK_a values of the phenols can be calculated. The pK_{auto} value of ethanol at 22° is 19.18.[6]

Table 1 summarizes the values of k_1 and k_2K_s for *p*-bromophenol, a substituted phenol convenient from the standpoint of its reaction rate, obtained with different base concentrations. The lower limit of base concentration, *ca.* 10^{-2}M, was chosen to avoid changes in the actual base concentration due to absorption of carbon dioxide by the reaction mixture.[7] The constancy of k_1 with changing base concentration indicates that k_1 is a true second-order rate constant. The value of k_2 determined by a stopped-flow technique with the ethoxide ion concentration varying in the range 0.01—0.025M is 107 ± 2 l mol^{-1} s^{-1} at 22°. Table 2 reports the values of k_1, pK_s, and pK_a for nine substituted phenols. The pK_a value of unsubstituted phenol in ethanol at 22° obtained by this method is 15.58, in good agreement with the value of 15.8 at 25° determined by England and House.[5b]

TABLE 1

Influence of base concentration on rate constants for the reaction of *p*-NPA with sodium *p*-bromophenolate in ethanol at 22° [a]

10^2[base]/M	10^2[ArOH]$_{free}$/M	$k_1{}^b$/l mol^{-1} s^{-1}	$10^3 k_2 K_s{}^b$	p$_s K$
0.91	1—9	0.353 (0.003)	3.47 (0.06)	4.49
1.97	1—6	0.346 (0.005)	3.06 (0.09)	4.54
3.00	2—6	0.340 (0.008)	3.51 (0.25)	4.48

[a] [*p*-NPA] = 4.06 × 10^{-5}M. [b] Obtained by a graphical method (see text) with at least seven points for each plot. The figures in parentheses are standard deviations.

Although kinetic methods for the determination of pK_a are not generally held in high regard,[8] the one reported here may be considered reasonably reliable, and in principle, it should be applicable with equal ease and rigour to other water-like solvents. Recently, Bunnett and Nudelman [9] have successfully applied a kinetic method to the determination of pK_a of thiophenol and other acids in methanol.

Closer inspection of Figure 1 reveals that the points at free phenol concentration >0.1M deviate from linearity (k_{obs}/[base] values at [ArOH]$_{free}$ 0.5M are *ca.* 30% lower than the expected values for both phenol and *o*-cresol, see Figure 1). This rate suppression could be due to a general medium effect or perhaps to some specific interaction between the reactants. Similar behaviour has also been found in aromatic nucleophilic substitution. Bunnett and Davis [10] have attributed the rate decrease observed in the reaction of phenoxide ion with 1-chloro-2,4-dinitrobenzene in 60% aqueous dioxan at high phenol concentration, to the formation of biphenoxide ion, PhOH·OPh$^-$, a weak nucleophilic species. A similar interpretation has been proposed by Liotta and Karelitz [5c] for the same reaction in methanol on the basis of the fact that no deviation from linearity was found when the sterically hindered *o*-cresol instead of phenol was used.

TABLE 2

Rate constants for the reactions of *p*-NPA with X-substituted phenolates in ethanol at 22°

	X	$k_1{}^a$/l mol^{-1} s^{-1}	10^2[ArOH]$_{free}$/M	1 + log k_1	p$K_s{}^a$	p$K_2{}^b$
1	*m*-Br	0.18 (<0.01)	1—6	0.26	4.87 (0.01)	14.31
2	*m*-Cl	0.19 (<0.01)	1—6	0.28	4.78 (0.02)	14.40
3	*m*-F	0.24 (<0.01)	1—8	0.38	4.57 (0.01)	14.61
4	*p*-Br	0.33 (<0.01)	1—9	0.52	4.49 (0.01)	14.69
5	*p*-Cl	0.39 (<0.01)	1—6	0.59	4.38 (0.01)	14.80
6	*m*-OMe	0.68 (0.02)	1—6	0.83	3.76 (0.02)	15.42
7	H [c]	1.01 (0.03)	1—50	1.00	3.60 (0.01)	15.58
8	*m*-Me	1.05 (0.04)	1—7	1.02	3.46 (0.01)	15.72
9	*o*-Me [c]	1.46 (0.08)	1—50	1.16	3.08 (0.01)	16.10

[a] Obtained by a graphical method (see text) with [base] 10^{-2}M and [*p*-NPA] 4.06 × 10^{-5}M. The figures in parentheses are standard deviations. [b] Values calculated from 19.18 (pK_{auto} of ethanol) −pK_s. The accuracy of the pK_a values cannot be given since that of the pK_{auto} at 22° is unavailable.[6] [c] For these phenols the standard deviations refers to the [ArOH]$_{free}$ range 0.1—0.01M.

In our case, since phenol and *o*-cresol show analogous behaviour, it seems more reasonable to attribute the rate decrease observed at high phenol concentrations to a medium effect rather than to the presence of a biphenoxide species.

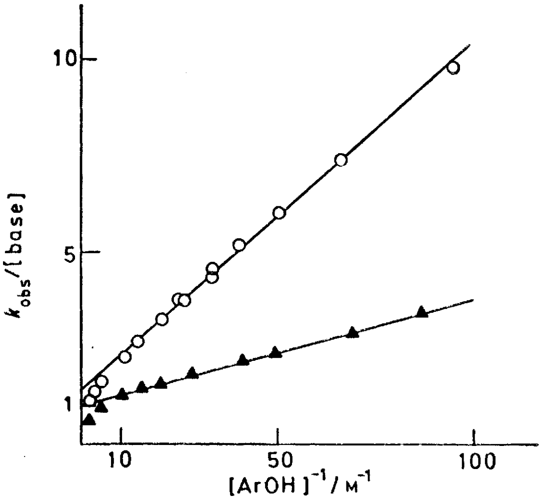


FIGURE 1 Plots of k_{obs}/[base] against [ArOH]$^{-1}$. For phenol (▲) the intercept is 1.01 ± 0.03 l mol^{-1} s^{-1} and the slope is (2.69 ± 0.06) × 10^{-2} s^{-1}. For *o*-cresol (○) the intercept is 1.46 ± 0.08 and the slope is (8.9 ± 0.2) × 10^2 s^{-1}. The lines are the least-squares fits for the points at [ArOH] ⩽0.1M (the interpretation of the curvature is given in the text)

From the data in Table 2 it appears that electron-donating substituents increase the reaction rate, whereas electron-withdrawing substituents have the opposite effect. Figure 2 shows the Brönsted plot obtained by correlating the rate constants for the phenoxide anions (1 + log k_1) with the pK_a values of the corresponding phenols. The β value calculated from the least-squares regression line for ***meta***-substituents is 0.57. It appears that the points corresponding to *p*-bromophenol, *p*-chlorophenol, and *o*-cresol deviate slightly from linearity. The increased nucleophilicity of phenolates bearing ***para***-substituents with a +*M* effect is similar to that observed for the corresponding arenethiolates in reactions with both *p*-NPA and other substrates, and different interpretations have been proposed.[1] The negative deviation for *o*-cresol may be attributed to steric hindrance.[11] The Brönsted plot drawn from our previous work on the reactivity of *p*-NPA with arenethiolates in ethanol[1] is also presented in Figure 2 (dashed line, slope 0.61). A comparison of the β values for phenolates and arenethiolates indicates that the sensitivity to basicity of the reactions with *p*-NPA in ethanol is similar for these two classes of nucleophiles. For a given substituent on the attacking atom the oxyanion is more basic (*ca.* 6 units of pK_a) and about four-fold more reactive towards *p*-NPA in ethanol than the corresponding thiol anion. However, arenethiolates are known to be far more effective nucleophiles than the corresponding phenoxide anions for attack on aromatic,[10,12] aliphatic,[12] and olefinic[13] carbon atoms. These results could be rationalized on the basis of the ' hard and soft acids and bases ' principle:[14] the thiol anion is a ' soft ' base and therefore it is expected to be more reactive than the oxyanion, a ' hard ' base, with a ' soft ' acid like an aromatic carbon atom; conversely, the oxyanion should be more reactive than the thiol anion with a ' hard ' acid like an ester sp^2 carbon atom. However, simple considerations on the mechanism of these reactions can furnish a more meaningful interpretation of the results. If we envisage the two classes of nucleophiles employed, phenolates and arenethiolates, we note that they differ considerably in basicity (for arenethiols pK_a 8.09—9.71; for phenols pK_a 14.31—16.10); on the other hand *p*-nitrophenol is the leaving group in both reactions and its pK_a can be estimated * to be *ca.* 12, which is intermediate between the pK_a values of the two classes of nucleophiles. On this basis it is possible that if, as is widely accepted,[4] these reactions proceed through stepwise pathways involving tetrahedral intermediates and the leaving group ability can be related to the pK_a of the leaving group, the observed similarities of the reactivities and of the β values for these two classes of nucleophiles are simply fortuitous and do not represent similar behaviour. In fact, when the nucleophile is ArS^- it is likely that the intermediate breaks down preferentially to give reactants and the expulsion of *p*-nitrophenol is rate determining ($k_2 < k_{-1}$ in the Scheme). Conversely, when the nucleophile is ArO^- it is likely that the intermediate breaks down preferentially to give products and the attack of ArO^- is rate-determining ($k_2 > k_{-1}$ in the Scheme). Therefore, while in the case of phenolates both reactivity and β should refer to the rate-determining nucleophilic attack and be directly dependent on the basicity of the nucleophile, in the case of arenethiolates these two parameters should represent rate-determining breakdown of the intermediate to products, and thus be primarily determined by the effects of substituents on the equilibrium constant for formation of the intermediate.

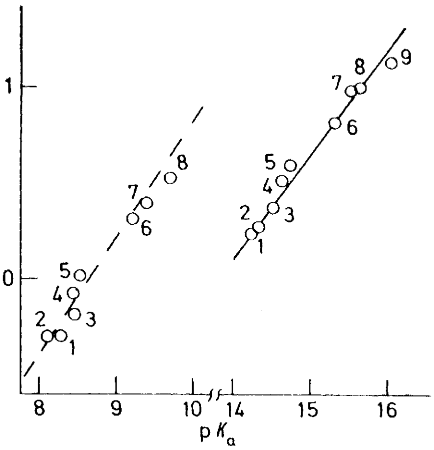
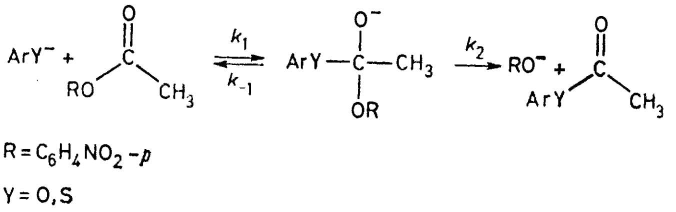


FIGURE 2 Logarithmic plot of the rate constants (1 + log k_1) of the reactions of *p*-NPA with substituted phenols in absolute ethanol at 22° *versus* the pK_a of the corresponding phenol. The slope calculated from *meta* substituents is 0.57 ± 0.02. The dashed line refers to arenethiols. Numbering of substituents corresponds to that in Table 2



$R = C_6H_4NO_2$-*p*

$Y = O, S$

SCHEME

As far as the nucleophilicity of ethoxide ion towards *p*-NPA in ethanol is concerned, we remark that the second-order rate constant, calculated from the Brönsted equation obtained for the phenols, is larger than the experimental value ($k_{calc.}$ 484 l mol^{-1} s^{-1}; $k_{exp.}$ 107 l mol^{-1} s^{-1}). Negative deviations with highly basic oxyanions have recently been observed in Brönsted plots for acyl-transfer[4,16,17] and for proton-transfer[18] reactions in water and have been attributed to some kind of ' solvation effect ' rather than to a Hammond postulate effect. A similar solvation effect could be invoked to account for the decreased reactivity of ethoxide ion in ethanol as well, although it must be noted that the negative deviation observed in ethanol is much smaller than the corresponding deviation in water.[4]

EXPERIMENTAL

Solvents.—Ethanol (99.8%) was distilled over magnesium activated by iodine.[19] Dioxan was purified as described in literature.[20] Solvents were degassed by bubbling in nitrogen and stored under nitrogen.

Materials.—The ester *p*-NPA was prepared as previously reported.[1,21] The following phenols were commercial specimens: phenol, *m*-methoxyphenol, *m*- and *p*-bromophenol. *m*-Fluorophenol, *m*- and *p*-chlorophenol, and *o*- and *m*-cresol were obtained by decomposition of the diazonium salts of the corresponding anilines, according to the general procedure described in the literature.[20] All phenols were carefully recrystallized or redistilled before use. M.p.s and b.p.s agreed with literature values.

Kinetics.—The spectrophotometers employed were Zeiss PMQ II and Gilford 2400 S instruments, both fitted with a thermostatted brass block for holding the cuvettes. Rate measurements of the reaction of ethoxide ion with *p*-NPA

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* A value of 11.7 ± 0.2 was calculated by correlating the pK_a values of phenols in ethanol obtained in this work with the pK_a values of the corresponding phenols in water.[15]

were carried out with a Durrum D 110 stopped-flow spectrophotometer.

For each phenol seven or eight solutions of different free phenol concentration and constant base concentration were prepared by mixing solutions of the appropriate phenol and sodium ethoxide. These solutions were freshly prepared by weighing respectively the phenol and sodium in absolute ethanol. All vessels were flushed with nitrogen to avoid absorption of carbon dioxide. Free phenol concentrations were calculated from the weighed amount of phenol and from the base concentration, this being taken as equal to that of sodium ethoxide titrated with 10^{-2}N-hydrochloric acid (Methyl Red–Bromocresol Green). A stock solution of *p*-NPA in dioxan (*ca.* 4×10^{-3}M) was prepared; this concentration was chosen so that the infinity absorbance was *ca.* 0.6—0.7.

Runs were initiated by adding *p*-NPA solution (20 μl) to the phenol-phenolate buffer (2 ml) thermostatted at 22 ± 0.1°. In all runs both concentrations of base (10^{-2}M) and phenol (10^{-2}—10^{-1}M) were in great excess over that of substrate (4×10^{-5}M). The kinetic runs were followed by direct observation of the absorbance increase of the reacting solution at 400 nm for at least three half-lives; the infinity absorbances agreed with that expected for quantitative conversion of *p*-NPA in *p*-nitrophenol. Plots of log ($\mathrm{O.D.}_{\infty} - \mathrm{O.D.}_t$) *versus* time were linear. Values of k_{obs} were reproducible to ±3%.

Product Analyses.—A quantitative assessment [by h.p.l.c., using a Waters liquid chromatograph equipped with u.v. and r.i. detectors, a column packed with Corasil II, and n-hexane–isopropyl ether (5 : 1) as solvent] of the yields of the products obtained in the reaction of *p*-NPA (10^{-3}M) with $[\mathrm{base}] = [\mathrm{PhOH}]_{\mathrm{free}} = 10^{-2}$M indicated the formation of *ca.* 75% ethyl acetate and *ca.* 25% phenyl acetate.

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