

Acid Dissociation Constants of Phenols and Reaction Mechanism for the Reactions of Substituted Phenyl Benzoates with Phenoxide Anions in Absolute Ethanol

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Abstract: Acid dissociation constants of 10 substituted phenols have been measured by a kinetic method together with second-order rate constants for the reactions of aryl benzoates ($X-C_6H_4CO-OC_6H_4-Y$) with *Z*-substituted phenoxide ($Z-C_6H_4O^-$) and EtO⁻ in absolute ethanol at $25.0 \pm 0.1^\circ\text{C}$. The kinetic results support a stepwise mechanism for the present acyl-transfer reaction. © 1997 Elsevier Science Ltd.

INTRODUCTION

It has been suggested that acyl-transfer reactions would occur *via* a stepwise mechanism with a tetrahedral addition intermediate, or *via* a concerted mechanism with a single transition state.¹⁻⁴ Buncl *et al.* have proposed that acyl-transfer reactions would proceed *via* a stepwise mechanism based on poor Hammett correlation of $\log k$ with σ^- substituent constants for the reaction of a series of substituted phenyl acetates with phenoxide.¹ However, Williams *et al.* have claimed that acyl-transfer reactions would occur *via* a concerted mechanism from the observation of a linear Brönsted-type plot for the reaction of *p*-nitrophenyl acetate with a series of substituted phenoxides.² Recently, a similar conclusion has been drawn from the studies of structure-reactivity correlations by Jencks³ and isotope effects by Hengge.⁴

Since substituents on the aromatic ring in phenol can influence nucleophilicity as well as nucleofugality by changing its acidity, phenoxides have been frequently used to investigate acyl-transfer reaction mechanism as entering or leaving groups. Although the effect of substituents has been known to be more significant in organic solvents than in H₂O, previous studies were performed mostly in H₂O. One of the reasons is considered to be lack of pK_a data in organic solvents. Scattered information on the pK_a values of phenols in absolute ethanol (EtOH) is available. England and House reported the pK_a value of 15.8 for unsubstituted phenol in EtOH at 25°C .⁵ Guanti *et al.* measured pK_a values

of a series of substituted phenols in EtOH at 22°C using a kinetic method.⁶ However, the pK_a values of substituted phenols in EtOH at 25°C are not available. Therefore, we have measured pK_a values of 10 substituted phenols in EtOH at $25.0 \pm 0.1^\circ\text{C}$ and performed a systematic kinetic study to investigate the mechanism of acyl-transfer reactions in EtOH as shown in the following Scheme.

Scheme



X = *p*-OMe, *p*-Me, *m*-Me, H, *p*-Cl, *m*-Cl, *p*-CN, *p*-NO₂.

Y = *p*-Me, *m*-Me, H, *p*-Cl, *m*-Cl, *p*-Br, *m*-MeCO, *p*-MeCO, *p*-EtOCO, *p*-CN, *p*-NO₂.

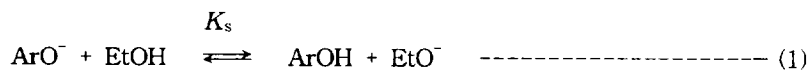
Nu⁻ = EtO⁻, Z-C₆H₄O⁻

Z = *p*-Me, *m*-Me, H, *p*-Cl, *m*-Cl, *p*-Br, *m*-MeCO, *p*-MeCO, *p*-EtOCO, *p*-CN.

RESULTS AND DISCUSSION

Measurement of Acid Dissociation Constants. - Reaction of aryl benzoates with ethoxide (EtO⁻) and substituted phenoxides (Z-C₆H₄O⁻) obeyed pseudo-first-order kinetics up to over 90% of the total reaction. Pseudo-first-order rate constants (k_{obs}) were obtained from the slope of the plots of $\ln (A_\infty - A_t)$ vs time. Generally, five different concentrations of nucleophile solutions were used to obtain second-order rate constants from the slope of the plot of k_{obs} vs the concentration of nucleophile. The plot of k_{obs} vs [EtO⁻] was linear with a slope of $12.1 \text{ M}^{-1}\text{s}^{-1}$ and passed through the origin, indicating that the contribution of EtOH to the pseudo-first-order rate constant is negligible. The corresponding plots for Z-C₆H₄O⁻ were also linear but did not pass through the origin (positive intercepts) due to the contribution of EtO⁻ to the k_{obs} in the present reaction conditions.

It has been well known that aryloxide (ArO⁻) is in equilibrium with EtO⁻ in absolute ethanol by solvolysis as eqn 1. The solvolysis constant of ArO⁻ in EtOH, K_s , can be written as eqn 2, in which K_a is the acid dissociation constant of ArOH in EtOH (eqn 3) and K_{auto} represents the autoprotolysis constant of EtOH (eqn 4).



$$\begin{aligned} K_s &= [\text{EtO}^-]_{\text{eq}}[\text{ArOH}]_{\text{eq}} / [\text{ArO}^-]_{\text{eq}} \\ &= K_{\text{auto}} / K_a \quad \text{-----} \quad (2) \end{aligned}$$



Both the anionic species, ArO^- and EtO^- , can react with PNPB with rate constants k^{ArO^-} and k^{EtO^-} , respectively. Accordingly, a simple pseudo-first-order rate equation can be written as eqn 5, in which $[\text{ArO}^-]_{\text{eq}}$ and $[\text{EtO}^-]_{\text{eq}}$ represent the equilibrium concentrations of ArO^- and EtO^- , respectively. Eqn 5 can be rewritten as eqn 6, in which $[\text{base}]_{\text{tot}}$ is the sum of $[\text{ArO}^-]_{\text{eq}}$ and $[\text{EtO}^-]_{\text{eq}}$. Eqn 6 can be further reduced to eqn 7 under a condition of $K_s / [\text{ArOH}]_{\text{eq}} \ll 1$.

$$k_{\text{obs}} = k^{\text{ArO}^-}[\text{ArO}^-]_{\text{eq}} + k^{\text{EtO}^-}[\text{EtO}^-]_{\text{eq}} \quad \text{-----} \quad (5)$$

$$k_{\text{obs}} = \frac{k^{\text{ArO}^-} + k^{\text{EtO}^-} K_s / [\text{ArOH}]_{\text{eq}}}{1 + K_s / [\text{ArOH}]_{\text{eq}}} [\text{base}]_{\text{tot}} \quad \text{-----} \quad (6)$$

$$k_{\text{obs}} / [\text{base}]_{\text{tot}} = k^{\text{ArO}^-} + k^{\text{EtO}^-} K_s / [\text{ArOH}]_{\text{eq}} \quad \text{-----} \quad (7)$$

In Figure 1 are demonstrated typical plots of $k_{\text{obs}} / [\text{base}]_{\text{tot}}$ vs $1 / [\text{ArOH}]_{\text{eq}}$. $[\text{base}]_{\text{tot}}$ was kept in the range of 0.02 – 0.1 M to avoid any changes in the actual base concentration due to absorption of CO_2 by the reaction mixtures. $[\text{ArOH}]_{\text{eq}}$ was kept below 0.05M to eliminate any possible homo-hydrogen bonding⁷ which would cause undesirable results. Good linear lines were obtained in all cases, and values of k^{ArO^-} and $k^{\text{EtO}^-} K_s$ were obtained from the intercepts and slopes of the plots, respectively. The k^{ArO^-} values obtained in this way appear to be comparable with the ones obtained from an independent method described in the preceding section, *i.e.* from the plots of k_{obs} vs $[\text{ArO}^-]$. Since k^{EtO^-} was

determined to be $12.1 \text{ M}^{-1}\text{s}^{-1}$ in the present system (Table 3), K_s values can be calculated from eqn 7. Therefore, K_a values can be calculated from eqn 2 using the known K_{auto} value of $10^{-19.18}$ at 25°C .⁸ The $\text{p}K_a$ values for Z-substituted phenols ($\text{Z-C}_6\text{H}_4\text{OH}$) determined in this way in EtOH at 25.0°C are summarized in Table 1 together with some reported $\text{p}K_a$ values of phenols in EtOH determined at 22°C .⁶

The $\text{p}K_a$ value of unsubstituted phenol (Z=H) in the present study is obtained to be 15.76, which is in excellent agreement with the value of 15.8 reported by England and House.⁵ The $\text{p}K_a$ value of phenols obtained in EtOH at 25.0°C appears to be about 0.1 $\text{p}K_a$ unit larger than the corresponding one obtained at 22°C in EtOH by Guanti *et al.*⁶ This difference is considered to be acceptable since K_a value has been known to be dependent on temperature.⁹

As shown in Table 1, the $\text{p}K_a$'s of phenols in EtOH appear to be about 5 $\text{p}K_a$ unit larger than those in H_2O , and such difference becomes even larger for the more basic phenols. It is found that the $\text{p}K_a$'s of Z- $\text{C}_6\text{H}_4\text{OH}$ in H_2O are linearly related with the ones in EtOH, *i.e.* $\text{p}K_a$ (in EtOH) = $1.30 \text{ p}K_a$ (in H_2O) + 2.70. A similar linearity has been obtained from the correlation of $\text{p}K_a$'s of 15 phenols in H_2O with the ones in 50% aqueous EtOH at 25°C by Cohen *et al.*¹⁰ The slope was calculated to be 1.19 ± 0.01 , slightly smaller than the one obtained in the present system.¹⁰ This is consistent with expectation, since the electronic effects of substituents on basicity are expected to be more significant in absolute EtOH than in 50% aqueous EtOH. Therefore, the $\text{p}K_a$ values of Z- $\text{C}_6\text{H}_4\text{OH}$ obtained in the present system are considered to be quite reliable, and the above relationship between the $\text{p}K_a$ in EtOH and the one in H_2O can be used to estimate the $\text{p}K_a$ value of any substituted phenol whose $\text{p}K_a$ in H_2O is known.

Reaction Mechanism. - In Table 1 are summarized second-order rate constants for the reactions of *p*-nitrophenyl benzoate (PNPB) with Z-substituted phenoxides ($\text{Z-C}_6\text{H}_4\text{O}^-$) together with the $\text{p}K_a$ values of these phenols determined in EtOH at 25.0°C . As shown in Table 1, the reactivity of phenoxide anions toward *p*-nitrophenyl benzoate (PNPB) increases

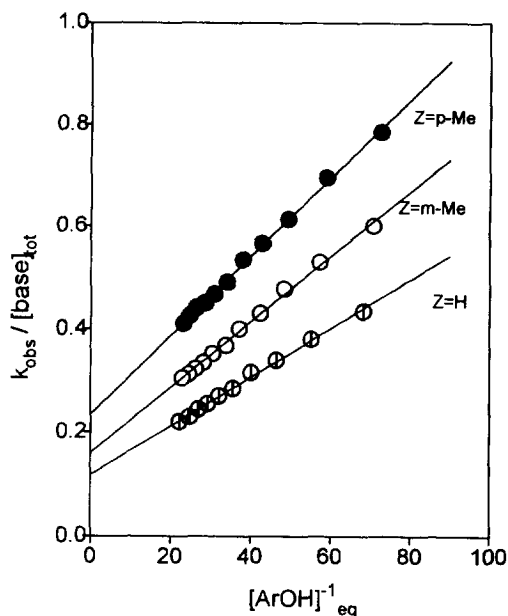


Figure 1. Typical plots of $k_{\text{obs}}/[\text{base}]_{\text{tot}}$ vs $1/[\text{ArOH}]_{\text{eq}}$ for the reactions of PNPB with Z- $\text{C}_6\text{H}_4\text{O}^-$ in absolute EtOH at $25.0 \pm 0.1^\circ\text{C}$.

Table 1. Summary of Second-Order Rate Constants (k^{ArO^-}) for the Reactions of PNPB with Z-Substituted Phenoxides ($Z-C_6H_4O^-$) and pK_a Values of Phenols in EtOH at $25.0 \pm 0.1^\circ C$.

Z	k^{ArO^-} , $M^{-1}s^{-1}$	pK_a
<i>p</i> -Me	.301	15.99 (10.19) ^b
<i>m</i> -Me	.184	15.83 (15.72) ^a (10.08) ^b
H	.144	15.76 (15.58) ^a (9.95) ^b
<i>p</i> -Cl	.0570	14.90 (14.80) ^a (9.38) ^b
<i>m</i> -Cl	.020	14.47 (14.40) ^a (9.02) ^b
<i>p</i> -Br	.0348	14.80 (14.69) ^a (9.34) ^b
<i>p</i> -EtOCO	.00446	13.78 (8.50) ^b
<i>m</i> -MeCO	.0321	14.64 (9.19) ^b
<i>p</i> -MeCO	.00260	13.26 (8.05) ^b
<i>p</i> -CN	.00165	13.04 (7.95) ^b

a) pK_a values determined at $22^\circ C$.⁶ b) pK_a values in H_2O at $25^\circ C$.¹⁷

with increasing the basicity of phenoxides. This is graphically demonstrated in Figure 2 by correlating the rate constant for phenoxide anions ($\log k^{ArO^-}$) with the pK_a of the corresponding phenol determined in this study. As shown in the plot, a good linear Brönsted-type plot has been obtained. However, EtO^- is found to be only 84 times more reactive than PhO^- toward PNPB in the present system (e.g. $k^{EtO^-} = 12.1 M^{-1}s^{-1}$, $k^{PhO^-} = 0.144 M^{-1}s^{-1}$), although the former is over 4 pK_a units more basic than the latter. Therefore, EtO^- would cause a significantly negative deviation from the linearity in Figure 2. Such a negative deviation in a Brönsted-type plot has been often observed for highly basic nucleophiles, such as HO^- , RO^- and oximate anions in aqueous medium, and solvation of these highly basic anions has been suggested to be responsible for the negative deviation.¹¹⁻¹³

The β_{Nuc} value in the present system was calculated to be 0.75 ± 0.03 , which is identical to the one obtained from the corresponding reactions performed in H_2O containing 20 mole % DMSO.¹⁴ Similar β_{Nuc} values (0.7 - 0.8) have been reported for the reactions of *p*-nitrophenyl acetate (PNPA) with a series of substituted phenoxides in H_2O .¹⁻³

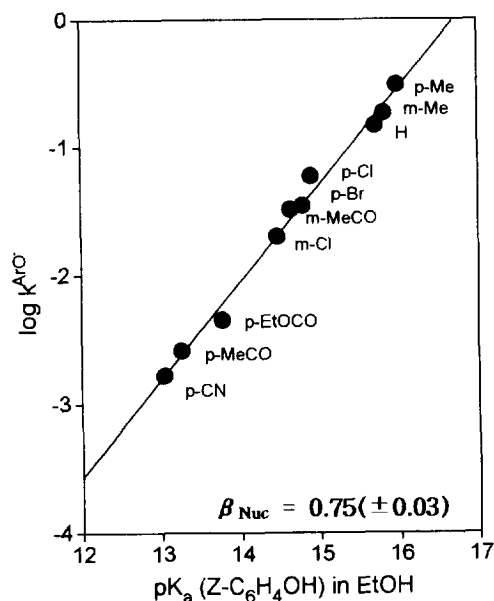


Figure 2. A Brönsted-type plot for the reactions of PNPB with various Z-substituted phenoxides in absolute EtOH at $25.0 \pm 0.1^\circ C$.

Table 2. Summary of Second-Order Rate Constants (k^{EtO^-}) and the Results of Hammett Treatment for the Reactions of Y-substituted Phenyl Benzoates ($\text{C}_6\text{H}_5\text{CO}-\text{OC}_6\text{H}_4-\text{Y}$) with EtO^- in Absolute EtOH at $25.0 \pm 0.1^\circ\text{C}$.

Y	k^{EtO^-} , $\text{M}^{-1}\text{s}^{-1}$	σ	σ^0	σ^-
<i>p</i> -Me	0.274	-0.17	-0.12	-0.17
<i>m</i> -Me	0.301	-0.07	-0.07	-0.07
H	0.389	0	0	0
<i>p</i> -Cl	1.35	0.23	0.27	0.23
<i>m</i> -Cl	1.84	0.37	0.37	0.37
<i>p</i> -Br	1.35	0.23	0.26	0.23
<i>p</i> -EtOCO	2.23	0.45	0.46	0.64
<i>m</i> -MeCO	1.73	0.38	0.38	0.38
<i>p</i> -MeCO	2.28	0.50	0.46	0.87
<i>p</i> -CN	7.59	0.66	0.69	1.00
<i>p</i> -NO ₂	12.1	0.78	0.82	1.27
ρ		1.7 (± 0.1)	1.8 (± 0.1)	1.1 (± 0.1)
r		0.986	0.996	0.956

The magnitude of β_{Nuc} value has been considered to represent the degree of bond formation at the transition state (TS) between the nucleophile and the substrate. Therefore, one can consider that the degree of bond formation between a phenoxide anion and the carbonyl carbon of PNPB is about the same both in EtOH and in H₂O based on the magnitude of the β_{Nuc} value.

Since the present β_{Nuc} value alone does not give any further information on the TS structure, we have studied the effect of substituents in the leaving group. The kinetic results are summarized in Table 2 for the reactions of Y-substituted phenyl benzoates ($\text{C}_6\text{H}_5\text{CO}-\text{OC}_6\text{H}_4-\text{Y}$) with EtO^- in absolute EtOH at 25.0°C along with the results of Hammett plots with use of σ , σ^0 , σ^- substituent constants. As shown in the Table, the reactivity of the substituted phenyl benzoates increases generally with increasing the acid strengthening ability of the substituent Y in the leaving phenoxide. This is demonstrated graphically in Figure 3. However, interestingly, the Brønsted-type plot in Figure 3 shows a relatively high degree of scatter compared with the one in Figure 2. Furthermore, the magnitude of β_{LG} has been calculated to be -0.40 ± 0.04 , which is significantly smaller than the β_{Nuc} value of 0.75 ± 0.03 . The comparison of β_{LG} with β_{Nuc} suggests that the effect of substituents in the leaving group is less sensitive than the one in the nucleophilic phenoxide, and leaving group departure is much less advanced than nucleophilic attack at the rate-determining step.

This argument can be further rationalized by comparing the Hammett correlations obtained using σ , σ^0 , and σ^- constants. As shown in Table 2, Hammett type treatment of leaving group effects results in the best correlation with σ^0 substituent constants while the poorest correlation is obtained when σ^- constants are used. When a partial negative charge develops in the oxygen atom of the leaving phenoxide upon the leaving group departure at the TS of the rate-determining step (RDS), the negative charge can be delocalized

on the aryl substituent by direct resonance. Therefore, one might expect the best correlation with σ^- constants if leaving group departure were involved in the RDS. The fact that σ^0 constants give the best correlation implies that direct resonance interaction between the substituents in the leaving group and the reaction centre is absent in the TS of the RDS. Therefore, one can suggest that leaving group departure is little advanced at the RDS for the present reaction system.

The present results are consistent with the previous results obtained for the acyl-transfer reactions of substituted phenyl acetates with phenoxide anions in H_2O and in $\text{DMSO-H}_2\text{O}$ mixtures of varying compositions, *i.e.* σ^- constants gave extremely poor Hammett correlation, while σ^0 constants resulted in better correlation but with a high degree of scatter.^{1a} Similar results have been also observed for nucleophilic substitution reactions at sulfur^{1b} and phosphorus centres,^{1c} *i.e.* Hammett treatment of leaving group effects in alkaline ethanolysis of substituted phenyl sulfonates and phosphinates gave much better correlation with σ^0 (or σ) than σ^- constant, supporting a stepwise mechanism.

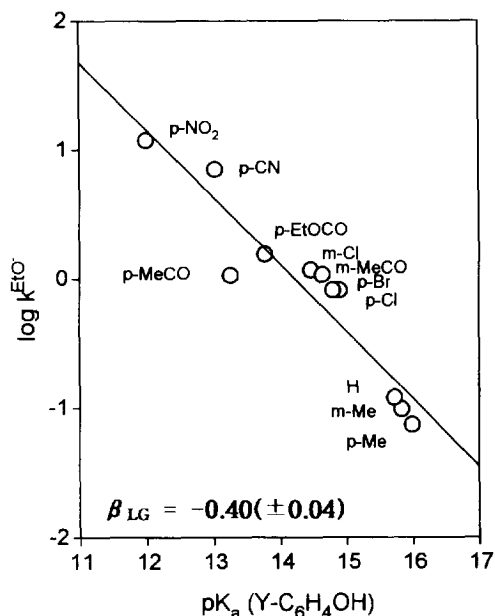


Figure 3. A Brønsted-type plot for the reactions of Y-substituted phenyl benzoates with EtO^- in absolute EtOH at $25.0 \pm 0.1^\circ\text{C}$.

Table 3. Summary of Second-Order Rate Constants for the Reactions of *p*-Nitrophenyl X-Substituted Benzoates ($\text{X-C}_6\text{H}_4\text{CO-OC}_6\text{H}_4\text{-NO}_2$ -*p*) with PhO^- and EtO^- in Absolute EtOH at $25.0 \pm 0.1^\circ\text{C}$.

X	$k^{\text{PhO}^-}, \text{M}^{-1}\text{s}^{-1}$	$k^{\text{EtO}^-}, \text{M}^{-1}\text{s}^{-1}$
<i>p</i> -MeO	0.0351	2.17
<i>p</i> -Me	0.0983	5.44
<i>m</i> -Me	0.129	8.50
H	0.144	12.1
<i>p</i> -Cl	1.26	85.1
<i>m</i> -Cl	2.21	171
<i>p</i> -CN	18.4	1,485
<i>p</i> -NO ₂	34.5	2,656

In order to get more information on the reaction mechanism, the effect of substituents in the benzoyl moiety of the substrate has been studied. Second-order rate constants are summarized in Table 3 for the reaction of *p*-nitrophenyl *X*-substituted benzoates ($X\text{-C}_6\text{H}_4\text{CO-OC}_6\text{H}_4\text{-NO}_2\text{-}p$) with PhO^- and EtO^- in absolute EtOH at 25°C. The reactivity of the substrates increases significantly with increasing the acid strengthening ability of the substituent *X* in the benzoyl moiety for both PhO^- and EtO^- systems. This has been graphically demonstrated in Figure 4. As shown in the plots, excellent Hammett correlations are obtained with σ constants. The ρ_X values are calculated to be significantly large, *e.g.* 2.85 and 2.96 for the reactions with PhO^- and EtO^- , respectively. Since the electronic effects of substituents on rates and equilibria are known to be more significant in EtOH than in H_2O , one needs to normalize ρ_X (rate) with ρ_X (equilibrium) in order to eliminate solvent effect and to get useful information about the TS structure at the RDS. The ρ_X value for dissociation of $X\text{-C}_6\text{H}_4\text{CO}_2\text{H}$ in EtOH has been reported to be 1.957.¹⁵ Division of the ρ_X values in the present system by 1.957 gives normalized ρ_X values of 1.46 and 1.51 for the PhO^- and EtO^- system, respectively. These normalized ρ_X values are still very large. One might attribute the large ρ_X values to a proximity effect, since the benzoyl substituents *X* are closely located from the reaction centre. However, the nature of reaction mechanism is considered to be more responsible for the large ρ_X values in the present system. An electron withdrawing substituent (EWS) in the benzoyl moiety would accelerate the nucleophilic attack to the carbonyl carbon of the substrate by increasing the electrophilicity of carbonyl carbon and by stabilizing the negatively charged TS at the RDS. Therefore, one might expect a large positive ρ_X value for the attacking process of anionic nucleophiles to the carbonyl carbon of the substrate. However, the negative charge in the TS would be diminished upon the departure of the anionic leaving group ($p\text{-NO}_2\text{-C}_6\text{H}_4\text{O}^-$). Consequently, an EWS in the benzoyl moiety would retard the departure of the leaving group. Therefore, one should have a small ρ_X value due to the opposite substituent effects, if the leaving group departure were involved in the RDS. In fact, much smaller ρ_X values compared

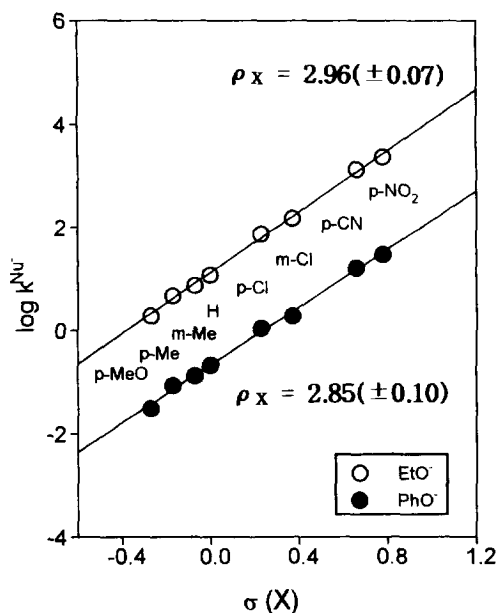


Figure 4. Hammett plots for reactions of *p*-nitrophenyl *X*-substituted benzoates ($X\text{-C}_6\text{H}_4\text{CO-OC}_6\text{H}_4\text{-NO}_2\text{-}p$) with PhO^- and EtO^- in absolute EtOH at $25.0 \pm 0.1^\circ\text{C}$.

with ρ_Y values have been reported for the aminolysis of Y-substituted phenyl X-substituted benzoates ($X-C_6H_4CO-OC_6H_4-Y$),¹⁶ in which leaving group departure is known to be the RDS. However, if the leaving group departure were not involved in the RDS or little advanced in TS of the RDS, one should obtain large ρ_X values, and this is what we observe.

Therefore, the large ρ_X values obtained in the present system clearly support that the present acyl transfer reaction proceeds *via* a stepwise mechanism in which bond formation by the anionic nucleophiles is significantly advanced but bond breaking by the anionic leaving group is little advanced at the TS of the RDS. This is consistent with the preceding argument based on the magnitude of β_{Nuc} and β_{LG} , and the results of better Hammett correlation with σ^0 than with σ^- constants.

EXPERIMENTAL

Materials. - Aryl benzoates ($X-C_6H_4CO-OC_6H_4-Y$) were easily prepared from the reactions of X-substituted benzoyl chloride with Y-substituted phenol in the presence of triethylamine in methylene chloride as reported in literature.¹⁸ Their purity was checked by means of melting points and spectral data such as IR and ¹H NMR characteristics. Phenols and other chemicals used were of the highest quality available (Aldrich) and recrystallized or distilled before use. Absolute ethanol was distilled over magnesium activated by iodine just before use under a nitrogen atmosphere.

Kinetics. - The Kinetic studies were preformed with a Hitachi U-2000 model UV-vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ seconds) or with an Applied Photophysics SX 17MV stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ seconds) equipped with a Neslab RTE-110 model constant temperature circulating bath to keep the temperature of reaction mixture at $25.0 \pm 0.1^\circ C$. The reactions were followed by monitoring the appearance of the leaving phenoxides at a fixed wavelength corresponding to the maximum absorption (λ_{max}) of $Y-C_6H_4O^-$. All the reactions were carried out under pseudo-first-order conditions in which the concentration of nucleophiles was at least 10 times greater than that of the substrate. Generally, five different concentrations of nucleophile solutions were used to obtain second-order rate constants from the slope of the plots of observed rate constants (k_{obs}) versus nucleophile concentrations. However, ten to twelve different concentrations of phenols in constant base (potassium ethoxide) concentration were used to determine pK_a of phenols in a kinetic method. All the solutions were prepared freshly just before use under a nitrogen atmosphere and transferred using Hamilton gas-tight syringes to avoid absorption of CO_2 . Other details in kinetic methods were similar to the ones described previously.^{1a,14}

ACKNOWLEDGEMENT

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