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Reinterpretation of Curved Hammett Plots in Reaction of Nucleophiles with Aryl Benzoates: Change in Rate-Determining Step or Mechanism versus Ground-State Stabilization

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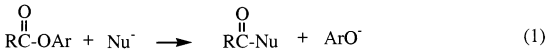
A kinetic study is reported for the reaction of the anionic nucleophiles OH^-, CN^-, and N_3^- with aryl benzoates containing substituents on the benzoyl as well as the aryloxy moiety, in 80 mol % H_2O−20 mol % dimethyl sulfoxide at 25.0 °C. Hammett log k vs σ plots for these systems are consistently nonlinear. However, a possible traditional explanation in terms of a mechanism involving a tetrahedral intermediate with curvature resulting from a change in rate-determining step is considered but rejected. The proposed explanation involves ground-state stabilization through resonance interaction between the benzoyl substituent and the electrophilic carbonyl center in the two-stage mechanism. Accordingly, the data are nicely accommodated on the basis of the Yukawa-Tsuno equation, which gives linear plots for all three nuceophiles. Literature reports of the mechanism of acyl transfer processes are reconsidered in this light.

Introduction

Due to their importance in biological processes as well as in synthetic applications, numerous studies have been performed to investigate the mechanism of acyl transfer processes.[2−12] One aspect of interest is whether nucleophilic attack at the carbonyl center occurs concertedly with leaving group departure (eq 1), or whether reaction occurs via a discrete tetrahedral intermediate (eq 2).



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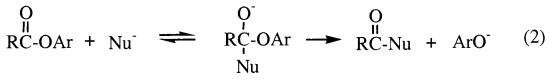

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In ester aminolysis, it is now firmly established that the two-step mechanism obtains, in which the rate-determining step (RDS) is dependent on the relative basicity of the amine and the leaving group.[3−5] Thus the RDS changes from breakdown of the intermediate to its formation as the attacking amine becomes more basic than the leaving group by 4−5 pK_a units.[3−5]

In a series of important studies by Williams and coworkers it was concluded that acyl transfer to aryloxide

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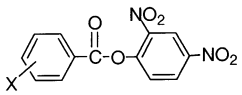
anions occurs through a concerted process.[6] The evidence consisted mainly of the absence of a break (or curvature) in the Brønsted-type plot when the pK_a of the aryloxide nucleophile corresponded to that of the aryloxide leaving group. Moreover, the concerted mechanism has been supported through structure−reactivity correlations reported by Jencks,[7a] Rossi,[7b,c] and Castro,[7d−f] as well as kinetic isotope effect studies of Hengge[8] and Marcus analysis by Guthrie.[9]

However, Buncel et al. argued against a concerted mechanism for acyl transfer to aryloxides, based on Hammett plots exhibiting rather poor correlation with σ (minus) but significantly better correlation with σ^o constants.[10] It was concluded that leaving group departure from a tetrahedral intermediate was little advanced, if at all, in the rate-determining transition state.[10] A similar conclusion supporting a stepwise mechanism has been drawn from kinetic studies of the alkaline hydrolyses of various sulfur and phosphorus esters.[11] Furthermore, we have recently reported the first spectroscopic evidence, along with kinetic evidence, for an addition intermediate in the reaction of a cyclic sulfinate ester with sodium ethoxide in anhydrous ethanol.[12a]

In contrast to the above, analogous mechanistic studies have not been reported as yet for acyl transfer involving various common anionic nucleophiles. In the present work we report the results of studies with OH^-, CN^-, and N_3^-, representing oxygen, carbon, and nitrogen centers, with a series of aryl substituted benzoates. The reaction series **1** comprised the 2,4-dinitrophenyl X-substituted benzoates, while series **2** and **3** are defined as below:



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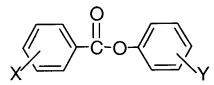
X = 4-MeO (**1a**), 4-Me (**1b**), 3-Me (**1c**), H (**1d**), 4-Cl (**1e**), 3-Cl (**1f**), 4-CN (**1g**), 4-NO_2 (**1h**), 4-Cl-3-NO_2 (**1i**), 3,5-$(NO_2)_2$ (**1j**)



2 or **3**

X = H (**2**) ; X = 3,5-$(NO_2)_2$ (**3**)

Y = 3,4-$(NO_2)_2$ (**a**), 4-NO_2 (**b**), 4-CHO (**c**), 4-CN (**d**), 3-CHO (**e**), 4-$COCH_3$ (**f**), 4-$CO_2CH_2CH_3$ (**g**), 3-$COCH_3$ (**h**) ,4-Cl (**i**), H (**j**), 4-CH_3 (**k**), 4-OCH_3 (**l**).

An unexpected observation ensued, namely that the Hammett plots, log k vs σ, for the three reaction series showed distinct curvature, though representation by two intersecting linear portions could also be made, as indicated in Figure 1.[13] This has prompted us to reexamine systems where curvature (or nonlinearity) in Hammett plots had previously been reported.

Traditionally, curvature in Hammett plots has been analyzed on the basis of either a change in mechanism[14] or a change in RDS.[15] An alternative explanation is presented herein, namely ground-state stabilization arising from electronic (resonance) interaction between the substituent (X) and the carbonyl function.

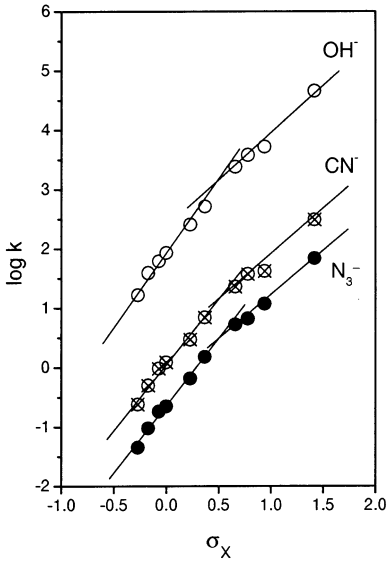


FIGURE 1. Hammett plots for the reactions of 2,4-dinitrophenyl X-substituted benzoates (**1a**−**j**) with OH^-, CN^-, and N_3^- in 80 mol % H_2O−20 mol % DMSO at 25 ± 0.1 °C. The values of σ, σ^-, σ^+, and σ^o constants were taken from: Jones, R. A. Y. *Physical and mechanistic organic chemistry*; Cambridge University Press: Cambridge, 1984; p 65.

Results

All reactions in the present study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obs}) were measured spectrophotometrically for the reactions of X-$C_6H_4CO_2C_6H_4$-Y with the anionic nucleophiles (OH^-, CN^-, and N_3^-) in 80 mol % H_2O−20 mol % dimethyl sulfoxide (DMSO) at 25.0 ± 0.1 °C. The k_{obs} values were determined from the slope of the plot of $\ln(A_\infty - A_t)$ vs time. Generally five different concentrations of nucleophile solutions were used to determine second-order rate constants from the slope of the linear plot of k_{obs} vs nucleophile concentration. Correlation coefficients of the plots were usually higher than 0.9995. It is estimated from replicate runs that the uncertainty in rate constants is less than ±3%. The second-order rate constants determined in this way are summarized in Tables 1 and 2.

Discussion

Curvature of Hammett Plots. The Hammett plots displayed in Figure 1 for reactions of the anionic nucleophiles OH^-, CN^-, and N_3^- with the reaction series **1** show clear evidence of nonlinear behavior. This observation calls for discussion in relation to other systems exhibiting curved Hammett behavior.

(13) Henceforth no differentiation is intended between these alternatives, i.e., curved plot versus two intersecting linear plots; the available evidence does not allow differentiation between these alternatives.

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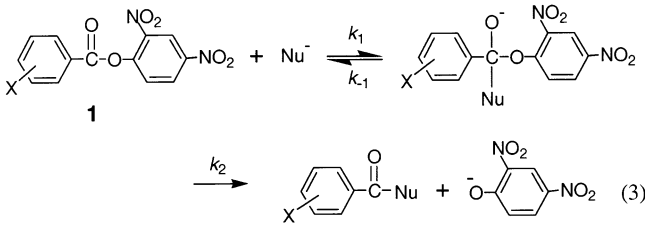
TABLE 1. Summary of Second-Order Rate Constants for Reactions of 2,4-Dinitrophenyl X-Substituted Benzoates (1a−j) with OH^-, CN^-, and N_3^- in 80 mol % H_2O−20 mol % DMSO at 25.0 ± 0.1 °C

X	$k_{OH^-}/M^{-1}\,s^{-1}$	$k_{CN^-}/M^{-1}\,s^{-1}$	$k_{N_3^-}/M^{-1}\,s^{-1}$
4-MeO (**1a**)	16.6 ± 0.09	0.241 ± 0.008	0.0438 ± 0.0006
4-Me (**1b**)	39.2 ± 0.27	0.500 ± 0.014	0.0947 ± 0.0013
3-Me (**1c**)	61.2 ± 1.34	0.964 ± 0.024	0.180 ± 0.003
H (**1d**)	85.9 ± 0.85	1.22 ± 0.01	0.224 ± 0.003
4-Cl (**1e**)	257 ± 2.5	2.95 ± 0.07	0.655 ± 0.010
3-Cl (**1f**)	515 ± 1.9	6.93 ± 0.003	1.53 ± 0.02
4-CN (**1g**)	2380 ± 30	22.9 ± 1.2	5.29 ± 0.14
4-NO_2 (**1h**)	3791 ± 60	37.0 ± 0.9	6.67 ± 0.03
4-Cl-3-NO_2 (**1i**)	5200 ± 150	41.7 ± 1.3	11.7 ± 0.2
3,5-$(NO_2)_2$ (**1j**)	45500 ± 860	310 ± 6	69.1 ± 0.3

The traditional explanation of curvature in Hammett plots considers two types of curvature: concave and convex (i.e., upward and downward curvature, respectively). The former case is ascribed to a change in reaction mechanism and is typified by nucleophilic substitution in benzylic systems where electron-releasing substituents are located on the downward portion of the plot (negative ρ) corresponding to the S_N1 mechanism, which then changes to the S_N2 mechanism for electron-withdrawing substituents found on the upward portion of the plot (positive ρ).[14,15] In contrast, convex curvature would correspond to a change in RDS within a given mechanism, on changing the substituents from electron releasing to electron withdrawing.[14,15] Such a nonlinear Hammett plot has been observed for the reaction of semicarbazide with a series of X-substituted benzaldehydes in weakly acidic solution (pH 3.9), i.e., the Hammett parameter changes from a large (positive) ρ value to a small one as the substituent changes from an electron-donating group (EDG) to a strong electron-withdrawing group (EWG).[16] The nonlinear Hammett plot has been ascribed to a change in the RDS.[16]

On the basis of the above, the apparent downward curvature in the Hammett plots observed in the present system (Figure 1) would, at first sight, correspond to the latter situation, i.e., a two-step mechanism with a change in RDS (eq 3).



Electron-withdrawing substituents will accelerate nucleophilic attack but retard departure of the negatively charged leaving group; one could then expect a change in RDS from formation of the intermediate (k_1 step) to its breakdown (k_2 step) upon substituent change from electron donating to strongly electron withdrawing. This situation evokes the explanation offered by Menger for ester aminolysis in aprotic solvents where the two-step mechanism was inferred.[17]

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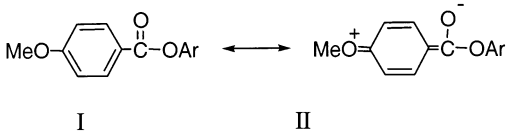
Ground-State Stabilization. However, we propose a different explanation for curvature in our system, other than due to a change in RDS, on the basis of the following arguments. First, the RDS is determined by the ratio of the nucleofugality of the nucleophile and that of the leaving group from an addition intermediate, k_{-1}/k_2. Also, both k_{-1} and k_2 processes would be accelerated by an EDG in the benzoyl moiety but retarded by EWG. Therefore, the k_{-1}/k_2 ratio would be independent of the electronic nature of the substituent X in the benzoyl moiety. In fact, we have recently shown for reactions of 2,4-dinitrophenyl X-substituted benzoates with a series of alicylic secondary amines that the magnitude of the k_{-1}/k_2 ratio is nearly constant upon changing the benzoyl substituent X.[5b] Second, OH^- is expected to be a poorer nucleofuge than the 2,4-dinitrophenoxide ion, based on the large basicity difference between the two anions. Therefore, nucleophilic attack by OH^- to form an addition intermediate should always be the RDS; a change in the RDS upon changing the substituent in the benzoyl moiety is hence unlikely. Third, the position of the break in the Hammett plot occurs at a σ_X value of ca. 0.5 for all three reactions (OH^-, CN^-, and N_3^-), despite the basicity and nucleophilic atom of these nucleophiles being very different.

The origin of the Hammett plot curvature in the present system that we propose is stabilization of the ground state through resonance interaction between the electron-releasing substituent on the benzoyl moiety and the carbonyl functionality as illustrated by resonance structures **I** and **II**. The situation arising from this type



I II

of resonance interaction is appropriately treated through the Yukawa−Tsuno equation,[18] eq 4. The term ($\sigma_X^+ -$

$$\log(k_X/k_H) = \rho_X\{\sigma_X^{\circ} + r(\sigma_X^{+} - \sigma_X^{\circ})\} \qquad (4)$$

σ_X°) is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron donor substituent, while the r value is a parameter characteristic of the given reaction.[18]

As shown in Figure 2, the Yukawa−Tsuno plots are all linear; the r values for the reactions with OH^-, CN^-, and N_3^- are 0.43, 0.47, and 0.54, respectively. When r = 0, eq 4 becomes the Hammett equation, and when r = 1, it becomes the Brown−Okamoto equation. Since the r value in the present system is neither 0 nor 1, the Yukawa−Tsuno equation results in better correlation than the Hammett or Brown−Okamoto equation, in which σ or σ^+ constants alone are used. Hence, we conclude that the break in the Hammett plots shown in

(17) Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3824−3829. ρ values were obtained using Hammett σ constants. Correlations were good, although small improvements were sometimes possible by using σ^+ for acyl-substituted esters and σ^- for esters substituted in the leaving group. For the sake of consistency, σ constants were used throughout.

(18) (a) Tsuno, Y.; Fujio, M. *Adv. Phys. Org. Chem.* **1999**, *32*, 267−385. (b) Tsuno, Y.; Fujio, M. *Chem. Soc. Rev.* **1996**, *25*, 129−139. (c) Yukawa, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 965−970.

TABLE 2. Summary of Second-Order Rate Constants for Alkaline Hydrolyses of Y-Substituted Phenyl X-Substituted Benzoates 2 and 3 (X-$C_6H_4CO_2C_6H_4$-Y) in 80 mol % H_2O−20 mol % DMSO at 25.0 ± 0.1 °C

Y, X = H	pK_a (Y-C_6H_4OH)[a]	k_{OH^-}/M^{-1} s^{-1}	Y, X = 3,5-$(NO_2)_2$	k_{OH^-}/M^{-1} s^{-1}
3,4-$(NO_2)_2$ (**2a**)	5.42	98.9 ± 1.7	3,4-$(NO_2)_2$ (**3a**)	28100 ± 500
4-NO_2 (**2b**)	7.14	13.4 ± 0.11	4-NO_2 (**3b**)	4890 ± 220
4-CHO (**2c**)	7.66	4.72 ± 0.05	4-CHO (**3c**)	1810 ± 14
4-CN (**2d**)	7.95	7.95 ± 0.11	4-CN (**3d**)	2710 ± 44
3-CHO (**2e**)	8.00	1.93 ± 0.03	3-CHO (**3e**)	1480 ± 22
4-$COCH_3$ (**2f**)	8.05	3.27 ± 0.01	4-$COCH_3$ (**3f**)	1500 ± 11
4-$CO_2CH_2CH_3$ (**2g**)	8.50	3.11 ± 0.04	4-$CO_2CH_2CH_3$ (**3g**)	1470 ± 35
3-$COCH_3$ (**2h**)	9.19	1.80 ± 0.04	3-$COCH_3$ (**3h**)	852 ± 23
4-Cl (**2i**)	9.38	1.35 ± 0.07	4-Cl (**3i**)	572 ± 23
H (**2j**)	9.95	0.449 ± 0.012	H (**3j**)	362 ± 9
4-CH_3 (**2k**)	10.19	0.316 ± 0.005	4-CH_3 (**3k**)	165 ± 5
4-OCH_3 (**2l**)	10.20	0.389 ± 0.003	4-OCH_3 (**3l**)	259 ± 4

[a] pK_a values in H_2O at 25.0 °C taken from: Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry*, 2nd ed.; Sober, H. A., Ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1970; p J-195.

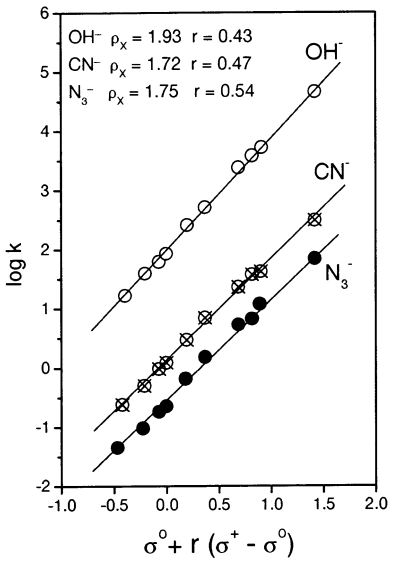


FIGURE 2. Yukawa−Tsuno plots for reactions of 2,4-dinitrophenyl X-substituted benzoates (**1a**−**j**) with OH^-, CN^-, and N_3^- in 80 mol % H_2O−20 mol % DMSO at 25 ± 0.1 °C.

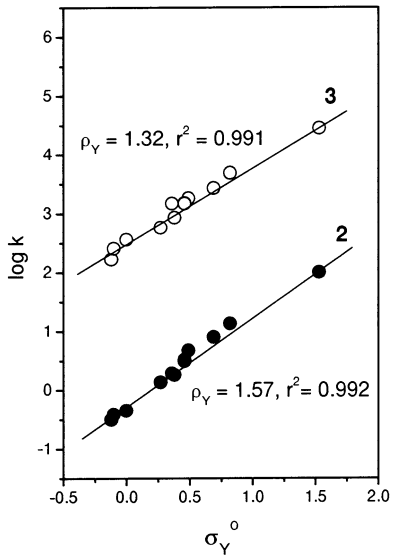


FIGURE 3. Hammett plots for alkaline hydrolyses of Y-substituted phenyl benzoates (**2a**−**l**) and 3,5-dinitro benzoates (**3a**−**l**) in 80 mol % H_2O−20 mol % DMSO at 25 ± 0.1 °C.

Figure 1 is not caused by a change in RDS but that it arises from resonance stabilization of the ground state of the substrates with π-electron donor substituents in the benzoyl moiety as illustrated by **I** ↔ **II**.

Effect of Leaving Group Substituents on Rate and Mechanism. As a test of the preceding argument of a change in RDS upon changing the substituent in the benzoyl moiety, the study was extended to **2a**−**l** and **3a**−**l**. Second-order rate constants (k_{OH^-}) for the alkaline hydrolyses of **2a**−**l** and **3a**−**l** are presented in Table 2. As shown in Table 2, the reactivity of **2a**−**l** toward OH^- ion increases as the leaving group substituent Y changes from EDG to EWG, i.e., k_{OH^-} increases first moderately from 0.389 M^{-1} s^{-1} to 0.449 M^{-1} s^{-1} and then greatly to 98.9 M^{-1} s^{-1} as Y changes from 4-MeO to H and 3,4-$(NO_2)_2$, respectively. A similar result is found in Table 2 for the reaction of **3a**−**l** with OH^-, although in each case **3** is much more reactive than the corresponding **2**.

The effect of leaving group substituents on rates is illustrated in Figure 3, which shows that the plots log k_{OH^-} vs σ_Y^o exhibit good linearity. However, poorer correlation results when σ_Y^- constants are used for the reactions of both **2a**−**l** and **3a**−**l** (figure not shown). If leaving group departure were involved in the RDS, the oxygen atom of the leaving aryloxide in the transition state should bear partial negative charge, which can be delocalized on the substituent through resonance interaction. In this case, use of σ_Y^- constants should give the best correlation. In fact, for ester aminolyses, in which the RDS was suggested to be the k_2 step, σ_Y^- constants have given the best correlation and a large ρ_Y value.[3] For example, for the reaction of pyrrolidine with Y-substituted phenyl acetates and benzoates, ρ_Y has been determined to be 4.03 and 3.67, respectively, using σ_Y^- constants.[19] However, in the present study, use of σ_Y^- constants results in poorer Hammett correlation than with σ_Y^o constants, even for the reactions of **3a**−**l** in which the RDS was considered to be the k_2 step, based on the nonlinear Hammett plots shown in Figure 1 as mentioned previously. The fact that the σ_Y^o substituent constants give better correlation than σ_Y^- constants implies that direct resonance interactions between the substituents Y in the leaving group and the reaction

(19) Calculated using the kinetic data in ref 17 for pyrrolidinolyses of Y-substituted phenyl acetates and benzoates performed in CH_3CN at 25 °C.

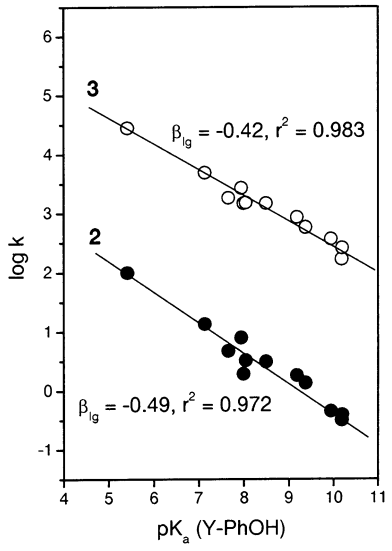


FIGURE 4. Brønsted-type plots for alkaline hydrolyses of Y-substituted phenyl benzoates (**2a**−**l**) and 3,5-dinitro benzoates (**3a**−**l**) in 80 mol % H_2O−20 mol % DMSO at 25 ± 0.1 °C.

center are not occurring in the transition state. This indicates that the C−OAr bond remains essentially intact and the phenolic oxygen does not bear negative charge in the transition state for the alkaline hydrolyses of both **2a**−**l** and **3a**−**l**.

The degree of leaving group expulsion can also be estimated from the magnitude of β_{lg} values. Figure 4 shows Brønsted-type plots for the reactions of **2a**−**l** and **3a**−**l** which exhibit rather small β_{lg} values (i.e., −0.49 ± 0.04 and −0.42 ± 0.03).[20] Similary, small β_{lg} values have often been observed for reactions involving nucleophilic attack to form an addition intermediate as the RDS (e.g., β_{lg} = −0.35 for alkaline hydrolyses of aryl acetates[21a,b] and cinnamates in H_2O[21c] and β_{lg} = −0.3 ± 0.1 for aminolyses of aryl acetates and aryl phenyl carbonates[3]). However, significantly larger β_{lg} values (−1.0 ± 0.2) have been reported for reactions involving leaving group expulsion as the RDS (e.g., aminolysis of aryl acetates, benzoates, etc.).[3,17,21] Accordingly, the small β_{lg} value obtained in the present system suggests that the reactions of both **2a**−**l** and **3a**−**l** proceed through an addition intermediate in which bond formation to the nucleophile is well advanced and bond rupture to the leaving group has proceeded to a negligible extent in the transition state.

Conclusions

We have shown in the present study that the downward-curved Hammett plot obtained in the reaction of OH^-, CN^-, and N_3^- nucleophiles with benzoyl esters, has as its origin ground-state stabilization, rather than the traditional explanation of a change in RDS in a two-step mechanism involving a tetrahedral intermediate. The generality in the nucleophilic atom, represented by OH^-, CN^-, and N_3^-, is rather noteworthy.

We note that past studies of acyl transfer processes may bear re-interpretation through the Yukawa−Tsuno equation. In fact, the Yukawa−Tsuno equation has been found to give better correlation than the Hammett or Brown−Okamoto equation for several studies reported previously: (1) Kirsch et al. have reported that the kinetic data for alkaline hydrolyses of aryl benzoates exhibit linear Hammett correlation.[22] However, better linearity is obtained when the kinetic data were treated with the Yukawa−Tsuno equation, with r values of 0.29−0.56. (2) We have reported that the Hammett plots for reactions of 4-nitrophenyl-substituted benzoates with HO^- and 4-chlorophenoxide are curved.[12c] However, the corresponding Yukawa−Tsuno plots are linear with r values of 0.45 and 0.57 for reactions with HO^- and 4-chlorophenoxide, respectively. (3) Menger et al. have obtained Hammett ρ values using σ constants for aminolyses of aryl-substituted benzoates, although small improvement was possible by using σ^+constants for the benzoyl substituent.[17] However, much better correlation follows when the ($\sigma^+ - \sigma^o$) term is used with r values of 0.37−0.94. (4) The kinetic data for the aminolysis of 2,4-dinitrophenyl-substituted benzoates reported by Um et al. have resulted in linear Hammett plots with σ^+constants for weakly basic amines and with σ constants for strongly basic amines (p$K_a \geq 9.85$).[5b] Again the use of the Yukawa−Tsuno equation gives much better correlation with r values of 0.70−1.13 for weakly basic amines and 0.60−0.61 for strongly basic amines.

Experimental Section

Materials. Aryl benzoates (X-$C_6H_4CO_2C_6H_4$-Y) were readily prepared from the reaction of X-substituted benzoyl chloride with Y-substituted phenol in the presence of triethylamine in anhydrous ether as reported in the literature.[17,22,23] Their purity was checked by means of melting points and spectral data such as IR and ^{1}H NMR characteristics. DMSO was distilled over calcium hydride at a reduced pressure (bp 64−66 °C at 6−7 mmHg) and stored under nitrogen. Doubly glass distilled water was further boiled and cooled under nitrogen just before use. Other chemicals used were of the highest quality available.

Kinetics. The kinetic studies were performed with a UV−vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ s) or with a stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) equipped with a constant temperature circulating bath to keep the temperature of the reaction mixture at 25 ± 0.1 °C. All the kinetics were performed in 80 mol % H_2O−20 mol % DMSO to eliminate a solubility problem. The reactions were followed by monitoring the appearance of the leaving phenoxide 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 50 times greater than that of the substrates. The nucleophile stock solution of ca. 0.2 M was

(20) The correlation coefficient is also poorer for the plots in Figure 4 than for those in Figure 3, supporting the argument that σ^- constants are not suitable parameters in the present system.

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prepared in a 25.0-mL volumetric flask just before use and transferred by Hamilton gastight syringes.

Typically, the reaction was initiated by adding 5 μL of ca. 0.02 M substrate solution to a 10-mm quartz cuvette containing 2.50 mL of the nucleophile stock solution. Generally the nucleophile concentration was varied over the range (1−100) $\times 10^{-3}$ M, while the substrate concentration was 4×10^{-5} M. Pseudo-first-order rate constants (k_{obs}) were calculated from the following equation, $\ln(A_\infty - A_t) = -k_{obs}t + C$. Usually, five different nucleophile concentrations were employed and replicate values of k_{obs} were determined to obtain the second-order rate constants from the slope of the linear plot of k_{obs} versus nucleophile concentrations.

Product Analysis. The Y-substituted phenoxide was identified as one of the products by comparison of the UV−vis spectrum at the end of the reaction with the authentic sample under the kinetic experimental conditions. The other products, X-substituted benzoyl cyanides and azides, were hydrolyzed to give the corresponding benzoate under the kinetic conditions.

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Supporting Information Available: Tables of kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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