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Effect of Acyl Substituents on the Reaction Mechanism for Aminolyses of 4-Nitrophenyl X-Substituted Benzoates

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Second-order rate constants (k_N) have been measured spectrophotometrically for the reaction of 4-nitrophenyl X-substituted benzoates with a series of alicyclic secondary amines in H_2O containing 20 mol % dimethyl sulfoxide at 25.0 °C. The magnitude of the k_N values increases with increasing the basicity of amines and with increasing the electron-withdrawing ability of the acyl substituent X. The Hammett plots obtained are not linear but show a break or curvature as the acyl substituent X becomes electron withdrawing for all the amines studied, while the Brønsted-type plots are linear with large β_{nuc} values for all the substrates investigated. The nonlinear Hammett plots suggest a change in the rate-determining step upon changing the acyl substituent X, whereas the linear Brønsted-type plots indicate that the rate-determining step does not change upon changing amine basicity. The Yukawa−Tsuno plots obtained are also linear with positive ρ_X and large r values, suggesting that the nonlinear Hammett plots are not due to a change in the rate-determining step upon changing the acyl substituent X, but due to resonance demand of the π-electron donor substituent on the acyl moiety. The magnitude of the ρ_X and β_{nuc} values increases with increasing the basicity of amines and with increasing the electron-withdrawing ability of the acyl substituent X, respectively, while that of the r values decreases with increasing ρ_X values and amine basicity.

Introduction

Reactions of nucleophiles with carbonyl compounds have been intensively studied due to the interest in chemistry and in biochemistry. The reaction of carboxylic acid derivatives with amines has been suggested to proceed through a stepwise mechanism with an addition intermediate or through a concerted mechanism without an intermediate.[1−5] The common and probably the most popular probes for the determination of reaction mechanism are linear free energy relationships of various kinds, e.g., Hammett and Brønsted correlation.[6−8] Brønsted-type plots have been obtained that are linear for reactions of carboxylic esters with a series of structurally similar amines when the nucleofugality of the leaving group is relatively poor.[7−9] However, aminolyses of carboxylic esters with a good leaving group have often shown a break or a curvature in Brønsted-type plots from a large slope ($\beta_{nuc} = 0.8 \pm 0.2$) to a small one ($\beta_{nuc} = 0.2 \pm 0.1$) as the basicity of amines increases.[7−9] Such a break or a curvature in Brønsted-type plots has been attributed to a change in the rate-determining step (RDS) of a multistep reaction.[7−9]

The pK_a value at the center of the curvature in the Brønsted-type plot has been defined pK_a^0.[10] An amine whose pK_a value is pK_a^0 has the same leaving group ability from the addition intermediate as the leaving group of the substrate, i.e., a change in the RDS of a stepwise reaction occurs at pK_a^0. It has been well-known that the position of the RDS change (pK_a^0) is strongly dependent on the basicity of the leaving group and the attacking amine, i.e., the RDS changes from the rate-determining breakdown of the addition intermediate to the rate-determining formation of the intermediate when the attacking amine becomes more basic than the leaving group by 4−5 pK_a units.[11] However, the effect of the acyl

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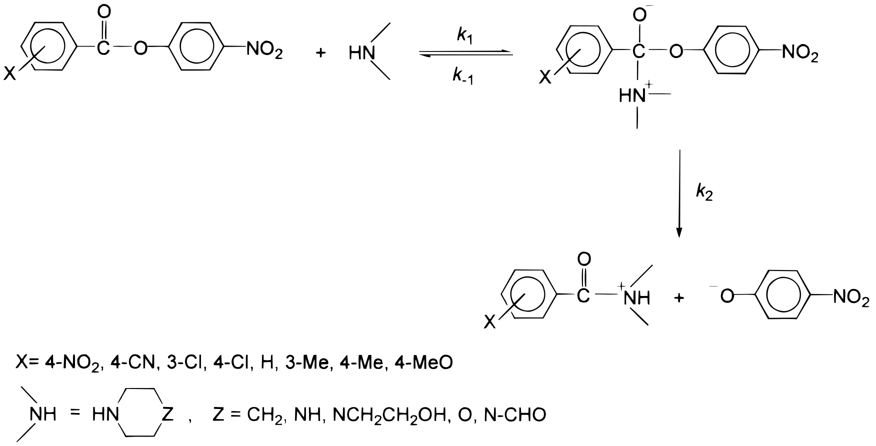
Scheme 1



group (the nonleaving group of the substrate) on pK_a^0 is controversial. Castro et al. have reported that the pK_a^0 values are 7.3 and 7.8 for pyridinolyses of 2,4-dinitrophenyl acetate and 2,4-dinitrophenyl methyl carbonate, respectively.[12] Besides, in the pyridinolyses of 2,4-dinitrophenyl X-substituted benzoates (X = 4-NO_2, 4-Cl, and H), the Brønsted-type plot is linear when X = 4-NO_2 and 4-Cl but curved when X = H.[13] Therefore, Castro et al. have concluded that an electron-withdrawing substituent in the acyl moiety causes an increase in the pK_a^0 value.[12,13] A similar conclusion has been drawn by Jencks et al. from the reaction of 2,4-dinitrophenyl aryl carbonates with quinuclidines.[10] However, we have recently suggested that the pK_a^0 value is not influenced by the electronic nature of the acyl substituent for the reaction of 2,4-dinitrophenyl X-substituted benzoates with amines.[9a]

In this study, we expand our work on the reaction of 4-nitrophenyl X-substituted benzoates with a series of alicyclic amines as shown in Scheme 1. We report the effect of acyl substituents on the reaction mechanism using linear free energy relationships including the Yukawa−Tsuno equation, which has never been employed in aminolyses of carboxylic esters.

Results

The kinetic study was performed spectrophotometrically, and all the reactions in the present study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obs}) were obtained from the well-known equation: $\ln(A_\infty - A_t) = -k_{obs}t + c$. The correlation coefficients of the linear regressions were always higher than 0.9995. Generally, five different concentrations of amine solutions were used to calculate second-order rate constants (k_N). The plots of k_{obs} vs amine concentration are linear and pass through the origin, indicating that there is no general base catalysis by a second amine molecule, and the contribution by H_2O or HO^- ion from the solvolysis of amine to k_{obs} is negligible. Therefore, a rate equation can be derived, as eq 1, where [S] and [>NH] represent the concentration of the substrate and the amine used, respectively. Under pseudo-first-order conditions, eq 1 can be simplified into eqs 2 and 3. It is estimated from replicate runs that the uncertainty in any particular measured rate constant is less than ±3%. The second-order rate constants (k_N) obtained in this way are summarized in Table 1 and illustrated graphically in Figures 1−3.

Table 1. Summary of Apparent Second-order Rate Constant k_N ($M^{-1}s^{-1}$) for Reactions of 4-Nitrophenyl X-Substituted Benzoates ($X\text{-}C_6H_4CO\text{-}OC_6H_4\text{-}4\text{-}NO_2$) with a Series of Alicyclic Secondary Amines, $Z(CH_2CH_2)_2NH$, in H_2O Containing 20 Mol % DMSO at 25.0 °C[a]

Z	NCHO	O	NCH_2CH_2OH	NH	CH_2
	k_N($M^{-1}s^{-1}$)				
pK_a	7.98	8.65	9.38	9.85	11.02
X = 4-MeO	0.00404	0.0365	0.0776	0.344	1.95
X = 4-Me	0.00707	0.0659	0.147	0.629	3.68
X = 3-Me	0.0082	0.081	0.172	0.79	4.56
X = H	0.0100	0.0876	0.195	0.851	5.94
X = 4-Cl	0.0126	0.111	0.267	1.14	8.14
X = 3-Cl	0.0165	0.15	0.396	1.67	12.8
X = 4-CN	0.0196	0.179	0.462	2.06	18.7
X = 4-NO_2	0.0204	0.201	0.487	2.30	21.0

[a] p*K*a values taken from ref 11c.

$$\text{rate} = k_1k_2[\text{S}]\,[>\text{NH}]/(k_{-1} + k_2) \tag{1}$$

$$\text{rate} = k_{obs}[\text{S}], \quad \text{where} \quad k_{obs} = k_1k_2[>\text{NH}]/(k_{-1} + k_2) \tag{2}$$

$$k_N = k_1k_2/(k_{-1} + k_2) \tag{3}$$

Discussion

Effect of Acyl Substituents on Rate. As shown in Table 1, second-order rate constants (k_N) increase with increasing amine basicity and with increasing electron-withdrawing ability of the acyl substituent X. The effect of substituent X on the reaction rate is graphically demonstrated in Figure 1, which shows nonlinear Hammett plots for all the amines studied. Since such a nonlinear Hammett plot has been understood to indicate a change in the RDS of a multistep reaction, one can suggest that the RDS of the present aminolysis reactions changes upon changing the acyl substituent X.

It has generally been suggested that a large ρ_X value is obtained for ester aminolyses whose RDS is the nucleophilic attack by an amine to form an addition intermediate (the k_1 step in Scheme 1), since the nucleo-

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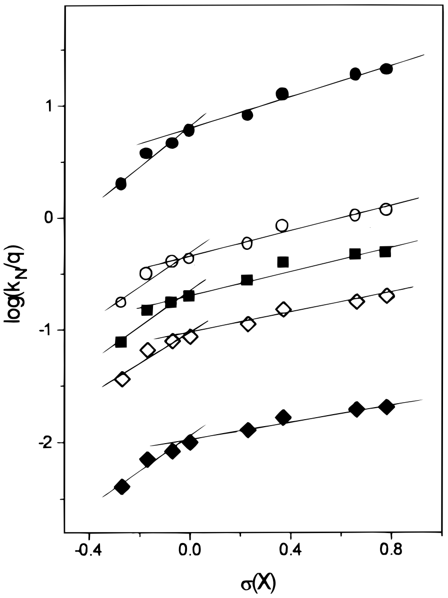

Figure 1. Hammett plots for reactions of 4-nitrophenyl X-substituted benzoates with a series of alicyclic secondary amines, $Z(CH_2CH_2)_2NH$, in H_2O containing 20 mol % DMSO at 25.0 °C. Z = CH_2 (●), NH (○), NCH_2CH_2OH (■), O (◇), NCHO (◆).

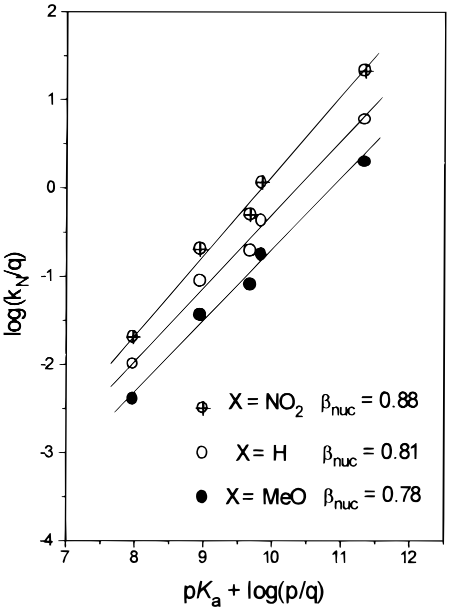

Figure 2. Brønsted-type plots for reactions of 4-nitrophenyl X-substituted benzoates with a series of alicyclic secondary amines in H_2O containing 20 mol % DMSO at 25.0 °C.

philic attack would be accelerated by an electron-withdrawing substituent but retarded by an electron-donating one.[9,14,15] However, on the contrary, the magnitude of ρ_X values has been suggested to be small for ester aminolyses whose RDS is the breakdown of the addition intermediate to products (the k_2 step in Scheme 1) due to the opposite substituent effect on the reaction rate,

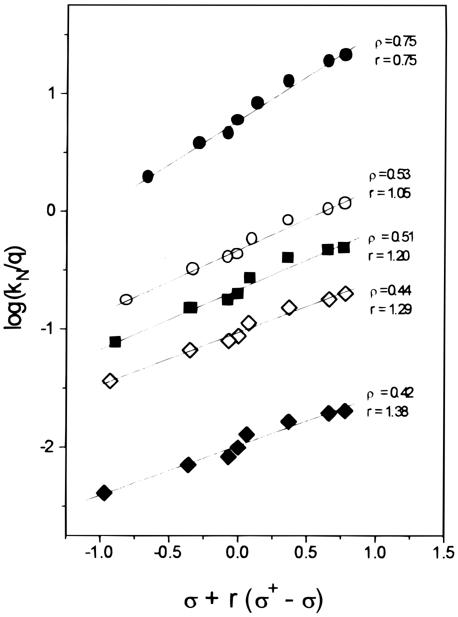

Figure 3. Yukawa–Tsuno plots for reaction of 4-nitrophenyl X-substituted benzoates with a series of alicyclic secondary amines, $Z(CH_2CH_2)_2NH$, in H_2O containing 20 mol % DMSO at 25.0 °C. Z = CH_2 (●), NH (○), NCH_2CH_2OH (■), O (◇), NCHO (◆).

i.e., an electron-withdrawing substituent X would accelerate nucleophilic attack but retard leaving group departure from the addition intermediate, while an electron-donating substituent X would delay nucleophilic attack but enhance leaving group departure.[9,14,15]

As shown in Figure 1, the magnitude of the slopes of the curved Hammett plots is larger for the electron-donating substituents than for the electron-withdrawing ones for all the amines investigated. Therefore, one may consider that the RDS in the present aminolysis reactions shifts from the k_1 step to the k_2 step as the acyl substituent X varies from electron-donating to electron-withdrawing group.

The effect of the acyl substituent on pK_a^0 has been studied by several investigators. Jencks et al. have found that the magnitude of the k_{-1} and k_2 values is dependent on the electronic nature of the substituent X of the aryl moiety in the reaction of aryl 3,4-dinitrophenyl carbonates with quinuclidines, i.e., a plot of pK_a^0 against the basicity of the aryl moiety gives a straight line with a slope ca. −0.4.[10] A similar result has been reported by Castro et al. in the pyridinolyses of 2,4-dinitrophenyl acetate and 2,4-dinitrophenyl methyl carbonate.[12] They found a larger pK_a^0 value (7.8 compared with 7.3) for the latter reactions, and attributed the increase in the pK_a^0 value to the larger electron-withdrawing inductive effect of CH_3O ($\sigma_I = 0.25$) compared with that of CH_3 group ($\sigma_I = -0.05$) in the tetrahedral intermediate.[12,16] The effect of the acyl substituent on pK_a^0 has also been investigated in pyridinolyses of 2,4-dinitrophenyl X-substituted benzoates (X = 4-NO_2, 4-Cl, and H) in aqueous ethanol. Castro et al. obtained linear Brønsted-type plots when the acyl substituent X was electron withdrawing, such as 4-NO_2 or 4-Cl, but a curved one when the substituent X was H.[13] Accordingly, it has been concluded that an electron-withdrawing substituent of the acyl moiety

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Scheme 2

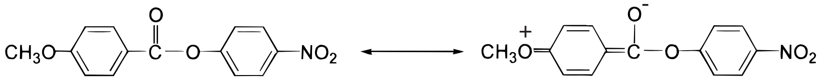

Table 2. Summary of β_{nuc} Values for Reactions of 4-Nitrophenyl X-Substituted Benzoates ($X-C_6H_4CO-OC_6H_4-4-NO_2$) with a Series of Alicyclic Secondary Amines in H_2O Containing 20 Mol % DMSO at 25.0 °C[a]

X	4-MeO	4-Me	3-Me	H	4-Cl	3-Cl	4-CN	4-NO$_2$
σ_X	−0.27	−0.17	−0.07	0	0.23	0.37	0.66	0.78
β_{nuc}	0.78	0.79	0.80	0.81	0.82	0.85	0.87	0.88

[a] σ_X values taken from ref 21.

Table 3. Summary of ρ_X and *r* Values for Reactions of 4-Nitrophenyl X-Substituted Benzoates ($X-C_6H_4CO-OC_6H_4-4-NO_2$) with a Series of Alicyclic Secondary Amines, $Z(CH_2CH_2)_2NH$, in H_2O Containing 20 Mol % DMSO at 25.0 °C[a]

Z	CH$_2$	NH	NCH$_2$CH$_2$OH	O	NCHO
pK_a	11.02	9.85	9.38	8.65	7.98
ρ_X	0.75	0.54	0.51	0.44	0.42
r	0.75	1.05	1.20	1.29	1.38

[a] pK_a data taken from ref 11c.

increases the pK_a^0 value.[10,12,13] In the present study, the Hammett plots in Figure 1 are linear if one exclude the points for the electron-donating substituents (e.g., 4-CH_3 and 4-CH_3O). Therefore, the nonlinear Hammett plots in Figure 1 seem to be consistent with the conclusion drawn by Jencks and Castro that the electronic nature of the acyl substituent influences the pK_a^0 value in aminolysis reactions.[10,12,13]

Effect of Amine Basicity on Rate. Figure 2 illustrates the effect of amine basicity on reaction rate. The Brønsted-type plots are linear, indicating that the aminolyses of these substrates proceed through the same mechanism regardless of the electronic nature of the acyl substituent X. It is also shown in Figure 2 and Table 2 that the slope of the straight line (β_{nuc}) increases as the acyl substituent X changes from an electron-donating to an electron-withdrawing group: 0.78 for X = 4-MeO to 0.81 and 0.88 for X = H and 4-NO$_2$, respectively. The magnitude of the β_{nuc} value has been frequently used as a measure to determine the RDS in various aminolysis reactions. Large β_{nuc} values (0.8 ± 0.2) have been generally obtained for aminolysis reactions whose RDS is the breakdown of the tetrahedral addition intermediate to products, while small β_{nuc} values (0.2 ± 0.1) have been obtained for the aminolysis reactions whose RDS is the formation of the addition intermediate.[7−12] Since the magnitude of β_{nuc} values is obtained to be 0.78−0.88, the RDS in the present aminolysis reactions is considered to be the k_2 step in Scheme 1. If a change in the RDS occurred as the acyl substituent X changes from electron-withdrawing to electron-donating groups as discussed in the preceding section, the magnitude of β_{nuc} values should have been reduced to ca. 0.2 ± 0.1. As shown in Table 2, the magnitude of β_{nuc} values decreases with decreasing σ_X constants of the acyl substituent X, i.e., $\beta_{nuc} = 0.096\sigma_X + 0.81$. However, to get a β_{nuc} value of 0.2, the σ_X value should be −6.4, which is practically impossible. Therefore, the electronic nature of the acyl substituents in the present system would not influence the pK_a^0 value. This argument is consistent with our recent report that the magnitude of the k_{-1}/k_2 values is nearly constant upon changing the acyl substituent X from a strong electron-donating group to a strong electron-withdrawing one for aminolyses of 2,4-dinitrophenyl X-substituted benzoates.[9a]

Clearly, there is inconsistency between the conclusion drawn from the nonlinear Hammett plots in Figure 1 and the conclusion based on the linear Brønsted-type plots with large β_{nuc} values in Figure 2. Possible reasons for the inconsistencies are discussed below.

Origin of the Nonlinear Hammett Plots: Unusual Ground-state Stabilization. A careful examination of Figure 1 reveals that two points (X = 4-CH_3O and 4-CH_3) deviate negatively from linearity. Since through-conjugation is possible for these substituents, another parameter is necessary as in the Yukawa−Tsuno eq 4. The term ($\sigma^+ - \sigma$) is the resonance substituent constant measuring the capability for π-delocalization of the π-electron donor substituent, while the *r* value is a parameter characteristic for the given reaction, measuring the extent of resonance demand.

$$\log k/k_0 = \rho[\sigma + r(\sigma^+ - \sigma)] \qquad (4)$$

In Figure 3, the Yukawa−Tsuno plots for the present aminolysis reactions are illustrated. Good linearity is seen for all the amines studied. The *r* values in Figure 3 have been calculated to be in the range of 0.75−1.38. 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 are used alone. This accounts clearly for the nonlinear Hammett plots in Figure 1.

Equation 4 has been applied to mostly benzylic solvolyses, in which a positive charge, which can be delocalized by the π-system of the ring, is generated.[17] Therefore, negative ρ values have usually been obtained for the reactions in which the Yukawa−Tsuno equation was applied.[17] Interestingly, as shown in Figure 3, the ρ_X values are positive. Such a positive ρ_X value in Yukawa−Tsuno plots is quite unusual and suggests that the ground-state stabilization by resonance as shown in Scheme 2 is significant for the present system.

In Table 3, the ρ_X and *r* values are summarized. The ρ_X values increase but the *r* values decrease as the amine basicity increases. The magnitude of the ρ_X values has been suggested to represent relative charge transfer from the nucleophile to the acyl moiety or the degree of rehybridization of the acyl moiety in the transition state. Therefore, the increasing ρ_X value with increasing amine basicity indicates that the degree of charge transfer or rehybridization of the acyl moiety becomes more significant for the more basic amine. This is reasonable since the electron-donating ability of a base is proportional to its basicity: the degree of charge transfer or rehybrid-

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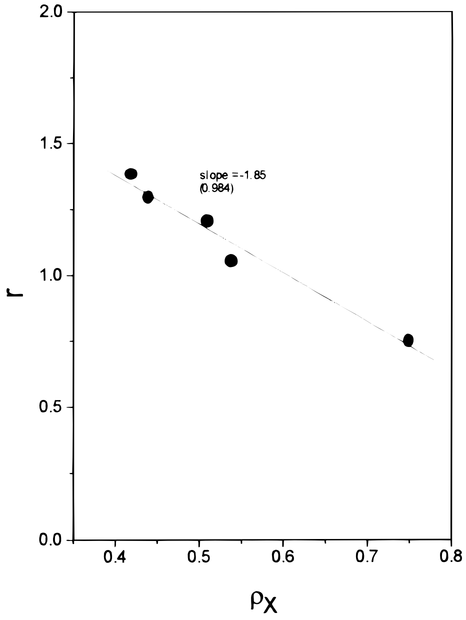

Figure 4. Plot showing dependence of the *r* value on the ρ_X value for reaction of 4-nitrophenyl X-substituted benzoates with a series of alicyclic secondary amines in H_2O containing 20 mol % DMSO at 25.0 °C.

ization of the acyl moiety should be more significant for the more basic amine.

It has been generally known that there is no correlation between the magnitude of ρ_X and *r* values.[17,18] However, interestingly, the magnitude of the *r* values in the present system increases linearly with decreasing ρ_X values as shown in Table 3 and Figure 4. The slope of the linear plot of *r* vs ρ_X has been calculated to be −1.85 with a relatively good correlation coefficient (0.984). Since the *r* value in eq 1 represents the extent of resonance demand, it may be suggested that resonance demand increases linearly with decreasing the ρ_X value in the present system.

Based on the above argument, the nonlinear Hammett plots in Figure 1 clearly are not due to a change in the RDS upon changing the acyl substituent X. Instead, large resonance demand in the ground state is considered to be responsible for the nonlinearity in Figure 1. Therefore, one can conclude that the Yukawa−Tsuno equation is more suitable than the Hammett or Brown−Okamoto equations to investigate the effect of acyl substituents on the reaction mechanism in the present system.

Conclusions

The present study has allowed us to conclude the following. (1) The nonlinear Hammett plots obtained for all the amines studied suggest a change in the reaction mechanism or the RDS. (2) However, the linear Brønsted-type plots obtained for all the substrates with β_{nuc} values of 0.8 ± 0.1 indicate that the present aminolyses proceed through the same mechanism, and the RDS is the breakdown of the addition intermediate to the products. (3) The Yukawa−Tsuno plots are linear with positive ρ_X and large *r* values, implying that ground-state stabilization by through-conjugation of the π-electron donor substituents on the acyl moiety of the substrate is significant. (4) The nonlinear Hammett plots are not due to a change in the RDS but arise from large resonance demand of the π-electron donor substituents on the acyl moiety. (5) The magnitude of the ρ_X and β_{nuc} values increases with increasing amine basicity and with increasing electron-withdrawing ability of the acyl substituent X, respectively. (6) The magnitude of the *r* value decreases with increasing ρ_X values and with increasing the basicity of amines used in the present study.

Experimental Section

Materials. 4-Nitrophenyl X-substituted benzoates were easily prepared from the reaction of X-substituted benzoyl chloride with 4-nitrophenol in the presence of triethylamine in methylene chloride.[19] Their purity was checked by means of melting points and spectral data such as IR and ^{1}H NMR characteristics. Other chemicals used, including secondary alicyclic amines, were of the highest quality available. The reaction medium was H_2O containing 20 mol % dimethyl sulfoxide (DMSO) in order to eliminate solubility problems. 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.

Kinetics. The kinetic study was performed with a Hitachi U-2000 model UV−vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ s) or with an Applied photophysics SX-17 MV stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) equipped with a Neslab RTE-110 constant temperature circulating bath to keep the reaction mixture at 25.0 ± 0.1 °C. The amine stock solution of ca. 0.2 M was prepared in a 25.0 mL volumetric flask under nitrogen by adding 2 equiv of amine to 1 equiv of standardized HCl solution in order to obtain a self-buffered solution. All the solutions were transferred by Hamilton gastight syringes. The reactions were followed by monitoring the appearance of the leaving 4-nitrophenoxide ion at 410 nm. All the reactions were carried out under pseudo-first-order conditions in which the amine concentrations were at least 20 times greater than the substrate concentration.

Typically, reaction was initiated by adding 5 μL of a 0.02 M solution of 4-nitrophenyl-substituted benzoate in acetonitrile by syringe to a 10-mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of solvent and aliquot of the amine stock solution. Generally, the amine concentration was varied over the range $(2{-}50) \times 10^{-3}$ M, while the substrate concentration was 4×10^{-5} M. Pseudo-first-order rate constant(k_{obs}) were calculated from the well-known equation, $\ln(A_\infty - A_t) = -k_{\mathrm{obs}}t + C$. The plots of $\ln(A_\infty - A_t)$ vs time were linear over ca. 90% reaction. Usually, five different amine concentrations were employed and replicate values of k_{obs} were determined to obtain the second-order rate constants (k_N) from the slope of linear plots of k_{obs} versus amine concentrations.

Product Analysis. One of the reaction products (4-benzoyl-1-piperazinecarboxaldehyde, 83−84 °C)[20] was anaylzed by HPLC using a Waters 600 liquid chromatograph equipped with a Waters 996 Photodiode Array detector, an Rheodyne 7725i manual injector and a column of Nova-Pak C18 60 Å (4 μm) (3.9 × 150 mm length). The flow rate was 1 mL/min, and the eluent was 50% MeCN in MeOH (v/v). Quantitative analysis was performed by comparison of the HPLC peak area of the reaction mixture with that of the authentic sample at 230 nm.

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