

A Kinetic Study for the Reaction of 2,4-Dinitrophenyl Benzoate with Secondary Cyclic Amines

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Apparent second-order rate constants (k_{app}) have been measured spectrophotometrically for the reaction of 2,4-dinitrophenyl benzoate (DNPB) with 6 secondary cyclic amines in H₂O containing 20 mole% DMSO at 25.0 ± 0.1 °C. The Brønsted-type plot (log k_{app} vs. p*K*_a) shows a break at p*K*_a near 9.1, e.g. two straight lines with β_{app} values of 0.67 and 0.44 for the low basic (p*K*_a < 9.1) and the highly basic (p*K*_a > 9.1) amines, respectively. Using an estimated k_2 value of 3 × 10⁹ sec⁻¹, all the other microconstants (k_1 , k_{-1} and K) involved in the present aminolysis have been calculated. The k_{-1} value decreases with increasing the basicity of amines while k_1 and K values increase with increasing the amine basicity, as expected. Good linear Brønsted-type plots have been obtained for these microconstants of the present aminolysis of DNPB. The magnitudes of the slope of the Brønsted-type plots, k_1 and k_{-1} have been calculated to be 0.43 and -0.24, respectively, indicating the k_{-1} step is about two folds less sensitive than the k_1 step to the amine basicity. The K value has been calculated to be 0.66, which appears to be much smaller than the one for other aminolyses showing general base catalysis. The small K value has been attributed to the absence of general base catalysis in the present aminolysis of DNPB.

Introduction

Due to importance in chemistry and enzymology, acyl-transfer reactions have attracted a great deal of attention, and numerous studies have been performed to investigate the reaction mechanism.¹⁻⁵ The mechanism of acyl-transfer reactions with anionic oxygen nucleophiles has been a subject of controversy, i.e. some studies suggest a stepwise mechanism⁶⁻⁹ while others support a concerted mechanism.¹⁰⁻¹² However, the reactions of aryl acetates with amines have been understood to proceed via an addition intermediate (a stepwise mechanism).¹³⁻¹⁵

Linear free energy relationships such as Hammett and Brønsted-type plots have been the most powerful tool for determination of reaction mechanisms.¹⁶ Aminolyses of esters having a poor leaving group have showed linear Brønsted-type plots, while the ones having a good leaving group have often exhibited a break or curvature in Brønsted-type plots.^{13,14} The break or curvature in Brønsted-type plots have been considered as a change in the rate-determining step (RDS) and as solid evidence of a stepwise mechanism.¹⁶

Recently, we have performed a systematic study to investigate the mechanism for the reaction of 4-nitrophenyl benzoate (PNPB) and (*O*)-4-nitrophenyl thiobenzoate (PNPTB) with a series of secondary cyclic amines.¹⁵ In continuation of our investigation, we carried out the reaction of 2,4-dinitrophenyl benzoate (DNPB) with 6 secondary cyclic amines whose p*K*_a value ranges from 5.95 to 11.02. We report in this paper the reaction mechanism and all the microconstants involved in the present aminolysis of DNPB.

Experimental

Materials. 2,4-Dinitrophenyl benzoate (mp 131-132 °C, lit.¹⁷ 131.5-132.5 °C) was easily prepared from the reaction of 2,4-dinitrophenol and benzoyl chloride in the presence of triethyl amine in methylene chloride. Other chemicals in-

cluding the secondary amines used were of the highest quality available from Aldrich (or Tokyo Kasei for 3-methylpiperidine). Dimethyl sulfoxide was distilled over CaH₂ under a reduced pressure (64-66 °C at 6-7 mmHg). Doubly glass distilled water was boiled and cooled under a nitrogen atmosphere just before use. All the solutions were prepared under a nitrogen atmosphere, and transferred by means of Hamilton gas-tight syringes. Only freshly made solutions were used.

Kinetics. The kinetic study for relatively slow reactions ($t_{1/2} \geq 10$ sec) was performed with a Hitachi U-2000 model UV-Vis spectrophotometer equipped with a Neslab RTE-110 model constant temperature circulator to keep the temperature in the UV cell at 25.0 ± 0.1 °C. For the kinetics of fast reactions ($t_{1/2} < 10$ sec), a stopped-flow technique was used with an Applied Photophysics SX. 17 MV model stopped-flow spectrofluorimeter. The reactions were followed by monitoring the appearance of the leaving 2,4-dinitrophenoxide at 410 nm. All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was in large excess over the substrate concentration. The stock solution of amines was prepared freshly with amine and 0.5 equivalent amount of HCl (or amine hydrochloride and 0.5 equivalent NaOH), to suppress formation of hydroxide by solvolysis as described previously.⁹ All the kinetics were carried out in H₂O containing 20 mole% DMSO to eliminate a solubility problem. Other details of kinetic methods have been reported previously.^{9,15}

Results

All the kinetics in this study obeyed pseudo-first-order kinetics up to over 90% of the total reaction. Pseudo-first-order rate constants (k_{obs}) were obtained from the equation, $\ln(A_{\infty} - A_t) = -k_{obs} \cdot t + C$. Correlation coefficients of the linear regressions were always higher than 0.9995. Apparent second-order rate constants (k_{app}) were determined

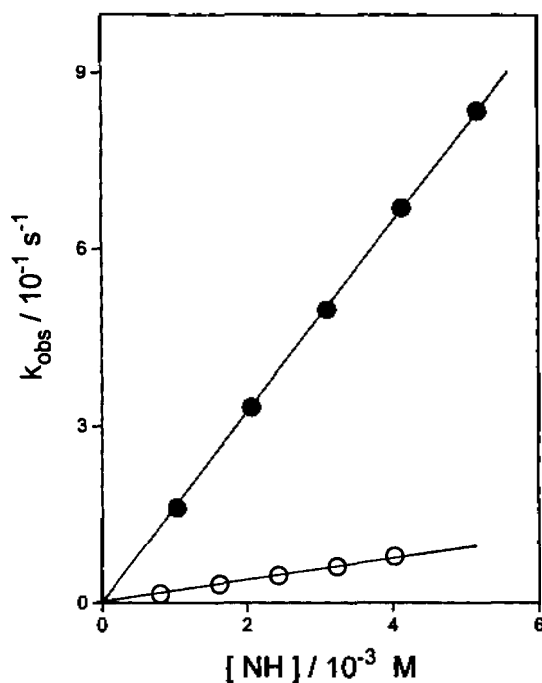


Figure 1. Plots of k_{obs} versus amines concentration for the reaction of DNPB with 3-methylpiperidine (●) and morpholine (○) in H_2O containing 20 mole% DMSO at 25.0 ± 0.1 °C.

Table 1. Summary of Apparent Second-Order Rate Constants, k_{app} ($\text{M}^{-1}\text{s}^{-1}$), for Reaction of Secondary Amines with DNPB and PNPB in H_2O containing 20 mole% DMSO at 25.0 ± 0.1 °C

Amines	pK_a^a	k_{app} ($\text{M}^{-1}\text{s}^{-1}$)	
		DNPB	PNPB ^b
1 piperidine	11.02	184	5.29
2 3-methylpiperidine	10.08	168	3.55
3 piperazine	9.85	87.5	0.841
4 morpholine	8.65	19.3	0.0841
5 1-formylpiperazine	7.98	5.72	-
6 piperazinium ion	5.95	0.450	0.000466

^a pK_a values determined under the kinetic experimental condition. Data from ref. 15. ^b k_{app} data from ref. 15.

from the slope of k_{obs} vs amine concentration. Generally, 5 different amine concentrations were used to determine the k_{app} value for a given amine (Figure 1). The k_{app} values obtained in this way are summarized in Table 1 and demonstrated graphically in Figure 2.

Discussion

Reaction mechanism. As shown in Figure 1, the plots of k_{obs} versus amine concentration show good linearities for the reaction of DNPB with 3-methylpiperidine and morpholine. The corresponding plots for the reactions of the other amines with DNPB exhibit also good linearities (Figure not shown). Such a linearity suggests that general base catalysis is absent in the present aminolysis of DNPB. Besides, the intercepts of the plots appear to be close to zero, indicating that contributions of OH^- and/or H_2O to the observed rate constant (k_{obs}) is negligible. Therefore, one

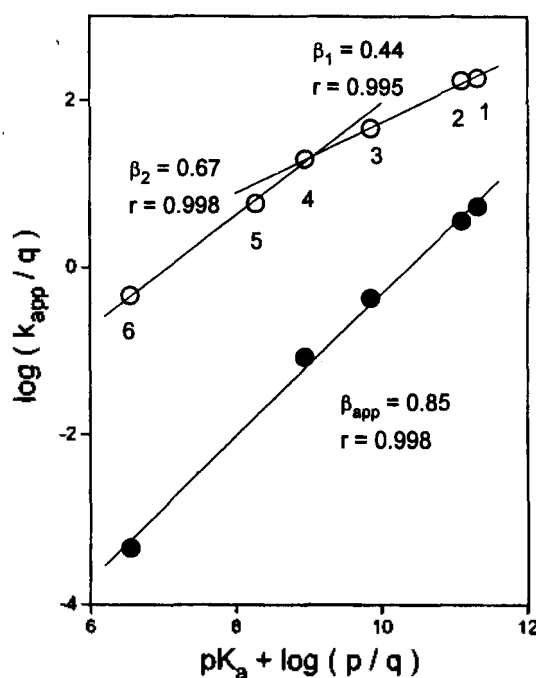
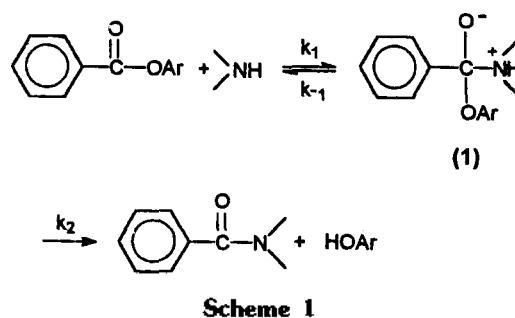


Figure 2. Brønsted-type plots for aminolyses of DNPB (○) and PNPB (●) in H_2O containing 20 mole% DMSO at 25.0 ± 0.1 °C. The identity of the points is given in Table 1.



can suggest that the reaction of DNPB with the present secondary amines would proceed via a typical addition-elimination mechanism as shown in Scheme 1. In this scheme, the rate-determining step (RDS) can be either k_1 or k_2 step, depending on the nucleofugality of the leaving aryloxy and the basicity of the attacking amines.

Based on Scheme 1, one can derive a rate equation as eq. (1), where [1] represents the concentration of the addition intermediate 1. Under a steady-state approximation, eq. (1) can be rewritten as eq. (2), where [S] and [NH] represent the concentration of the substrate and the secondary amine, respectively. Since the concentration of the amines was much more concentrated than that of the substrate (pseudo-first-order condition) for all the amines used in the present system, eq. (2) can be simplified as eq. (3) and (4), where k_{obs} and k_{app} represent pseudo-first-order rate constant and apparent second-order rate constant, respectively.

$$\text{Rate} = k_2[1] \quad (1)$$

$$\text{Rate} = \frac{k_1 k_2}{k_{-1} + k_2} [S][\text{NH}] \quad (2)$$

$$\text{Rate} = k_{\text{obs}}[\text{S}], \text{ where } k_{\text{obs}} = \frac{k_1 k_2}{k_{-1} + k_2} [\text{NH}] \quad (3)$$

$$k_{\text{app}} = \frac{k_1 k_2}{k_{-1} + k_2} \quad (4)$$

In Table 1 are summarized k_{app} values for the reaction of DNPB with 6 secondary amines in H₂O containing 20 mole% DMSO at 25.0±0.1 °C together with the data for the reaction of PNPB with the corresponding secondary amine for comparison purpose. As shown in Table 1, the reactivity of these amines increases with increasing the amine basicity. However, the rate enhancement appears to be less significant for the DNPB system than the PNPB system. For example, the rate enhancements are 4.1×10² and 1.1×10⁴ as the amine changes from piperazinium ion (p*K_a*=5.95) to piperidine (p*K_a*=11.02) for the DNPB and PNPB system, respectively. More interestingly, DNPB is about 1000 folds more reactive than PNPB toward low basic piperazinium ion, but only 30 folds toward highly basic piperidine. Since the basicity difference between 4-nitrophenoxide and 2,4-dinitrophenoxide is about 3 p*K_a* units, the reactivity difference of 30 folds between DNPB and PNPB toward piperidine is unexpectedly small.

In Figure 2 are demonstrated Brønsted-type plots for the aminolysis of DNPB and PNPB. The plots are statistically corrected by using *p* and *q*, i.e. *p*=2 (except *p*=4 for piperazinium ion) and *q*=1 (except *q*=2 for piperazine) for all the amines used.¹⁸ As shown in the plots, the PNPB system shows a linear Brønsted-type plot, while the DNPB system exhibits a break. A linearity in Brønsted-type plots is suggestive of the same RDS for the given series of reactants, while a break in Brønsted-type plots is an indication of a change in RDS.¹⁶ Therefore, one can consider that the aminolysis of PNPB would proceed via the same mechanism for all the secondary amines listed in Table 1. Since the Brønsted-type plot of the DNPB system exhibits a break at p*K_a* near 9.1, one can suggest that there is a change in the RDS at this point. The position of the break (p*K_a*⁰) in the present system is consistent with the previous results obtained from aminolyses of various types of carboxylic esters in aqueous medium.¹³⁻¹⁵

As the basicity of the secondary amines increases, the RDS for the aminolysis of DNPB is considered to change from *k*₂ to *k*₁ step. This is because *k*₂ would be much smaller than *k*₁ for low basic secondary amines, while the former would be much larger than the latter for highly basic amines. Accordingly, eq. (4) becomes eq. (5) and (6), where *K* represents *k*₁/*k*₋₁.

$$k_{\text{app}} = \frac{k_1 k_2}{k_{-1} + k_2} = \frac{k_1 k_2}{k_{-1}} = K k_2 \quad (k_2 \ll k_{-1}) \quad (5)$$

$$\text{or } k_{\text{app}} = \frac{k_1 k_2}{k_2} = k_1 \quad (k_2 \gg k_{-1}) \quad (6)$$

The slope, β_{app}, for the PNPB system in Figure 2 is calculated to be 0.85,¹⁵ while the ones for the DNPB system are 0.67 and 0.44 for the low basic amines (p*K_a*<9.1) and for the highly basic amines (p*K_a*>9.1), respectively. The RDS for the reaction of PNPB with all the secondary amines used is considered to be the same as the one for the reaction of DNPB with the low basic secondary amines

(p*K_a*<9.1). Therefore, the large difference in β_{app} between the PNPB and DNPB system is considered to be consistent with the reactivity-selectivity principle.

Evaluation of microconstants. Let β₂ and β₁ represent the slopes for the Brønsted-type plot for the reaction of DNPB with the low basic and highly basic amines, respectively. As mentioned in the preceding section, *k*_{app} represents *k*₁*k*₂/*k*₋₁ for the low basic amines (p*K_a*<9.1) and *k*₁ for the highly basic amines (p*K_a*>9.1). Therefore, one can express β₁ and β₂ as eq. (7) and (8), respectively.

$$\beta_1 = d(\log k_1)/d(\text{p}K_a) \quad (7)$$

$$\begin{aligned} \beta_2 &= d(\log k_1 k_2 / k_{-1}) / d(\text{p}K_a) \\ &= d(\log k_1) / d(\text{p}K_a) + d(\log k_2 / k_{-1}) / d(\text{p}K_a) \\ &= \beta_1 + d(\log k_2 / k_{-1}) / d(\text{p}K_a) \end{aligned} \quad (8)$$

Eq. (8) can be rearranged as eq. (9). Integral of eq. (9) from p*K_a*⁰ to p*K_a* gives eq. (10), where p*K_a*⁰ represents the p*K_a* at the break point in Figure 2 for the aminolysis of DNPB.

$$\beta_2 - \beta_1 = d(\log k_2 / k_{-1}) / d(\text{p}K_a) \quad (9)$$

$$\begin{aligned} \text{or } d(\log k_2 / k_{-1}) &= (\beta_2 - \beta_1) d(\text{p}K_a) \\ (\log k_2 / k_{-1})_{\text{p}K_a} - (\log k_2 / k_{-1})_{\text{p}K_a^0} &= (\beta_2 - \beta_1)(\text{p}K_a - \text{p}K_a^0) \end{aligned} \quad (10)$$

The values for β₂ and β₁ in the present system are obtained to be 0.67 and 0.44, respectively, and p*K_a*⁰ is calculated to be 9.1. Since *k*₂=*k*₋₁ at p*K_a*⁰, the term (log *k*₂/*k*₋₁)_{p*K_a*⁰} is zero. Therefore, one can simplify eq. (10) as eq. (11). Eq. (11) allows us to calculate *k*₂/*k*₋₁ values for all the secondary amines used in the present system. The values of *k*₂/*k*₋₁ obtained in this way are summarized in Table 2 for the reaction of DNPB with all the secondary amines used in the present system.

$$\begin{aligned} (\log k_2 / k_{-1})_{\text{p}K_a} &= (0.67 - 0.44)(\text{p}K_a - 9.1) \\ &= 0.23(\text{p}K_a - 9.1) \end{aligned} \quad (11)$$

In order to calculate *k*₋₁ value, one needs to know the *k*₂ value. There would be little or no electron donation from the cationic amine moiety of the addition intermediate (1) to expel the leaving aryloxy ion. Therefore, the *k*₂ value has been suggested to be independent on the basicity of attacking amine, but dependent on the structure of the substrate and the basicity of the leaving group.^{14,15} Since the *k*₂ value cannot be measured directly, estimation of the *k*₂ value is necessary. Recently, Castro *et al.* have found that eq. (12) is good for estimation of the *k*₂ value in aminolyses of aryl acetates, where p*K_a*(lg) represents the basicity of the leaving aryloxides.¹⁴ Since the p*K_a* value of 2,4-dinitrophenol (the conjugate acid of the leaving group in the present system) is known to be 4.11 in H₂O at 25.0 °C, the

Table 2. Summary of Microconstants Involved in the Reaction of DNPB with Secondary Amines in H₂O Containing 20 mole% DMSO at 25.0±0.1 °C

Amines	<i>k</i> ₂ / <i>k</i> ₋₁	<i>k</i> ₋₁ /10 ⁹ s ⁻¹	<i>k</i> ₁ /M ⁻¹ s ⁻¹	<i>K</i> /10 ⁻⁹ M ⁻¹
1 piperidine	3.19	0.940	242	257
2 3-methylpiperidine	2.84	1.06	227	214
3 piperazine	1.46	2.05	147	71.7
4 morpholine	0.909	3.30	40.5	12.3
5 1-formylpiperazine	0.638	4.70	14.7	3.13
6 piperazinium ion	0.255	11.8	2.22	0.188

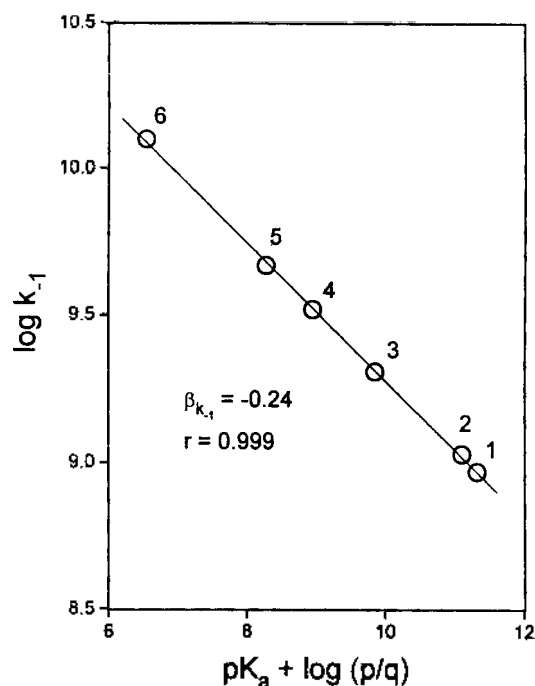


Figure 3. Brønsted-type plot for the aminolysis of DNPB in H₂O containing 20 mole% DMSO at 25.0±0.1 °C. The identity of the points is given in Table 2.

k_2 value in the present system is calculated to be $3 \times 10^9 \text{ s}^{-1}$ from eq. (12).

$$\log k_2 = 11.5 - 0.5 \text{ p}K_a(\text{lg}) \quad (12)$$

From the k_2 value of $3 \times 10^9 \text{ s}^{-1}$, k_1 values are calculated for all the secondary amines used in the present aminolysis of DNPB. In Table 2 are summarized the k_{-1} values. As shown in the Table, the k_{-1} value decreases with increasing amine basicity, as expected. This is graphically demonstrated in Figure 3, in which a good linear Brønsted-type plot is presented. The slope of the plot, $\beta_{k_{-1}}$, is calculated to be -0.24 . Such a small $\beta_{k_{-1}}$ value indicates that the k_{-1} step is not much sensitive to the basicity of amines in the present system.

The values of k_1 can be calculated from eq. (13) for all the secondary amines used in the present reaction of DNPB. The calculated k_1 values are summarized in Table 2 and demonstrated graphically in Figure 4. As shown in the plot, the Brønsted-type plot exhibits a good linearity with a slope of 0.43 , β_{k_1} . As expected, the k_1 value increases with increasing amine basicity. The magnitude of β_{k_1} is calculated to be 0.43 , which is much larger than that of $\beta_{k_{-1}}$, -0.24 . Therefore, the k_1 step is about twice as sensitive as the k_{-1} step to the amine basicity in the present aminolysis.

$$\begin{aligned} k_{\text{app}} &= k_1 k_2 / (k_{-1} + k_2) \\ \text{or } k_1 &= k_{\text{app}} (k_{-1} + k_2) / k_2 \end{aligned} \quad (13)$$

The β_{k_1} value of 0.43 is practically identical to the β_1 value (the Brønsted slope for the highly basic amines in Figure 2). As discussed in the preceding section, k_{app} becomes k_1 for highly basic amines (eq. (6), when $\text{p}K_a > 9.1$). Therefore, it is natural that the magnitude of β_{k_1} is the same as that of β_1 in Figure 2.

The equilibrium constant K values are also calculated

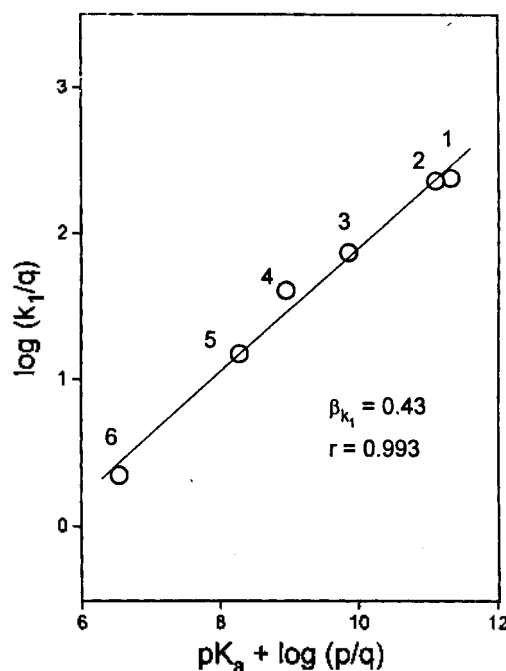


Figure 4. Brønsted-type plot for the aminolysis of DNPB in H₂O containing 20 mole% DMSO at 25.0±0.1 °C. The identity of the points is given in Table 2.

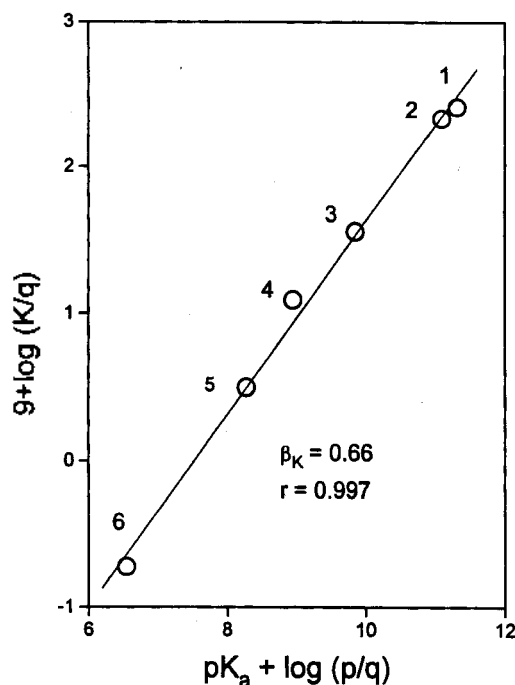


Figure 5. Brønsted-type plot for the aminolysis of DNPB in H₂O containing 20 mole% DMSO at 25.0±0.1 °C. The identity of the points is given in Table 2.

from the values of k_1 and k_{-1} , and summarized in Table 2. As shown in the Table, the K value increases with increasing the amine basicity in the present system. This is graphically demonstrated in Figure 5, in which a good linear Brønsted-type correlation is shown with a slope of 0.66 , β_K .

The magnitude of β_K is also practically identical to that

of β_2 in Figure 2 (0.66 vs. 0.67). This is not surprising either. As mentioned in eq. (5), k_{app} becomes Kk_2 for the low basic amines ($pK_a < 9.1$). Therefore, one can derive eq. (14) from eq. (5). Since the k_2 value has been suggested to be constant for aminolysis of a given substrate with a series of amines, the magnitude of $\beta_{k_{app}}$ and K should be same, as observed in the present system.

$$k_{app} = k_1 k_2 / k_{-1} = K k_2 \quad (5)$$

$$\log k_{app} = \log K + \log k_2 \quad (14)$$

The microconstants listed in Table 2 might involve some extent of uncertainty due to the estimated k_2 value. However, these values can account for the experimental plots nicely. Furthermore, Brønsted-type plots in Figures 3-5 show excellent linearity, indicating that the microconstants obtained in the present system are reliable.

β_K values for aminolysis of (*O*)-4-nitrophenyl thiobenzoate (PNPTB), (*O*)-phenyl thioacetate (PTA) and phenyl dithioacetate (PDTA) have been reported to be 0.93, 1.0 and 1.2, respectively.^{14,15} These β_K values are much larger than the one in the present system (0.66). The magnitude of β_K has been suggested to represent the effective charge developed on the nitrogen atom of the amine moiety in the addition intermediates, **1**.^{14,15} Thus, the effective charge on the nitrogen atom in the present system is considered to be insignificantly developed, based on the small β_K value. Deprotonation from the amine moiety in **1** would become easier for the system having larger β_K value (e.g. more positive charge on the nitrogen atom of the amine moiety in **1**). In fact, general base catalysis has been observed for aminolysis of PNPTB, PTA and PDTA, whose β_K values are significantly large as mentioned above. Therefore, it is proposed that the small β_K value would be one possible reason for the absence of general base catalysis in the present aminolysis of DNPB.

Summary

The reaction of DNPB with the secondary amines is considered to proceed via an addition intermediate without general base catalysis. The Brønsted-type plot for the present aminolysis of DNPB shows a break at pK_a near 9.1, indicating that the RDS changes from the k_2 to the k_1 step as the basicity of amines increases. Using the estimated k_2 value of $3 \times 10^9 \text{ s}^{-1}$, all the other microconstants (k_1 , k_{-1} and K) are calculated. The Brønsted-type plots for these microconstants exhibit good linearities. The small β_K value in the present system is considered to be a plausible reason for the absence of general base catalysis.

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