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Aminolysis of X-Substituted Phenyl Diphenylphosphinates: Effect of Amine Nature on Reactivity and Transition-State Structure

Ik-Hwan Um,* Jeong-Yoon Han, and Young-Hee Shin

Department of Chemistry and Nano Science, Ewha Womans University, Seoul 120-750, Korea

ihum@ewha.ac.kr

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1a-i

X = 2,4-$(NO_2)_2$ (**1a**), 3,4-$(NO_2)_2$ (**1b**), 4-Cl-2-NO_2 (**1c**), 4-NO_2 (**1d**), 4-CN (**1e**), 4-COMe (**1f**), 3-Cl (**1g**), 3-COMe (**1h**), 4-Cl (**1i**)

RNH_2: 8 different primary amines

A kinetic study is reported for aminolysis of X-substituted phenyl diphenylphosphinates (**1a**−**i**) in 80 mol % H_2O/20 mol % dimethyl sulfoxide at 25.0 ± 0.1 °C. The Brønsted-type plot for the reactions of 2,4-dinitrophenyl diphenylphosphinate (**1a**) with primary amines is linear with $\beta_{nuc} = 0.53$. The reactions of **1a**−**i** with ethylamine also result in a linear Brønsted-type plot with $\beta_{lg} = -0.81$. These β_{nuc} and β_{lg} values are slightly larger than those reported previously for the reactions of **1a** with secondary amines ($\beta_{nuc} = 0.38$) and for those of **1a**−**i** with piperidine ($\beta_{lg} = -0.66$) but typical for reactions that proceed through a concerted mechanism. It has been concluded that aminolysis of **1a**−**i** proceed through a concerted mechanism and the nature of amines does not affect the reaction mechanism. However, the reactions with primary amines have been suggested to proceed through a later transition state (i.e., more bond formation and bond rupture in the transition state) on the basis of the larger β_{nuc} and β_{lg} values. The concerted mechanism has been further supported from the fact that the Yukawa−Tsuno plot for the reactions of **1a**−**i** with ethylamine exhibits an excellent linear correlation with $\rho = 2.24$ and $r = 0.22$. Weakly basic primary amines are less reactive than secondary amines of similar basicity. However, strongly basic ethylamine is ca. 2-fold more reactive than piperidine toward **1a**, although the former is 0.35 pK_a units less basic than the latter.

Introduction

Aminolysis of carboxylic esters has been intensively investigated and generally has been understood to proceed through a stepwise mechanism on the basis of curved Brønsted-type plots found for reactions of esters possessing a weakly basic nucleofuge (e.g., 2,4-dinitrophenoxide).[1−4] The rate-determining step (RDS) has been reported to change from breakdown of a zwitterionic tetrahedral intermediate to its formation as the entering amine becomes more basic than the leaving group or the nucleofuge becomes less basic than the amine nucleophile by 4−5 pK_a units.[1−4]

In contrast, only few reports are available on reactions of phosphorus centered esters with amines,[5,6] although the reactions with anionic nucleophiles have been comprehensively investigated due to their importance in biological processes.[7−9] Accordingly, their mechanisms have not been completely understood. Cook et al. have performed a systematic study on the aminolysis of aryl diphenylphosphinates.[5a] Studies of leaving-group effects, solvent effects, and activation parameters have led them to conclude that the reactions proceed through a

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stepwise mechanism, in which breakdown of a pentacoordinate intermediate is the RDS.[5a] On the contrary, Lee et al. have concluded that reactions of phenyl-substituted phenyl chlorophosphates with pyridines proceed through a concerted mechanism in MeCN on the basis of linear Brønsted-type plots with small β_{nuc} values (0.16−0.18).[5b]

We have recently performed two series of kinetic studies to investigate the reaction mechanism of the aminolysis of 2,4-dinitrophenyl diphenylphosphinate (**1a**) with seven different alicyclic secondary amines and reactions of piperidine with nine different X-substituted phenyl diphenylphosphinates (**1a**−**i**) in water containing 20 mol % dimethyl sulfoxide (DMSO) at 25.0 ± 0.1 °C.[6] The reactions have been concluded to proceed through a concerted mechanism on the basis of the linear Brønsted-type plots with $\beta_{nuc} = 0.38$ and $\beta_{lg} = -0.66$.[6]

Our kinetic study has been extended to reactions of **1a** with eight different primary amines and to those of **1a**−**i** with ethylamine to investigate effects of amine nature on reactivity and reaction mechanism (Scheme 1). The nature of amines (e.g., primary vs secondary) has been reported to influence not only the reactivity but also the reaction mechanism for aminolysis of *O*-4-nitrophenyl thionobenzoate[4g] and phenyl thionocarbonate.[4a] We have shown that secondary amines are more reactive than isobasic primary amines. Furthermore, reactions with secondary amines have been found to proceed through two intermediates (a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated anionic form T^{-}), while the deprotonation process is absent for the corresponding reactions with primary amines.[4a,g] We wish to report the effect of the nature of the amine on reactivity and reaction mechanism including the transition-state structure by comparing the kinetic data in this study with those reported previously for the corresponding reactions with secondary amines.

SCHEME 1

1a-i

X = 2,4-$(NO_2)_2$ (**1a**), 3,4-$(NO_2)_2$ (**1b**), 4-Cl-2-NO_2 (**1c**), 4-NO_2 (**1d**), 4-CN (**1e**), 4-COMe (**1f**), 3-Cl (**1g**), 3-COMe (**1h**), 4-Cl (**1i**)

RNH_2: 8 different primary amines

TABLE 1. Summary of Second-Order Rate Constants (k_N) for Reactions of 2,4-Dinitrophenyl Diphenylphosphinate (1a) with Primary and Alicyclic Secondary Amines[a]

	amine	pK_a	10^2 k_N (M^{-1} s^{-1})
1	ethylamine	10.67	905
2	ethylenediamine	10.32	506
3	ethanolamine	9.67	180
4	benzylamine	9.46	134
5	glycylglycine	8.31	35.1
6	glycine ethyl ester	7.68	15.7
7	1,2-diaminopropane-H^+	7.13	11.8
8	trifluoroethylamine	5.68	1.63
9	piperidine	11.02	419
10	3-methylpiperidine	10.80	429
11	piperazine	9.85	234
12	1-(2-hydoxyethyl)-piperazine	9.38	93.9
13	morpholine	8.65	57.3
14	1-formylpiperazine	7.98	33.2
15	piperazinium ion	5.95	7.09

[a] In 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. pK_a values in 20 mol % DMSO were taken from refs 6 and 14c. Data for the reactions with secondary amines were taken from ref 6.

Result and Discussion

All reactions in this study obeyed pseudo-first-order kinetics in the presence of a large excess of amine. Pseudo-first-order rate constants (k_{obsd}) were determined from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. The correlation coefficient for the linear regression was usually higher than 0.9995. The plots of k_{obsd} versus amine concentration were linear and passed through the origin, indicating that general base catalysis by the second amine molecule is absent and the contribution of H_2O and/or OH^- ion to k_{obsd} is negligible. Thus, the second-order rate constants (k_N) were determined from the slope of the linear plots of k_{obsd} versus amine concentration. The uncertainty in the k_N values is estimated to be less than 3% from replicate runs. The k_N values determined in this study are summarized in Tables 1 and 2 together with those reported previously for the corresponding reactions with secondary amines for comparison purposes.

Effect of Amine Basicity on Reactivity and Mechanism. Table 1 shows that the second-order rate constants for the

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TABLE 2. Summary of Second-Order Rate Constants (k_N) for Reactions of X-Substituted Phenyl Diphenylphosphinates (1a−i) with Ethylamine and Piperidine[a]

			10^2 k_N (M^{-1} s^{-1})	
entry	X	$pK_a^{(X\text{-}C_6H_4OH)}$	ethylamine	piperidine
1a	2,4-$(NO_2)_2$	4.11	905	419
1b	3,4-$(NO_2)_2$	5.42	55.2	66.4
1c	2-NO_2-4-Cl	6.46	9.94	
1d	4-NO_2	7.14	1.14	3.06
1e	4-CN	7.95	0.595	1.57
1f	4-COMe	8.05	0.215	0.587
1g	3-Cl	9.02	0.0947	0.245
1h	3-COMe	9.19	0.0651	0.211
1i	4-Cl	9.38	0.0492	0.149

[a] In 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The pK_a of phenols and the k_N data for reactions with piperidine were taken from ref 6.

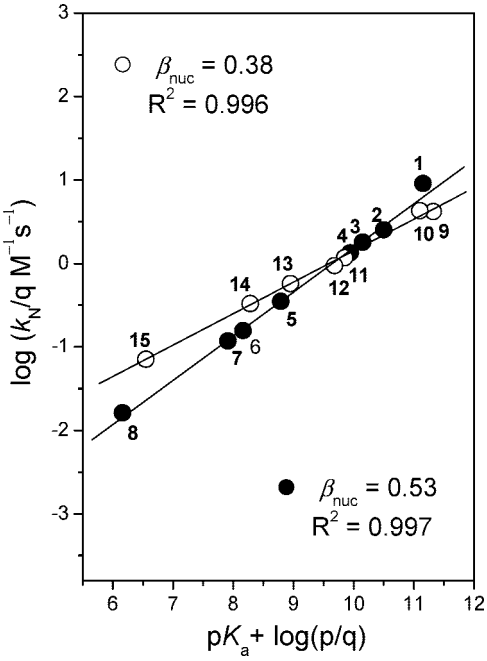

FIGURE 1. Brønsted-type plots for the reactions of 2,4-dinitrophenyl diphenylphosphinate (**1a**) with primary amines (●) and alicyclic secondary amines (○) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of numbers is given in Table 1.

reactions of **1a** with primary amines decrease as the basicity of amine decreases, e.g., k_N decreases from 9.05 to 0.351 and 0.0163 M^{-1} s^{-1} as the pK_a of the conjugate acid of amines decreases from 10.67 to 8.31 and 5.68, in turn. A similar result is shown for the reactions with alicyclic secondary amines. The effect of amine basicity on reactivity is illustrated in Figure 1. The Brønsted-type plots exhibit excellent linear correlations with β_{nuc} values of 0.53 and 0.38 for the reactions with primary and secondary amines, respectively, when the k_N and pK_a values are corrected statistically using p and q (i.e., $p = 3$ except $p = 6$ for 1,2-diaminopropane-H^+ and $q = 1$ except $q = 2$ for ethylenediamine for the primary amines, and $p = 2$ except $p = 4$ for piperazinium ion and $q = 1$ except $q = 2$ for piperazine for the secondary amines).[10]

The magnitude of β_{nuc} values has been used as a measure of reaction mechanism for nucleophilic substitution reactions of various esters.[1−4,11] It has generally been reported that β_{nuc} decreases from 0.8 ± 0.1 to 0.2 ± 0.1 when the RDS for a stepwise mechanism changes from breakdown of an intermediate to its formation.[1−4,11] In fact, we have recently concluded that reactions of 2,4-dinitrophenyl benzoate and benzenesulfonate with primary and alicyclic secondary amines proceed through a stepwise mechanism with a change in RDS on the basis of curved Brønsted-type plots, i.e., $\beta_{nuc} = 0.74-0.88$ for reactions with weakly basic amines and $\beta_{nuc} = 0.34-0.39$ for those with strongly basic amines.[4f,14d]

As shown in Figure 1, the reactions of **1a** with primary amines result in a β_{nuc} value slightly larger than for the corresponding reactions with secondary amines (i.e., 0.53 vs 0.38). However, the β_{nuc} value of 0.53 is typical for reactions that proceed through a concerted mechanism.[1−4,12] Thus, one can suggest that the current reactions of **1a** with the primary amines proceed also through a concerted mechanism, although bond formation between incoming amine and the electrophilic center is considered to be slightly more advanced for the reactions with primary amines than for those with secondary amines. To get further information on the reaction mechanism, second-order rate constants have been measured for reactions of X-substituted phenyl diphenylphosphinates (**1a−i**) with strongly basic ethylamine.

Effect of Leaving-Group Basicity on Reactivity and Mechanism. Table 2 shows that the effect of the leaving-group substituent on reactivity is significant, e.g., the k_N value for the reactions with ethylamine decreases from 9.05 to 5.95 × 10^{-3} and 4.92 × 10^{-4} M^{-1} s^{-1} as the substituent X changes from 2,4-$(NO_2)_2$ to 4-CN and 4-Cl, in turn. A similar result is shown for the corresponding reactions with piperidine. The effect of leaving-group basicity on reactivity is illustrated in Figure 2 for the reactions of **1a−i** with ethylamine and piperidine. The statistically corrected Brønsted-type plots are linear with $\beta_{lg} = -0.81$ for the reactions with ethylamine and $\beta_{lg} = -0.66$ for the corresponding reactions with piperidine, indicating that departure of the leaving group in the transition state is slightly more advanced for the reactions with the primary amine than for those with the secondary amine.

The linear Brønsted-type plots shown in Figure 2 contrast to the curved Brønsted-type plots reported previously for aminolysis of diaryl carbonates and aryl benzoates.[13,14a,b] Gresser and Jencks have found that the Brønsted-type plots exhibit a downward curvature upon changing the leaving-group basicity for reactions of aryl phenyl carbonates with quinuclidines, i.e., β_{lg} changes from −1.3 to −0.2 as the leaving aryloxide becomes less basic than the incoming quinuclidine by 4−5 pK_a units.[13] Similarly curved Brønsted-type plots have been reported for reactions of aryl benzoates with piperidine, i.e., the β_{lg} value changes from −1.5 ± 0.2 to −0.3 ± 0.1 with decreasing the basicity of the nucleofuge.[14a,b] The curved Brønsted-type plots have been attributed to a change in RDS, i.e., from breakdown to formation of a zwitterionic tetrahedral intermediate.[13,14a,b]

It is apparent that the β_{lg} value of −0.81 for the reactions of **1a−i** with ethylamine is much larger than that reported for

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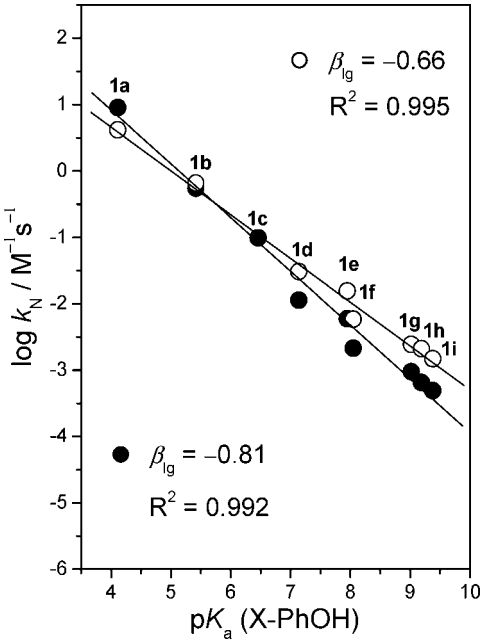


FIGURE 2. Brønsted-type plots for reactions of X-substituted phenyl diphenylphosphinates (**1a**−**i**) with ethylamine (●) and piperidine (○) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of numbers is given in Table 2.

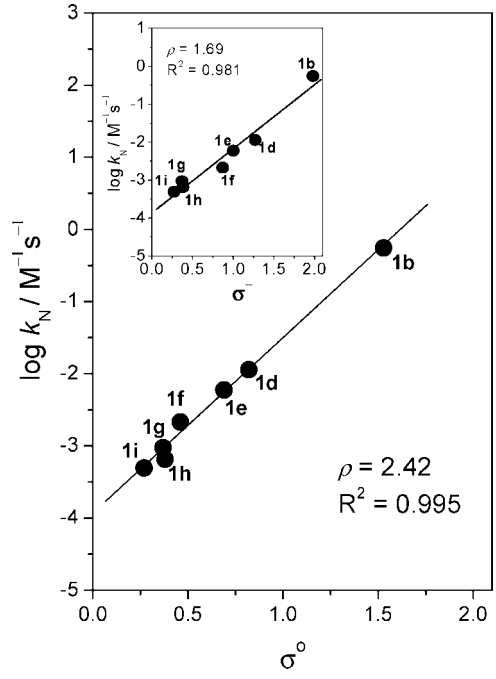
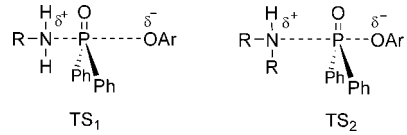


FIGURE 3. Hammett plots correlated with σ^o and σ^- (inset) constants for reactions of X-substituted phenyl diphenylphosphinates (**1b** and **1d**−**i**) with ethylamine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of numbers is given in Table 2.

reactions proceeding through rate-determining formation of the addition intermediate (e.g., $\beta_{lg} = -0.3 \pm 0.1$) but much smaller than that for reactions undergoing through rate-determining breakdown of the intermediate (e.g., $\beta_{lg} = -1.5 \pm 0.2$) as mentioned above. The β_{lg} values for reactions reported to proceed through a concerted mechanism are −0.79 for nucleophilic substitution reactions of 4-nitrophenyl diphenylphosphinates with phenoxide,[15] -0.7 ± 0.2 for alkaline hydrolysis of aryl phenyl sulfates,[16] and -0.5 ± 0.1 for alkaline hydrolysis of *O*-aryl dimethylphosphinates,[17] dimethylphosphinothioates,[12] and diphenylphosphinates,[18] alkaline ethanolysis of *O*-aryl diphenylphosphinates,[19] and aminolysis of aryl thiocarbamates.[20] The β_{lg} value of −0.81 supports that the reactions of **1a**−**i** with ethylamine proceed also through a concerted mechanism as reported for the corresponding reactions with piperidine. Thus, one can suggest that the nature of amines does not influence the reaction mechanism but affects the structure of the transition state for aminolysis of phosphorus esters **1a**−**i**, i.e., the reactions with primary amines proceed through a later transition-state structure (e.g., more bond formation and bond rupture) than those with secondary amines on the basis of the β_{nuc} and β_{lg} values (TS_1 vs TS_2).



Mechanism Determined from Hammett and Yukawa−Tsuno Plots. To obtain more conclusive evidence that the reactions of **1a**−**i** with ethylamine proceed through a concerted mechanism, Hammett plots have been constructed using σ^- and σ^o constants. If the reactions of **1a**−**i** proceed through a concerted mechanism, a partial negative charge would develop on the oxygen atom of the leaving aryloxide. Since the negative charge can be delocalized on the substituent X through resonance, one can expect that σ^- constants would result in a better Hammett correlation than σ^o constants. Figure 3 shows that σ^- constants result in much poorer correlation than σ^o constants, implying that the leaving-group departure is not advanced in the transition state of the RDS. Accordingly, one might suggest the reactions of **1a**−**i** with ethylamine proceed through a stepwise mechanism, in which the leaving group departs after the RDS. Clearly, this argument is inconsistent with the concerted mechanism suggested in the preceding section on the basis of β_{lg} value.

We have recently shown that deduction of a reaction mechanism based on Hammett correlations with σ^o and σ^- constants alone can be misleading for nucleophilic substitution reactions of various phosphorus centered esters.[6,18,19,21] The Yukawa−Tsuno equation (eq 1) has been found to be highly effective to elucidate ambiguities in reaction mechanism for the aminolysis of aryl diphenylphosphinates,[6] alkaline hydrolysis of aryl diphenylphosphinates[18] and diphenylphosphinothioates,[21] and alkaline ethanolysis of aryl diphenylphosphinates.[19] Thus, a Yukawa−Tsuno plot has been constructed in Figure 4 for the reactions of **1b** and **1d**−**i**.

$$\log \frac{k_N^X}{k_N^H} = \rho[\sigma^o + r(\sigma^- - \sigma^o)] \quad (1)$$

It is seen that the Yukawa−Tsuno plot exhibits an excellent correlation with $\rho = 2.24$ and $r = 0.22$. Since the r value determined in the current reactions is neither 0 nor 1, the Yukawa−Tsuno plot results in a better linear correlation than the Hammett plot using σ^- or σ^o constants alone. The r value

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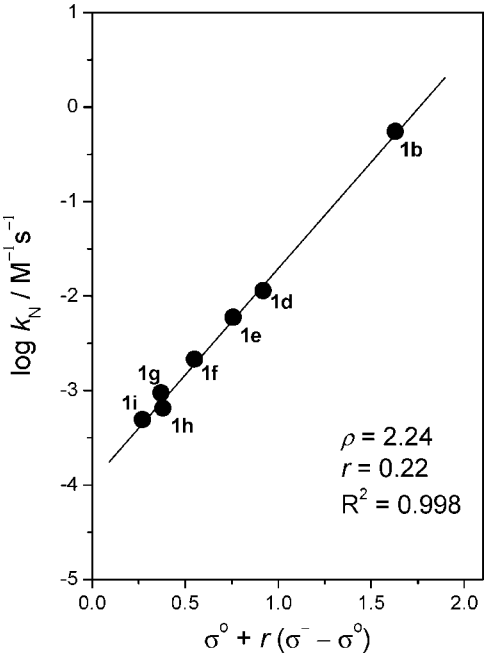

FIGURE 4. Yukawa−Tsuno plot for reactions of X-substituted phenyl diphenylphosphinates (**1b** and **1d**−**i**) with ethylamine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of numbers is given in Table 2.

in eq 1 represents the resonance demand of the reaction center or the extent of resonance contribution.[22,23] The *r* value shown in Figure 4 is small but not zero, indicating that a partial negative charge, which can be delocalized on the substituent X through resonance interactions, develops on the oxygen atom of the leaving aryloxide. This idea is consistent with the concerted mechanism suggested in the preceding section.

Effect of Amine Nature on Reactivity. As shown in Table 1 and Figure 1, weakly basic primary amines are less reactive than secondary amines of similar basicity (e.g., pK_a < ca. 10). However, it is noted that the reactivity difference between the primary and secondary amines becomes smaller as the amine basicity increases due to the difference in the β_{nuc} values between the reactions of **1a** with the primary amines and those with secondary amines. Consequently, strongly basic ethylamine is ca. 2-fold more reactive than piperidine toward **1a**, although the former is even 0.35 pK_a units less basic than the latter. Interestingly, Table 2 and Figure 2 demonstrate that ethylamine is more reactive than piperidine toward **1a**, but it becomes less reactive than piperidine as the basicity of the leaving aryloxide increases. It is apparent from Figure 2 that the difference in the reactivity between ethylamine and piperidine is also caused by the difference in the β_{lg} values between the two series of reactions.

It has generally been reported that primary amines are less reactive than isobasic secondary or tertiary amines, e.g., in the comprehensive investigation by Heo and Bunting for reactions of 72 primary and secondary amines with 1-methyl-4-vinylpyridinium ion,[24] in the recent systematic study by Mayr et al. for reactions of benzhydrylium ions,[25] in the deprotonation of carbon acids such as nitroethane[26a] and 4-nitrophenyl- and 2,4-dinitrophenylacetonitriles,[26b−d] in combination reactions of tris(*p*-anisyl)methyl cation,[27] and in nucleophilic displacement reactions of chloramines[28a] and *N*-(4,6-diphenoxy-1,3,5-triazine-2-yl) pyridinium ion.[28b] We have also shown that primary amines are less reactive in the aminolysis of 2,4-dinitrophenyl benzoate[4f] and benzenesulfonate.[14d]

Since solvation energy increases in the order $R_3NH^+ < R_2NH_2^+ < RNH_3^+$, solvent effect has been suggested to be responsible for the higher reactivity shown by secondary amines compared with primary amines of similar basicity.[26,27,29] If the solvent effect is solely responsible for the reactivity order, primary amines should be always less reactive than isobasic secondary amines regardless of substrates. However, the current study has clearly shown that primary amines are not always less reactive than secondary amines of similar basicity, i.e., amine reactivity is strongly dependent on the basicity of the incoming amine and leaving aryloxide. It is apparent that solvation effect cannot be solely responsible for the difference in reactivity between primary and secondary amines. We suggest that the nature of transition-state structure (early or late) are also an important factor to influence the reactivity order.

Conclusions

The current study has allowed us to conclude the following: (1) The Brønsted-type plots for reactions of **1a** with primary amines and for those of **1a**−**i** with ethylamine are linear with $\beta_{nuc} = 0.53$ and $\beta_{lg} = -0.81$, respectively. These values are slightly larger than those reported previously for the corresponding reactions with secondary amines ($\beta_{nuc} = 0.38$ and $\beta_{lg} = -0.66$) but typical for reactions that proceed through a concerted mechanism. (2) The β_{nuc} and β_{lg} values suggest that the degree of bond formation and bond rupture in the transition state is slightly more advanced for the reactions with the primary amines than for those with the secondary amines. (3) Ethylamine is ca. 2-fold more reactive than piperidine toward **1a**, although the former is 0.35 pK_a units less basic than the latter, indicating that solvation effect is not the only factor to govern the reactivity

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of primary and secondary amines. The difference in β_{nuc} and β_{lg} values for the reactions with primary and secondary amines is responsible for their reactivity order toward substrates **1a**−**i**.

Experimental Section

Materials. Aryl diphenylphosphinates **1a**−**i** were readily prepared as reported previously.[6] Their purity was checked by their melting points and ^{1}H NMR spectra. Amines and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use. Due to the low solubility of **1a**−**i** in pure water, aqueous DMSO (80 mol % H_2O/20 mL % DMSO) was used as the reaction medium.

Kinetics. The kinetic study was performed with a UV−vis spectrophotometer equipped with a constant temperature circulating bath to maintain the reaction mixture at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of the leaving aryloxides. All reactions were carried out under pseudo-first-order conditions in which amine concentrations were at least 20 times greater than the substrate concentration. The amine stock solution of ca. 0.2 M was prepared by dissolving 2 equiv of amine hydrochloride and 1 equiv of standardized NaOH solution to make a self-buffered solution in a 25.0 mL volumetric flask.

Typically, the reaction was initiated by adding 5 μL of a 0.02 M solution of 2,4-dinitrophenyl diphenylphosphinate (**1a**) in acetonitrile to a 10-mm quartz UV cell containing 2.50 mL of the thermostatted reaction mixture made up of solvent and aliquot of the amine stock solution. All solutions were transferred by gastight syringes. Generally, the amine concentration was varied over the range (5−100) × 10^{-3} M, while the substrate concentration was ca. 4 × 10^{-5} M. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. The plots of $\ln(A_\infty - A_t)$ versus time were linear over ca. 90% of the total reaction. Usually, five different amine concentrations were employed, and replicate values of k_{obsd} were determined to obtain the second-order rate constants (k_N) from the slope of linear plots of k_{obsd} versus amine concentrations.

Products Analysis. X-Substituted phenoxide (and/or its conjugate acid) was liberated quantitatively and identified as one of the products in the reaction of **1a**−**i** with ethylamine by comparison of the UV−vis spectra after completion of the reactions with those of authentic samples under the same reaction conditions.

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Supporting Information Available: Tables S1−S8 for the reaction conditions and the kinetic results for reactions of **1a** with eight different primary amines and Tables S9−S16 for reactions of **1a**−**i** with ethylamine. This material is available free of charge via the Internet at http://pubs.acs.org.

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