

Origin of the α -Effect in Aminolysis of Y-Substituted Phenyl Diphenylphosphinates: Ground-state Versus Transition-state Contribution

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Nucleophiles possessing one or more nonbonding electron pairs at the atom α to the nucleophilic site have often been reported to exhibit abnormally higher reactivity than would be expected from their basicity.¹⁻²⁰ Accordingly, these nucleophiles and the enhanced reactivity were termed as α -nucleophiles and the α -effect, respectively.²

Numerous studies have been performed to investigate the origin of the α -effect.¹⁻²⁰ Some theories advanced to explain the cause of the α -effect are: (1) destabilization of the ground-state (GS) due to repulsion of the nonbonding electron pairs, (2) stabilization of transition state (TS) including general acid/base catalysis, (3) thermodynamic product stability, (4) solvent effects.¹⁻⁹ However, the origin of the α -effect is not clearly understood. Particularly, solvent effects on the α -effect remain controversial.¹⁰⁻²⁰ Recent calculations have shown that the α -effect is present in gas-phase reactions.¹²⁻¹⁴ Thus, solvent effect has been suggested to be unimportant for the α -effect.¹²⁻¹⁴ However, our systematic study has revealed that solvent effect on the α -effect is significantly important.¹⁵⁻²⁰

The evidence provided was that the α -effect is strongly dependent on solvent compositions for reactions of aryl acetates, benzoates and thionobenzoates with butane-2,3-dione monoximate (an α -nucleophile) and 4-chlorophenoxide (a reference nucleophile) in DMSO-H₂O mixtures of varying compositions, e.g., the magnitude of the α -effect increases as the DMSO content in the medium increases up to ca. 50 mol% DMSO and then decreases thereafter (a bell-shaped α -effect profile).¹⁵⁻²⁰ Dissection of the α -effect into GS and TS contributions through combination of the kinetic data with our calorimetric data has led us to conclude that GS destabilization is mainly responsible for the increasing α -effect up to ca. 50 mol% DMSO, while differential TS stabilization contributes to the decreasing α -effect in the DMSO-rich region.¹⁵⁻²⁰

We have also reported that TS stabilization through general acid/base catalysis plays an important role for the α -effect found in reactions of Y-substituted phenyl benzoates with

hydrazine and glycylglycine.²¹ Our study has been extended to reactions of Y-substituted phenyl diphenylphosphinates (**1a-f**) with hydrazine and glycine ethyl ester (Scheme 1) to investigate the origin of the α -effect (e.g., GS and TS contributions).

Results and Discussion

The kinetic study was performed under pseudo-first-order conditions with the concentration of amines maintained in excess relative to substrate concentration. All reactions obeyed first-order kinetics with quantitative liberation of Y-substituted phenoxide ion (and/or its conjugate acid). Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln(A_{\infty} - A_t) = -k_{\text{obsd}}t + C$. The plots of k_{obsd} vs. amine concentration were linear passing through the origin. Thus, second-order rate constants (k_N) were determined from the slope of the linear plots. From replicate runs, it is estimated that the uncer-

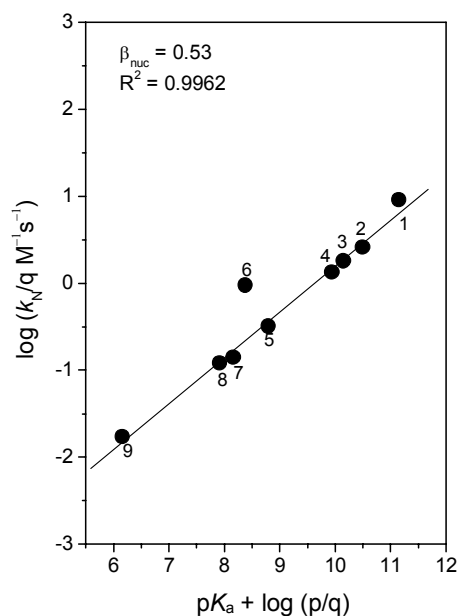
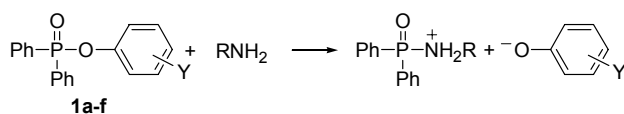


Figure 1. Brønsted-type plot for reactions of 2,4-dinitrophenyl diphenylphosphinate (**1a**) with primary amines in 80 mol% H₂O/20 mol% DMSO at 25 ± 0.1 °C. The identity of amines: 1 = ethylamine, 2 = ethylenediamine, 3 = ethanolamine, 4 = benzylamine, 5 = glycylglycine, 6 = hydrazine, 7 = glycine ethyl ester, 8 = 1,2-diaminopropane-H⁺, 9 = trifluoroethylamine. The kinetic data were taken from ref. 22 except for the reaction of **1a** with hydrazine, 6.



Y = 2,4-(NO₂)₂ (**1a**), 3,4-(NO₂)₂ (**1b**), 2-Cl-4-NO₂ (**1c**), 4-NO₂ (**1d**), 4-CN (**1e**), 4-COMe (**1f**)

RNH_2 : Hydrazine and Glycine ethyl ester

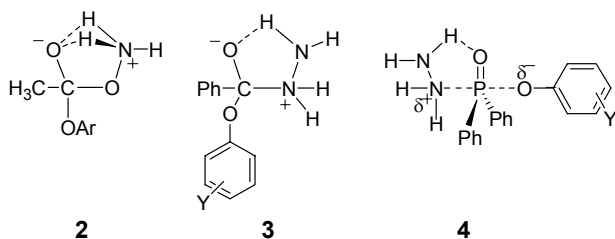
Scheme 1

tainty in the rate constant is less than $\pm 3\%$.

The α -Effect in Phosphorus Electrophile. The term α -effect was originally given to abnormally enhanced reactivity exhibited by α -nucleophiles.² Since this definition is somewhat ambiguous, an alternative definition of the α -effect was proposed, i.e., a positive deviation exhibited by an α -nucleophile from a Brønsted-type nucleophilicity plot.⁹ To examine whether hydrazine exhibits a positive deviation (i.e., the α -effect) in the current electrophilic center, a Brønsted-type plot has been constructed using the kinetic data reported recently for the reactions of 2,4-dinitrophenyl diphenylphosphinate (**1a**) with a series of primary amines²² together with the k_N value for the reaction of **1a** with hydrazine determined in this study. As shown in Figure 1, the Brønsted-type plot exhibits a good linearity except hydrazine (i.e., entry 6), which exhibits positive deviation from the linear Brønsted-type plot (i.e., the α -effect).

A careful examination of Figure 1 reveals that the α -effect shown by hydrazine is only ca. 10^1 , which is much smaller than the α -effect reported for the reactions of C=O and SO₂ electrophilic centers.¹⁸ It has been reported that the α -effect decreases as the β_{nuc} value decreases.^{6,23-25} The β_{nuc} value determined in Figure 1 is 0.53, which is much smaller than that reported for the corresponding reactions of 2,4-dinitrophenyl benzoate ($\beta_{\text{nuc}} = 0.78$)²⁶ or 2,4-dinitrophenyl benzenesulfonate ($\beta_{\text{nuc}} = 0.88$).²⁷ Accordingly, one might suggest the small β_{nuc} value is responsible for the small α -effect found in this study.

Origin of the α -Effect: GS vs. TS Contribution. Intramolecular H-bonding interaction has been suggested to be responsible for the α -effect found in the reactions of carboxylic esters with HONH₂ and NH₂NH₂, which is probably one of the first explanations proposed for the α -effect shown by these α -nucleophiles.²⁸ Hengge and his coworkers suggested that H-bonding structure **2** is responsible for the enhanced reactivity shown by HONH₂ in the acyl-transfer reaction of 4-nitrophenyl acetate with HONH₂,²⁸ since such H-bonding structure is not possible for the reference nucleophile (e.g., trifluoroethylamine). We have also proposed that 5-membered H-bonding structure **3** is an important factor that governs the magnitude of the α -effect for the reactions of Y-substituted phenyl benzoates with hydrazine,²¹ since the α -effect found in that system was found to be dependent on the electronic nature of the substituent Y. Thus, one might suggest intramolecular H-bonding structure **4** is responsible for the α -effect for the reaction of **1a** with hydrazine.



To examine whether H-bonding structure **4** is responsible for the α -effect in this study, second-order rate constants (k_N) have been measured for reactions of Y-substituted phenyl diphenylphosphinates (**1a-f**) with hydrazine and glycine ethyl

Table 1. Summary of Second-order Rate Constants (k_N , M⁻¹s⁻¹) for Reactions of Y-Substituted Phenyl Diphenylphosphinates (**1a-f**) with Hydrazine and Glycine Ethyl Ester in 80 mol% H₂O / 20 mol% DMSO at 25.0 \pm 0.1 $^{\circ}$ C.

entry	Y	$\text{p}K_a^{(\text{Y-C}_6\text{H}_4\text{OH})}$	$10^4 k_N/\text{M}^{-1}\text{s}^{-1}$		α -effect ^a
			hydrazine	glycine ethyl ester	
1a	2,4-(NO ₂) ₂	4.11	18900	1570	12
1b	3,4-(NO ₂) ₂	5.42	803	106	7.6
1c	4-Cl-2-NO ₂	6.46	112	35.9	3.1
1d	4-NO ₂	7.14	10.8	3.74	2.9
1e	4-CN	7.95	4.54	2.09	2.2
1f	4-COMe	8.05	8.56	0.511	17

$$^a \alpha\text{-effect} = k_N^{\text{NH}_2\text{NH}_2} / k_N^{\text{glycine ethyl ester}}$$

ester, as an α -nucleophile and its reference nucleophile, respectively. The results are summarized in Table 1 together with the magnitude of the α -effect calculated for each substrate.

As shown in Table 1, the k_N value decreases as the leaving group basicity increases for the reactions with hydrazine and glycine ethyl ester. The effect of leaving group basicity on reactivity is illustrated in Figure 2. The Brønsted-type plots for the reactions with hydrazine and glycine ethyl ester are linear, although some points deviate from the linearity. The β_{lg} values determined are -0.90 and -0.82 for the reactions with hydrazine and glycine ethyl ester, respectively. These β_{lg} values are practically the same as that reported recently for the corresponding reactions with ethylamine (i.e., $\beta_{\text{lg}} = -0.81$). Since the reactions of **1a-f** with a series of primary amines have recently been reported to proceed through a concerted mechanism on the basis of the magnitude of β_{nuc} (0.53, see Figure 1) and β_{lg} (-0.81),²² one might suggest that reactions of

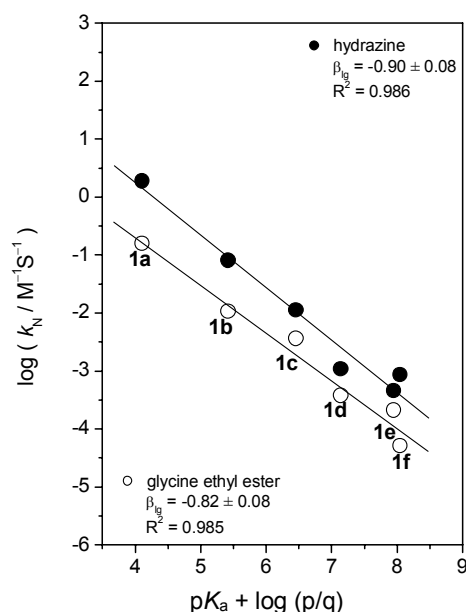


Figure 2. Brønsted-type plots for reactions of Y-substituted phenyl diphenylphosphinates (**1a-f**) with hydrazine (●) and glycine ethyl ester (○) in 80 mol% H₂O/20 mol% DMSO at 25.0 \pm 0.1 $^{\circ}$ C. The identity of points is given in Table 1.

1a-f with hydrazine and glycine ethyl ester proceed also through a concerted mechanism.

Table 1 shows that the α -effect is very small, i.e., hydrazine is only *ca.* 2 to 17 times more reactive than its reference nucleophile, glycine ethyl ester. Furthermore, the magnitude of the α -effect is independent of the electronic nature of substituent Y. This is contrasting to our previous report that the α -effect for the corresponding reactions of Y-substituted phenyl benzoates is linearly dependent on the electronic nature of the substituent Y.²¹

The TS can be stabilized through 5-membered H-bonding structure **4**. Thus, if H-bonding structure **4** is responsible for the α -effect in the current reactions, one might expect that the α -effect should be dependent on the electronic nature of substituent Y. This is because the electronic nature of substituent Y influences charge polarization of the P=O bond (e.g., the more charge polarization the stronger H-bonding interaction). However, in fact, the α -effect shown in Table 1 is independent of the electronic nature of the substituent Y, indicating that TS stabilization through H-bonding structure **4** is not responsible for the α -effect in this study.

Since hydrazine and glycine ethyl ester were used as an α -nucleophile and its reference nucleophile, respectively, the difference in the GS energy between the two nucleophiles remains constant for all reactions of **1a-f**. Thus, if the GS contribution is responsible for the α -effect, one can expect that the α -effect would not be influenced by the nature of substituent Y. The fact that the magnitude of the α -effect is independent of the substituent Y suggests that the GS effect is more important than the TS contribution for the α -effect found in the current study.

In summary, hydrazine deviates positively from the linear Brønsted-type plot. However, the α -effect is only *ca.* 10^1 . The small α -effect has been attributed to GS effect together with a small β_{nuc} value. Although intramolecular H-bonding TS (i.e., **4**) is conceivable for the reactions of **1a-f** with hydrazine, it has been concluded that stabilization of TS through the H-bonding interaction is not responsible for the α -effect on the basis of the fact that the α -effect is independent of the electronic nature of the substituent Y.

Experimental Section

Materials. Y-Substituted phenyl diphenylphosphinates (**1a-f**) were prepared readily from the reaction of diphenylphosphinyl chloride with Y-substituted phenol in anhydrous ether under the presence of triethylamine as reported previously.²² Their purity was checked by means of melting points and spectral data such as IR and ¹H NMR characteristics. Since 2,4-dinitrophenyl diphenylphosphinate (**1a**) is highly reactive and unstable, **1a** was not purified completely and contained some impurities. Other chemicals including hydrazine and glycine ethyl ester were of the highest quality available. The reaction medium was H₂O containing 20 mol% DMSO due to low solubility of substrates **1a-f** in pure water. Doubly glass-distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic study was performed using a UV-Vis

spectrophotometer equipped with a constant temperature circulating bath. The reactions were followed by monitoring the appearance of Y-substituted phenoxide (or its conjugate acid) at a fixed wavelength corresponding the maximum absorption (λ_{max}). The amine stock solution of *ca.* 0.2 M was prepared in 25.0 mL volumetric flask under nitrogen by adding 2 equiv. of amine hydrochloride to 1 equiv. of standardized NaOH solution to obtain a self-buffered solution. Transfers of solutions were carried out by means of gas-tight syringes.

Product Analysis. Y-Substituted phenoxide (or its conjugate acid) was identified as one of the products by comparison of the UV-Vis spectra at the end of the reactions with the authentic sample.

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