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A Kinetic Study on Nucleophilic Substitution Reactions of Phenyl Y-Substituted-Phenyl Carbonates with Z-Substituted-Phenoxides: Effect of Modification of Nonleaving Group from Benzoyl to Phenyloxycarbonyl on Reactivity and Reaction Mechanism

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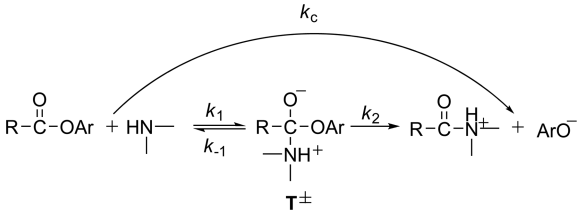
Second-order rate constants for the reactions of phenyl Y-substituted-phenyl carbonates **5a-g** with Z-substituted-phenoxides ($k_{Z\text{-}PhO^-}$) have been measured spectrophotometrically in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. 4-Nitrophenyl phenyl carbonate (**5e**) is up to 235 times more reactive than 4-nitrophenyl benzoate (**4e**). The Brønsted-type plot for the reactions of **5e** with Z-substituted-phenoxides is linear with β_{nuc} = 0.54, which is typical for reactions reported previously to proceed through a concerted mechanism. Hammett plots correlated with σ^o and σ^- constants for the reactions of **5a-f** with 4-chlorophenoxide exhibit highly scattered points. In contrast, the Yukawa-Tsuno plot results in an excellent linear correlation with ρ_Y = 1.51 and r = 0.52, indicating that the leaving-group departure occurs at the rate-determining step (RDS). A stepwise mechanism, in which leaving-group departure occurs at RDS, has been excluded since the incoming 4-$ClPhO^-$ is more basic and a poorer nucleofuge than the leaving Y-substituted-phenoxides. Thus, the reaction has been concluded to proceed through a concerted mechanism. Our study has shown that the modification of the nonleaving group from benzoyl to phenyloxycarbonyl causes a change in the reaction mechanism (*i.e.*, from a stepwise mechanism to a concerted pathway) as well as an increase in the reactivity.

Key Words : Nonleaving group, Phenolysis, Brønsted-type plot, Yukawa-Tsuno plot, Concerted mechanism

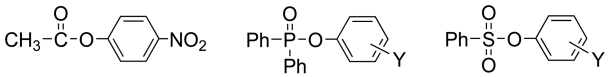
Introduction

Acyl-group transfer reactions have been intensively investigated due to their importance in biological processes as well as in synthetic applications.[1-15] As shown in Scheme 1, aminolysis of esters is generally known to proceed through a stepwise pathway with a zwitterionic tetrahedral intermediate $T^{\pm}$, in which the rate-determining step (RDS) is dependent on the basicity of the incoming amine and the leaving group, or through a concerted mechanism depending on the reaction conditions (*e.g.*, the nature of electrophilic center and reaction medium).[1-8]

However, the mechanisms for reactions with anionic nucleophiles (*e.g.*, aryloxides and OH^- ions) are controversial.[9-15] We have suggested that acyl-group transfer reactions of 4-nitrophenyl acetate (**1**) with aryloxides proceed through a stepwise mechanism on the basis of the kinetic result that σ^o constants exhibit a better Hammett correlation than σ^- constants.[9] In contrast, Williams *et al.* have concluded the reactions proceed through a concerted mechanism on the basis of a linear Brønsted-type plot for the reactions of **1** with a series of aryloxides whose pK_a values straddle the basicity of the leaving 4-nitrophenoxide.[10] On the other hand, Haake *et al.* have concluded that alkaline hydrolysis of Y-substituted-phenyl diphenylphosphinates **2** proceeds through a stepwise mechanism since σ^o constants exhibited a better Hammett correlation than σ^- constants.[11] However, we have proposed that alkaline hydrolysis of **2** proceeds through a concerted mechanism on the basis of a linear Brønsted-type plot with β_{lg} = 0.49 and a linear Yukawa-Tsuno plot with ρ_Y = 1.42 and r = 0.35.[12]

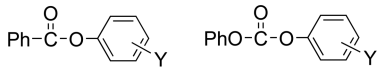


Scheme 1

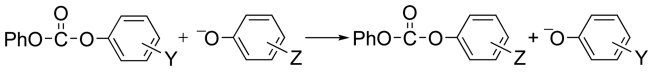


1 **2** **3**

Alkaline hydrolysis of Y-susbtituted-phenyl benzenesulfonates **3** was reported to proceed through a stepwise mechanism, in which formation of an intermediate is the RDS, because σ^o constants resulted in a better Hammett correlation than σ^- constants.[13] In contrast, Williams *et al.* concluded that the reaction of 4-nitrophenyl 4-nitrobenzenesulfonate with aryloxides proceeds through a concerted mechanism.[14] The evidence provided for a concerted mechanism was a linear Brønsted-type plot for the reactions with a series of aryloxides whose pK_a values straddle the basicity of the leaving 4-nitrophenoxide.[14]



4 **5**



5a-g

Y= 3-CHO (**5a**), 4-$COCH_3$ (**5b**), 4-CHO (**5c**), 3-NO_2 (**5d**), 4-NO_2 (**5e**), 3,4-$(NO_2)_2$ (**5f**), 2,4-$(NO_2)_2$ (**5g**).
Z= 4-Me, H, 4-Cl, 3-Cl, 4-COMe, 4-CN.

Scheme 2

We have previously reported that Y-substituted-phenyl benzoates **4** with aryloxides proceed through a stepwise mechanism, in which leaving-group departure occurs after the rate-determining step (RDS) on the basis of a linear Brønsted-type plot with β_{lg} = 0.72 and a good Hammett correlation with σ^o constants.[15] We have now extended our study to the reactions of phenyl Y-substituted-phenyl carbonates **5** with a series of Z-substituted-phenoxides to investigate the effect of changing the nonleaving group from benzoyl to phenyloxycarbonyl on reactivity and reaction mechanism (Scheme 2).

Results and Discussion

All reactions in this study obeyed pseudo-first-order kinetics. 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} *vs*. concentration of aryloxides were linear and passed through the origin, indicating that the contribution of H_2O and/or OH^- from hydrolysis of aryloxides to k_{obsd} is negligible. Thus, the rate low can be expressed as Eq. (1) and the second-order rate constants ($k_{Z\text{-}PhO^-}$) were calculated from the slope of the linear plots of k_{obsd} *vs*. aryloxides concentration. The uncertainty in $k_{Z\text{-}PhO^-}$ values is estimated to be less than 3% from replicate runs. The $k_{Z\text{-}PhO^-}$ values for the reactions of 4-nitrophenyl phenyl carbonate (**5e**) with Z-substituted-phenoxides are summarized in Table 1 together with those reported previously for the corresponding reactions of 4-nitrophenyl benzoate (**4e**) for comparison purpose. In Table 2 are summarized the $k_{4\text{-}Cl\text{-}PhO^-}$ values for the reactions of phenyl Y-substituted-phenyl carbonates **5a-f** with 4-chlorophenoxide (4-$ClPhO^-$).

Rate = k_{obsd}[Substrate], where $k_{obsd} = k_{Z\text{-}PhO^-}$[aryloxide] (1)

Effect of Modification of Nonleaving Group on Reactivity. As shown in Table 1, the $k_{Z\text{-}PhO^-}$ value for the reactions of **5e** decreases as the incoming aryloxide becomes less basic, *e.g.*, it decreases from 52.0 $M^{-1}s^{-1}$ to 18.6 and 1.20 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the aryloxide decreases from 11.7 to 10.2 and 8.60, in turn. A similar result is shown for the corresponding reactions of **4e**, although the $k_{Z\text{-}PhO^-}$ value is much larger for the reactions of **5e** than for those of **4e**. This appears to be consistent with the previous reports that aryl benzoates are less reactive than the corresponding aryl phenyl carbonates toward OH^- and pyridine nucleophiles.[16]

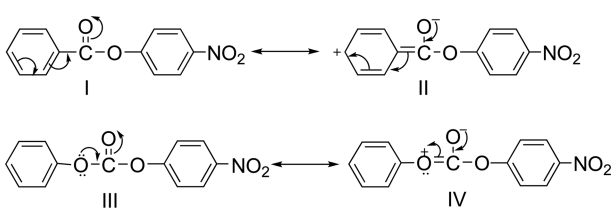
Table 1. Summary of Second-Order Rate Constants ($k_{Z\text{-}PhO^-}$) for the Reactions of 4-Nitrophenyl Benzoate (**4e**) and 4-Nitrophenyl Phenyl Carbonate (**5e**) with Z-Substituted-Phenoxides in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

Entry	Z	pK_a	$k_{Z\text{-}PhO^-}/M^{-1}s^{-1}$	
			4e	**5e**
1	4-Me	11.7	0.925[a]	52.0
2	H	11.4	0.452[a]	36.5
3	4-Cl	10.5	0.185[a]	25.9
4	3-Cl	10.2	0.0903	18.6
5	4-COMe	8.94	0.00888	1.80
6	4-CN	8.60	0.00510[a]	1.20

[a]The kinetic data for the reactions of **4e** were taken from ref. 15.

Many factors can influence the reactivity of **4e** and **5e**, *e.g.*, steric, resonance and inductive effects. It is well known that rates of nucleophilic substitution reactions are strongly influenced by steric effect. The steric constant (E_S) of PhO is not available but is expected to be similar to that of $PhCH_2$ (E_S = –0.38).[17] Since E_S = –2.55 for Ph,[17] one can expect that PhO would exert much less steric hindrance than Ph. Thus, one might suggest that the reduced steric hindrance is responsible for the fact that **5e** is more reactive than **4e**. However, **1** has been reported to be less reactive than **5e** toward a series of primary amines,[18] although the CH_3 in **1** is much smaller than the PhO in **5e**. Accordingly, one can suggest that the steric effect is not solely responsible for the reactivity order shown by **4e** and **5e**.

The ground state (GS) of **4e** and **5e** can be stabilized through resonance interactions as modeled by I ↔ II and III ↔ IV, respectively. Since PhO is expected to be a stronger EDG than Ph on the basis of their σ_R values (*i.e.*, σ_R = –0.34 for PhO and –0.11 for Ph),[17] the resonance structure IV would be more favorable than the resonance structure II. It is evident that stabilization of the GS through such resonance interactions would cause a decrease in reactivity. Thus, one might expect that **5e** would be less reactive than **4e**, if resonance effect is an important factor to govern the reactivity of **4e** and **5e**. However, Table 1 shows that **5e** is up to 235 times more reactive than **4e** toward 4-cyanophenoxide, indicating that stabilization of the GS through resonance interactions is not an important factor to determine the reactivity of **4e** and **5e**.



It is well known that PhO is also a stronger EWG than Ph in an inductive sense, since σ_I = 0.38 for PhO and σ_I = 0.10 for Ph.[17] Thus, one can suggest that the PhO in the carbonate **5e** would increase the electrophilicity of the reaction center more strongly than the Ph in the benzoate **4e** through an

inductive manner. This is consistent with the fact that **5e** is more reactive than **4e**. Thus, one can conclude that the inductive effect is a more important factor than the resonance effect in the current reaction. A similar conclusion has been drawn for pyridinolysis of 2,4-dinitrophenyl phenyl carbonate and benzoate.[16b] Dissection of the macroscopic rate constants (k_N) for the reactions with pyridines into the microscopic rate constants (k_1 and k_2/k_{-1} ratio) has revealed that the carbonate ester exhibits much larger k_1 values than the corresponding benzoate ester regardless of the pyridine basicity.[16b] Accordingly, it has been concluded that the PhO in the carbonate ester increases the electrophilicity of the reaction site more strongly than the Ph in the benzoate ester by acting as a stronger EWG.[16b]

Reaction Mechanism Deduced from Brønsted-type plots. Useful information on reaction mechanisms can be obtained from the shape and slope of Brønsted-type plots. A curved Brønsted-type plot often reported for nucleophilic substitution reactions of esters possessing a weakly basic leaving group (*e.g.*, 2,4-dinitrophenoxide) has been interpreted as a change in rate-determining step (RDS).[1-8] It is now firmly understood that a change in RDS occurs at the center of the Brønsted curvature, defined as pK_a^o.[1-8] The magnitude of β_{nuc} values has also been used as a criterion of reaction mechanisms, *e.g.*, $\beta_{nuc} = 0.5 \pm 0.1$ for a concerted mechanism while $\beta_{nuc} = 0.2 \pm 0.1$ or 0.8 ± 0.1 for a stepwise reaction depending on RDS.[1-8]

To investigate the reaction mechanism for the current reactions, Brønsted-type plots have been constructed in Figure 1. The Brønsted-type plots are linear with β_{nuc} values of 0.54 and 0.72 for the reactions of **5e** and **4e**, respectively. It is noted that the β_{nuc} value is much smaller for the reactions of **5e** than for the corresponding reactions of **4e**, which were suggested to proceed through a stepwise mechanism with formation of an intermediate being the RDS.[15] However, the β_{nuc} value of 0.54 obtained for the current reactions performed in 80 mol % H_2O/20 mol % DMSO is similar to that reported for the reactions of asymmetric diaryl carbonates with a series of aryloxides in pure H_2O, which were concluded to proceed through a concerted mechanism, (*e.g.*, $\beta_{nuc} = 0.48$ and 0.61 for the reactions of 4-nitrophenyl 4-methylphenyl carbonate and 4-nitrophenyl phenyl carbonate with aryloxides, respectively).[19] Thus, one can suggest that the current reactions of **5e** proceed also through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.54$.

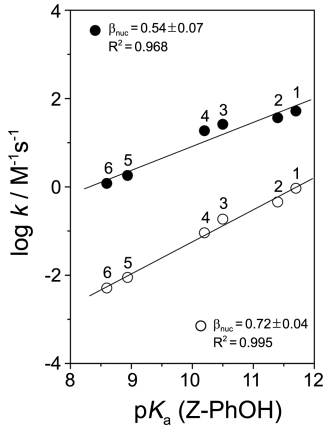


Figure 1. Brønsted-type plot for the reactions of 4-nitrophenyl phenyl carbonate **5a** (●) and 4-nitrophenyl benzoate **4e** (○) with Z-substituted-phenoxides in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

Reaction Mechanism Deduced from Hammett and Yukawa-Tsuno Plots. To get further information on the reaction mechanism, nucleophilic substitution reactions of phenyl Y-substituted-phenyl carbonates **5a-g** with 4-chlorophenoxide (4-ClPhO$^-$) have been performed. The kinetic results for the reactions of **5a-g** are summarized in Table 2. It is noted that **5g** is less reactive than **5f** although the former possesses a less basic leaving group than the latter. This is consistent with the previous reports that **5g** is less reactive than **5f** toward quinuclidine and piperidine.[20] The steric hindrance exerted by the 2-NO_2 group has been suggested to be responsible for the decreased reactivity shown by **5g**.[20]

If the reactions of **5a-g** proceed through a concerted mechanism as discussed in the preceding section, the C-OAr bond rupture occurs at the RDS. On the contrary, if the reactions proceed through a stepwise mechanism, the C-OAr bond rupture should occur after the RDS, since the incoming 4-ClPhO$^-$ is more basic and a poorer nucleofuge than the leaving aryloxides in this study. Accordingly, if the reactions proceed through a concerted mechanism, a partial negative charge would develop on the O atom of the leaving aryloxide in the transition state (TS). Since such a negative charge can be delocalized on the substituent Y through resonance interactions, one can expect that σ^- constants would result in a better Hammett correlation than σ^o constants. In contrast, if the reactions proceed through a stepwise mechanism, in which the C-OAr bond rupture occurs after the RDS, no negative charge would develop on the leaving aryloxide in the TS. Thus, σ^o constants should show a better Hammett correlation than σ^- constants if the reactions proceed through a stepwise mechanism.

To explore the reaction mechanism, Hammett plots have been constructed using the kinetic data in Table 2 for reactions of phenyl Y-substituted-phenyl carbonates **5a-f** with 4-ClPhO$^-$. As shown in Figures 2(a) and (b), the Hammett plots correlated with σ^o and σ^- constants exhibit highly scattered points with $\rho_Y = 1.61$ and 1.27, respectively. Thus,

Table 2. Summary of Second-Order Rate Constants for the Reactions of Phenyl Y-Substituted-Phenyl Carbonates **5a-g** with 4-ClPhO$^-$ in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

Entry	Y	$k_{4\text{-ClPhO}^-}/M^{-1}s^{-1}$
5a	3-CHO	2.00
5b	4-$COCH_3$	5.43
5c	4-CHO	9.35
5d	3-NO_2	9.47
5e	4-NO_2	25.9
5f	3,4-$(NO_2)_2$	276
5g	2,4-$(NO_2)_2$	131

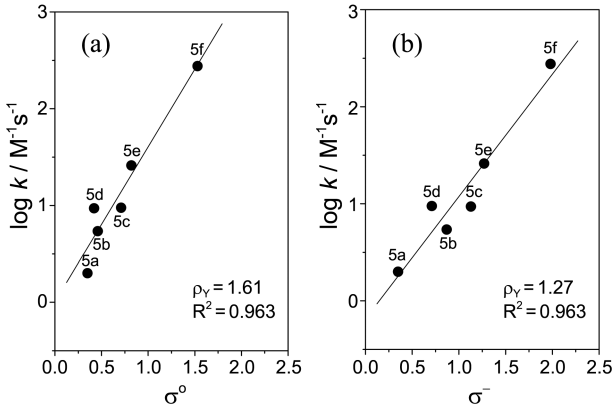


Figure 2. Hammett plots correlated with σ^{o} (a) and σ^{-} (b) constants for the reactions of phenyl Y-substituted-phenyl carbonates **5a-f** with 4-ClPhO^{-} in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

the Hammett plots in the current study cannot provide any reliable information on the reaction mechanism.

We have recently shown that the dual-parameter Yukawa-Tsuno equation, Eq. (2) is highly effective in elucidating ambiguities in reaction mechanisms for various acyl-group transfer reactions, *e.g.*, benzoyl-, thionobenzoyl-, benzenesulfonyl-, and phosphinyl-transfer reactions.[6-8] Accordingly, the Yukawa-Tsuno plot for the reactions of **5a-f** with 4-ClPhO^{-} has been constructed using the kinetic data in Table 2. As shown in Figure 3, the Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_Y = 1.51$ and $r = 0.52$.

$$\log k_Y/k_H = \rho\,(\sigma^{o} + r\,(\sigma^{-} - \sigma^{o})) \quad (2)$$

The r value in Eq. (2) represents the resonance demand of the reaction center or the extent of resonance contribution between the reaction site and the substituent.[21,22] The r value of 0.52 obtained for the reactions of **5a-f** with 4-ClPhO^{-} clearly indicates that a partial negative charge develops on the O atom of the leaving aryloxide in the TS, which can be delocalized on the substituent Y through resonance interactions. One can exclude a stepwise mechanism, in which

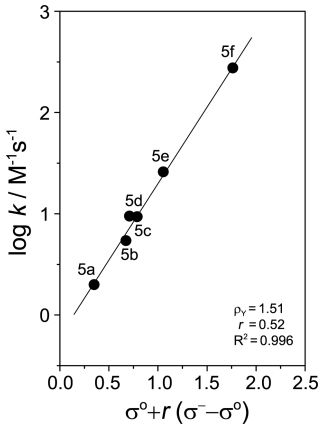


Figure 3. Yukawa-Tsuno plot for the reactions of phenyl Y-substituted-phenyl carbonates **5a-f** with 4-ClPhO^{-} in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

breakdown of the C-OAr bond occurs at the RDS, because 4-ClPhO^{-} is more basic and a poorer nucleofuge than the leaving aryloxides employed in this study. Thus, the linear Yukawa-Tsuno plot with $\rho_Y = 1.51$ and $r = 0.52$ supports the preceding conclusion that the reactions of **5e** with Z-PhO^{-} proceed through a concerted mechanism.

Conclusions

The current study has allowed us to conclude the following: (1) 4-Nitrophenyl phenyl carbonate (**5e**) is more reactive than 4-nitrophenyl benzoate (**4e**). Reduced steric hindrance and/or an inductive effect are responsible for the high reactivity of **5e**. (2) The linear Brønsted-type plot with $\beta_{nuc} = 0.54$ for the reactions of **5e** with Z-substituted-phenoxides suggests that the reactions proceed through a concerted mechanism. (3) Hammett plots correlated with σ^{o} and σ^{-} constants for the reactions of **5a-f** with 4-ClPhO^{-} exhibit highly scattered points. In contrast, the Yukawa-Tsuno plot for the reactions of **5a-f** with 4-ClPhO^{-} results in an excellent linear correlation with $\rho_Y = 1.51$ and $r = 0.52$, implying that the C-OAr bond rupture occurs in the RDS and that the reactions proceed through a concerted mechanism.

Overall, our study has shown that modification of the nonleaving group from benzoyl to phenyloxycarbonyl causes a change in reaction mechanism from a stepwise mechanism to a concerted pathway as well as an increase in reactivity.

Experimental Section

Materials. Phenyl Y-substituted-phenyl carbonates (**5a-g**) were readily prepared from the reaction of phenyl chloroformate with Y-substituted phenol in anhydrous ether under the presence of triethylamine. DMSO 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 low solubility of **5a-g** in pure water, aqueous DMSO (80 mol % H_2O/20 ml % DMSO) was used as the reaction medium.

Kinetics. The kinetic study was performed using 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 Y-substituted phenoxide ion. All the reactions were carried out under pseudo-first-order conditions.

Typically, the reaction was initiated by adding 5 μL of a 0.02 M solution of **5a-g** in acetonitrile to a 10-mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of solvent and aliquot of aryloxide stock solution. All solutions were transferred by gas-tight syringes. Generally, the aryloxide concentration in the reaction mixtures 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 $\ln (A_\infty - A_t)$ *vs.* time were linear over 90% of the total reaction. Usually, five different aryloxide concentrations were employed and repli-

cate values of k_{obsd} were determined to obtain the second-order rate constants ($k_{Z\text{-}PhO^-}$) from the slope of linear plots of k_{obsd} *vs*. aryloxide concentrations.

Products Analysis. Y-Substituted phenoxide was liberated quantitatively and identified as one of the products by comparison of the UV-vis spectrum after completion of the reaction with that of authentic sample under the same reaction condition.

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