DOI 10.5012/bkcs.2010.31.7.2015

Kinetics and Mechanism of Alkaline Hydrolysis of Y-Substituted Phenyl Phenyl Carbonates

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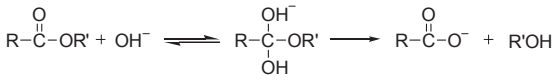
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Received May 20, 2010, Accepted May 27, 2010

Second-order rate constants (k_{OH^-}) have been measured spectrophotometrically for alkaline hydrolysis of Y-substituted phenyl phenyl carbonates (**2a-j**) and compared with the k_{OH^-} values reported previously for the corresponding reactions of Y-substituted phenyl benzoates (**1a-j**). Carbonates **2a-j** are 8 ~ 16 times more reactive than benzoates **1a-j**. The Hammett plots correlated with σ^- and σ^o constants exhibit many scattered points, while the Yukawa-Tsuno plot results in excellent linear correlation with $\rho = 1.21$ and $r = 0.33$. Thus, the reaction has been concluded to proceed through a concerted mechanism in which expulsion of the leaving group is advanced only a little. However, one cannot exclude a possibility that the current reaction proceeds through a forced concerted mechanism with a highly unstable intermediate.

Key Words: Alkaline hydrolysis, Concerted mechanism, Inductive effect, Hammett plot, Yukawa-Tsuno plot

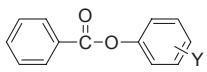
Introduction

Alkaline hydrolysis of carboxylic esters has generally been reported to proceed through a stepwise mechanism with a discrete tetrahedral intermediate as shown in Scheme 1.[1-5] The evidence for a stepwise mechanism comes from the ^{18}O exchange experiments on alkaline hydrolysis of alkyl benzoates in $H_2{}^{18}O$ performed by Bender *et al*.[3a] and heavy-atom isotope effects on reactions of methyl formate by Marlier.[3b] The stepwise mechanism, which was proposed based on the experimental results, has also been supported by theoretical calculations on the MP2/6-31+G* level of theory by Hori *et al*.[4a] and on MP2/6-31++G(d,p)//B3LYP/6-31++G(d,p) calculations by Zhan *et al*.[4b]



Scheme 1

We have recently performed alkaline hydrolysis of Y-substituted phenyl benzoates (**1a-j**) and 4-nitrophenyl X-substituted benzoates to investigate the effect of substituents X and Y on reactivity and mechanism.[5] The reaction of **1a-j** with HO^- has been concluded to proceed through a stepwise mechanism in which formation of an addition intermediate is the rate-determining step (RDS), since σ^o constants result in a better Hammett correlation than σ^- constants.[5]



1a-j

Y = 3,4-$(NO_2)_2$ (**1a**), 4-NO_2 (**1b**), 4-CHO (**1c**), 4-COMe (**1d**), 3-NO_2 (**1e**), 4-CO_2Et (**1f**), 3-CHO (**1g**), 3-Cl (**1h**), 3-COMe (**1i**), H (**1j**).

On the other hand, the Hammett plot for the reaction of 4-nitrophenyl X-substituted benzoates has been found to consist of two intersecting straight lines, i.e., from a large slope (ρ_X) to a small one as the substituent X changes from electron-donating groups (EDG) to electron-withdrawing groups (EWG). Such a nonlinear Hammett plot has traditionally been interpreted as a change in RDS upon changing the substituent X.[6] However, we have proposed that the nonlinear Hammett plot is not due to a change in RDS but is caused by ground-state (GS) stabilization through resonance interactions between the EDG and the C=O bond of the substrate, since the Yukawa-Tsuno plot for the same reaction exhibits excellent linear correlation with $r = 0.5$.[5]

Although scattered information on alkaline hydrolysis of organic carbonates is available, its mechanism has not clearly been understood due to lack of systematic studies.[7] Thus, we have performed a systematic study on alkaline hydrolysis of Y-substituted phenyl phenyl carbonates (**2a-j**) to investigate the reaction mechanism (Scheme 2). It has been suggested that PhO is a stronger EWG than Ph on the basis of their σ_I values (e.g., $\sigma_I = 0.38$ for PhO and $\sigma_I = 0.10$ for Ph),[8] while the former is also known to be a stronger EDG than the latter on the basis of their σ_R values (e.g., $\sigma_R = -0.34$ for PhO and $\sigma_R = -0.11$ for Ph).[8] We wish to report the effect of replacing the Ph group in **1a-j** by PhO on reactivity and reaction mechanism.

Results and Discussion

All reactions in this study obeyed pseudo-first-order kinetics in the presence of a large excess of OH^- ion. Pseudo-first-order



2a-j

Y = 3,4-$(NO_2)_2$ (**2a**), 4-NO_2 (**2b**), 4-CHO (**2c**), 4-COMe (**2d**), 3-NO_2 (**2e**), 4-CO_2Et (**2f**), 3-CHO (**2g**), 3-Cl (**2h**), 3-COMe (**2i**), H (**2j**).

Scheme 2

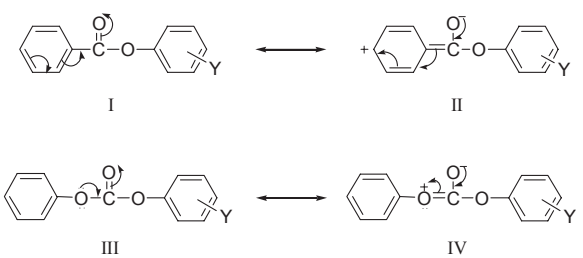
Table 1. Summary of second-order rate constants for reactions of Y-substituted phenyl benzoates (**1a-j**) and Y-substituted phenyl phenyl carbonates (**2a-j**) with OH^- in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

entry	Y	$pK_a^{Y\text{-PhOH}}$	$k_{OH^-}/M^{-1}s^{-1}$	
			1	**2**
a	3,4-$(NO_2)_2$	5.42	98.9	794
b	4-NO_2	7.14	13.4	140
c	4-CHO	7.66	4.72	50.8
d	4-COMe	8.05	3.27	34.7
e	3-NO_2	8.35	5.97	-
f	4-COOEt	8.50	3.11	35.1
g	3-CHO	8.98	1.93	25.7
h	3-Cl	9.02	-	21.4
i	3-COMe	9.19	1.80	21.2
j	H	9.95	0.449	7.31

[a]The data for the reactions of **1a-j** were taken from ref. 5.

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.* $[OH^-]$ were linear passing through the origin. The second-order rate constants (k_{OH^-}) were determined from the slope of the linear plots of k_{obsd} *vs.* $[OH^-]$. The uncertainty in the k_{OH^-} values is estimated to be less than 3% from replicate runs. The k_{OH^-} values determined in this way for the reactions of carbonates **2a-j** are summarized in Table 1 together with those reported previously for the corresponding reactions of benzoates **1a-j** for comparison purpose.

Origin of enhanced reactivity of 2a-j. One might expect that the GS of **1a-j** and **2a-j** can be stabilized through resonance interactions as modeled by I ↔ II and III ↔ IV, respectively. Since PhO has been suggested to be a stronger EDG than Ph on the basis of their σ_R values,[8] resonance structure IV would be more favorable than resonance structure II. Thus, one might expect that **2a-j** are more stable and less reactive than **1a-j** if resonance effect is an important factor to govern the reactivity of these benzoates and carbonates. However, Table 1 shows that **2a-j** are 8 ~ 16 times more reactive than **1a-j**, indicating that stabilization of the GS through resonance interactions is not an important factor in the current reactions.



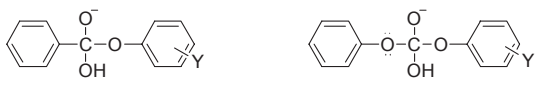
I II

III IV

The fact that **2a-j** are more reactive than **1a-j** suggests that PhO behaves a stronger EWG than Ph. This idea can be supported by their σ_I values (e.g., $\sigma_I = 0.38$ for PhO and $\sigma_I = 0.10$ for Ph).[8] Thus, one can suggest that inductive effect is more significant than resonance effect in the current reaction. A similar conclusion has recently been drawn for pyridinolysis of 2,4-dinitrophenyl phenyl carbonate, which has been found to be more reactive than 2,4-dinitrophenyl benzoate.[10] Pyridinolyses of these esters have been concluded to proceed through a stepwise mechanism with a change in the RDS.[10] Dissection of the macroscopic rate constants (k_N) into the microscopic rate constants (k_1 and k_2/k_{-1} ratio) has revealed that the carbonate exhibits much larger k_1 values than the benzoate regardless of the pyridine basicity, while the k_2/k_{-1} ratio is dependent on the pyridine basicity.[10] Thus, it has been concluded that the PhO group in **2a-j** increases the electrophilicity of the reaction site by acting as a stronger EWG than Ph.[10]

Another possibility which might account for the reactivity order is steric effect. 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 expected to be similar to that of $PhCH_2$ ($E_S = -0.38$).[9] Since the E_S value of Ph is −2.55,[9] PhO is considered to be much less bulkier than Ph. Thus, one might suggest that steric effect is also responsible for the fact that **2a-j** are more reactive than **1a-j**. However, the k_{OH^-} value for alkaline hydrolysis of 4-nitrophenyl acetate (PNPA) was reported to be 9.5 $M^{-1}s^{-1}$,[11] which is much smaller than that for the reaction of 4-nitrophenyl phenyl carbonate **2b** (e.g., $k_{OH^-} = 794\ M^{-1}s^{-1}$). Although the CH_3 group in PNPA would exert less steric hindrance than the PhO group in **2b**, PNPA is less reactive than **2b**. Thus, one can suggest that steric effect may not be significant for the current reactions.

Reaction mechanism. Alkaline hydrolysis of **1a-j** has been reported to proceed through a stepwise mechanism, in which formation of intermediate V is the RDS.[5] Alkaline hydrolysis of **2a-j** would proceed also through a stepwise mechanism with intermediate VI or through a concerted pathway. If the reaction proceeds through a concerted mechanism, a partial negative charge would develop on the oxygen atom of the leaving Y-substituted phenoxide in the transition state (TS). Since such a negative charge can be delocalized on the substituent Y through resonance interaction, one might expect that σ^- constants result in better Hammett correlation than σ^o constants.[6] In contrast, if the reaction proceeds through a stepwise mechanism, formation of intermediate VI should be the RDS. This is because OH^- ion is much more basic and a poorer nucleofuge than Y-substituted phenoxide. Accordingly, if the reaction proceeds through a stepwise mechanism, leaving-group departure would occur after the RDS. In this case, σ^o constants should result in better Hammett correlation than σ^- constants since no negative charge would develop on the oxygen atom of the leaving Y-substituted phenoxide in the TS.[6]



V VI

To investigate the reaction mechanism, Hammett plots have been constructed in Figures 1A and 1B. One can see that the Hammett plot correlated with σ^- constants (A) exhibits highly scattered points with a poor correlation coefficient (i.e., R^2 =

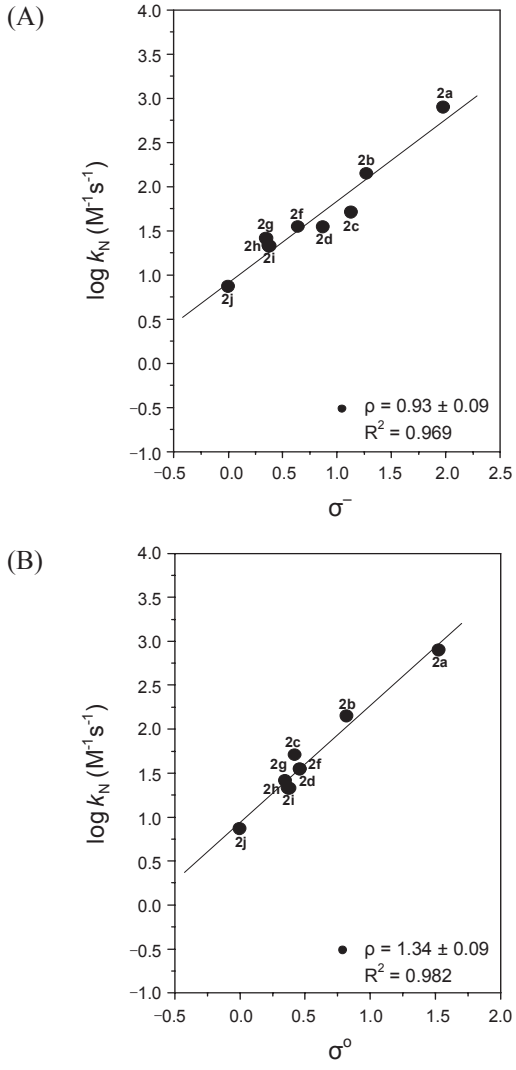


Figure 1. Hammett plots correlated with σ^- (A) and σ^o (B) constants for alkaline hydrolysis of Y-substituted phenyl phenyl carbonates **2a-j** in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

0.969). The plot correlated with σ^o constants (B) results in slightly better linearity (i.e., $R^2 = 0.982$) but still exhibits many scattered points. Thus, one cannot get conclusive information on the reaction mechanism from these Hammett plots.

We have recently shown that Yukawa-Tsuno plots are highly effective to elucidate ambiguities in reaction mechanism for various nucleophilic substitution reactions (e.g., alkaline hydrolysis and ethanolysis of Y-substituted phenyl diphenylphosphinates,[12] aminolysis of aryl benzoates[13] and related esters).[14,15] Thus, a Yukawa-Tsuno plot has been constructed. As shown in Figure 2, the Yukawa-Tsuno plot exhibits an excellent linear correlation with ρ = 1.21 and r = 0.33. The r value in eq (1) represents the resonance demand of the reaction center or the extent of resonance contribution, while the term $(\sigma_Y^+ - \sigma_Y^o)$ is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron donor substituent.[16,17] The r value of 0.33 determined in the reaction of **2a-j** indicates that a partial negative charge develops on the oxygen atom of the leaving group in the TS, which delocalizes on the substituent

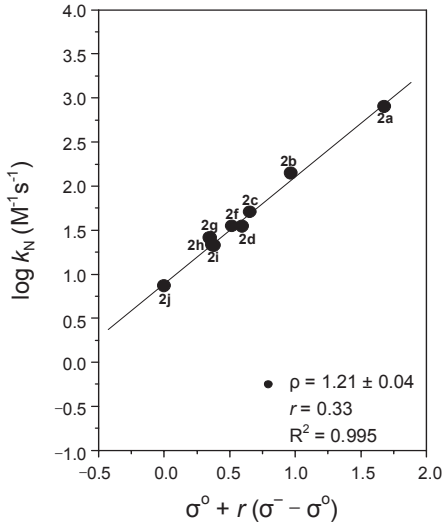


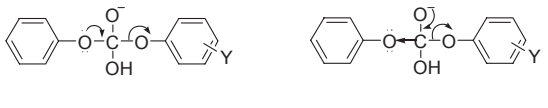
Figure 2. Yukawa-Tsuno plot for alkaline hydrolysis of Y-substituted phenyl phenyl carbonates **2a-j** in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

Y through resonance interactions. Thus, one can conclude that the current reaction proceeds through a concerted mechanism, in which expulsion of the leaving group is advanced in the TS but only a little on the basis of the small r value (i.e., r = 0.33).

$$\log (k_Y/k_H) = \rho[\sigma_Y^o + r(\sigma_Y^+ - \sigma_Y^o)] \quad (1)$$

Nucleophilic substitution reactions of α-d-glucopyranosyl fluoride with anionic nucleophiles have been reported to proceed with glucosyl oxocarbenium ion as an intermediate in aqueous solution.[18] However, it has been suggested that the intermediate has no significant lifetime when it is in contact with a strong nucleophile.[18] Thus, Banait and Jencks have concluded that the reaction proceeds through a forced concerted mechanism.[18]

One might suggest that the current reaction of **2a-j** proceeds through a forced concerted mechanism with highly unstable intermediate (i.e., VI). One might expect that VI would be less stable than V due to the nature of PhO. As shown in VI_a, the push provided by PhO would accelerate the expulsion of the leaving group. On the other hand, the electron-withdrawing nature of PhO would encourage formation of the C=O bond, which expels the leaving group as shown in VI_b. Accordingly, one might suggest that PhO in VI decreases the stability of VI by increasing the rate of leaving-group departure whether PhO behaves as a stronger EDG (e.g., VI_a) or EWG (e.g., VI_b) than Ph. Thus, one might suggest that the reaction proceeds through a forced concerted mechanism with a highly unstable intermediate, although the kinetic result for the reaction of **2a-j** is consistent with a concerted mechanism. This idea can be supported by the small r value obtained from the reaction of **2a-j**.



VI_a VI_b

Conclusions

The current study has allowed us to conclude the following: (1) Carbonates **2a-j** are more reactive than benzoates **1a-j**. (2) PhO behaves as a stronger EWG than Ph, indicating that inductive effect is more significant than resonance effect in the current reaction. (3) Hammett plots correlated with σ^- and σ^o exhibit many scattered points, while the Yukawa-Tsuno plot results in excellent linear correlation with $\rho = 1.21$ and $r = 0.33$. (4) The reaction of **2a-j** proceeds through a concerted mechanism, in which the expulsion of the leaving group is advanced only a little. (5) One might suggest that the current reaction proceeds also through a forced concerted mechanism with a highly unstable intermediate, although the kinetic result supports a concerted pathway.

Experimental Section

Materials. Substrates **2a-j** were readily prepared from the reaction of phenyl chloroformate with Y-substituted phenol in the presence of triethylamine in anhydrous ether as reported previously.[19] Their purity was confirmed from melting point and spectral data such as ^{1}H NMR. 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 the low solubility of **2a-j** in pure H_2O, 80 mol % H_2O/20 mol % DMSO was used as the reaction medium.

Kinetics. The kinetic study was performed using a UV-vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ s) or a stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) equipped with a constant temperature circulating bath to keep the reaction temperature at 25.0 ± 0.1 °C. All the reactions were carried out under pseudo-first-order conditions in which the sodium hydroxide concentration was at least 20 times greater than the substrate concentration. Solutions were transferred with gas-tight syringes under nitrogen. The reactions were followed by monitoring the leaving Y-substituted phenoxide.

Product analysis. Y-Substituted phenoxide was liberated quantitatively and identified as one of the reaction products by comparison of the UV-vis spectra after completing the reactions with those of authentic samples under the same kinetic conditions.

Acknowledgments. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2009-0075488). S. I. Kim and E. M. Jung are grateful for the BK 21 and Intern Scholarship, respectively.

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