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critical point.[11] In the not too distant future we shall discuss the above effects on the circular intensity differences.

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A Mechanistic Study on Acyl Transfer Reactions of Aryl Substituted Benzoates Between Aryloxides

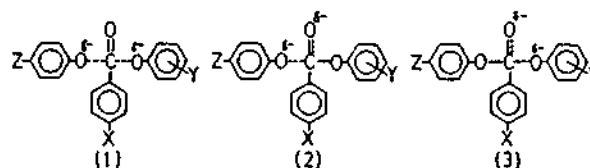## Ik-Hwan Um*, Jae-Shin Jeon, and Dong-Sook Kwon

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Second order rate constants have been measured spectrophotometrically for reactions of 4-nitrophenyl substituted benzoates with various aryloxides and aryl benzoates with p-chlorophenoxide. The reactivity has exhibited significant dependences on the electronic nature of the substituent in the acyl moiety of the substrate and in the nucleophilic phenoxide, while the substituent in the leaving phenoxide has little influenced the reactivity. The Bronsted coefficient β values so obtiained support that the present acyl transfer reaction proceeds *via* a stepwise mechanism in which the nucleophilic attack would be the rate-determining step. Interestingly, the magnitude of the β_{acyl} and β_{nuc} increases with increasing reactivity, implying that the reactivity selectivity principle is not operative in the present system. The failure of the reactivity selectivity principle is attributed to a change in transition state structure upon the substituent variation in the present acyl transfer reaction.

Introduction

Elucidation of reaction mechanism in chemical reactions has been a main goal for mechanistic chemists.[12] Numerous types of linear free energy relationships (LFERs) have been performed to investigate reaction mechanism,[3-6] especially for biologically important reactions such as acyl transfer reactions. However, acyl transfer reactions have not fully been understood. Two distinct mechanisms have been suggested, *i.e.*, one-step concerted pathway[3,4] and stepwise addition-elimination pathways.[5,6] The one-step pathway has been suggested to proceed with a single transition state (1) in which bond formation by nucleophile occurs concertedly with leaving group departure. This mechanism has been supported by the result of ab initio calculations for the reaction of CH_3COCl with Cl^- ion[4a] as well as by experimental results for many types of acyl transfer reactions.[3,4b] On the other hand, numerous evidences have been reported in favor of the formation of a tetrahedral intermediate in which the TS structure would resemble either 2 or 3 depending on the nature of the rate-determining step.[5,6]

Therefore the following acyl transfer reactions have been chosen to investigate reaction mechanism systematically. Since the aryl acetates system has only two places (the aromatic rings of the leaving and attacking phenoxides) to place subs-

tituent without changing the structure significantly, limited information (β_{lg} and β_{nuc}) has been obtained from the LFER study. Unlike the effect of substituent on the nucleophile (β_{nuc}) and on the leaving group (β_{lg}), it has been suggested that the effect of substituent on the acyl moiety (β_{acyl}) would give information not just on the charge development but also the hybridization change upon reaching the TS.[7] Thus, the present system would be considered to be better than the previous aryl acetate system for a systematic study of reaction mechanism, particularly on the nature of the TS structure.[8] We report here the result of kinetic studies for reac-
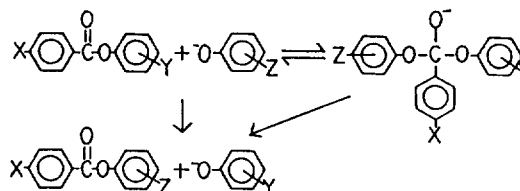
Acyl Transfer Reaction Mechanism

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Table 1. Summary of Second-Order Rate Constant k_2 $(M^{-1}s^{-1})$ for Reactions of p-Nitrophenyl Substituted Benzoates $(X-C_6H_4CO_2$ $C_6H_4-4-NO_2)$ with Substituted Phenoxides $(Z-C_6H_4O^-)$ in 20 mole% $DMSO-H_2O$ Mixture at 25℃

X/Z	k_2, $M^{-1}s^{-1}$				
	4-CN	4-Cl	H	4-CH₃	4-OCH₃
4-CN	0.121	5.92	18.9	37.0	64.9
4-Cl	0.0135	0.604	2.05	4.37	5.58
H	0.00510	0.185	0.452	0.925	1.27
4-ʰBu	0.00247	0.0726	0.184	0.376	0.540
4-OCH₃	0.00133	0.0344	0.0889	0.165	0.268

tions of aryl substituted benzoates with aryloxides.

Experimental

Materials. The aryl substituted benzoates in the present study were easily prepared by literature procedures[9] using benzoyl chlorides prepared from the corresponding acids with thionyl chloride. Their purity was checked by means of their melting point and spectral data such as IR and ¹H NMR characteristics. The phenols and benzoic acids were of the highest quality available (Aldrich) and were generally recrystallized before use. Doubly glass distilled water was boiled and cooled under nitrogen just before use. Only freshly prepared solutions were used in the kinetic study.

Kinetics. The kinetic studies were performed with a Hitachi U-2000 Model UV-Vis spectrophotometer equipped with a Neslab RTE-110 Model constant temperature circulating bath to keep the temperature in the UV cell at 25.0± 0.1 ℃.

The reactions were followed by monitoring the appearance of leaving phenoxides at a fixed wavelength corresponding to the maximum absorption (λ_{max}) of $Y-C_6H_4O^-$. All the reactions were carried out under pseudo-first-order conditions in which the concentration of nucleophile was generally 20 times, but at least 10 times greater than the substrate concentration. The stock solutions of the nucleophilic aryloxides were made up with NaOH solution and 2 equivalent corresponding phenol to suppress formation of hydroxide ion by solvolysis as described previouly.[5a]

Results

All the reactions studied here obeyed pseudo-first-order kinetics up to over 90% of the total reaction. Pseudo-first-order rate constants (k_{obs}) were obtained from the Guggenheim equation, $\ln(A_\infty - A_t) = k_{obs}t + c$. Generally, five different concentrations of nucleophile were used to get second-order
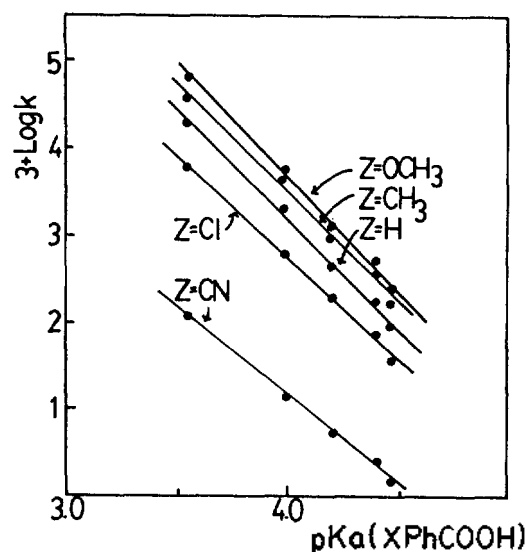

Figure 1. Bronsted type plots for reactions of p-nitrophenyl substituted benzoates $(4-X-C_6H_4CO_2C_6H_4-4-NO_2)$ with substituted phenoxides $(4-Z-C_6H_4O^-)$ in 20 mole% $DMSO-H_2O$ mixture at 25℃. The particular substituted phenoxide is fixed for each line as indicated.

rate constants from the plots of k_{obs} vs the concentration of nucleophile. The intercept values of these plots were very small indicating the contribution of hydroxide ion and/or solvent to the rate was negligible for the present reaction condition.

In Table 1 are presented the second-order rate constants for the reactions of p-nitrophenyl X-substituted benzoates with Z-substituted phenoxides at 25.0℃ in water containing 20 mole % dimethyl sulfoxide (DMSO) to eliminate a solubility problem. The corresponding data for the reactions of Y-substituted phenyl benzoates with p-chlorophenoxide are given in Table 2. The kinetic data are shown graphically in Figures 1, 2 and 3. The results of the Bronsted correlations are summarized in Tables 3 and 4 for the reaction of p-nitrophenyl X-substituted benzoates with Z-substituted phenoxides.

Discussion

Reaction Mechanism. In Table 1 are summarized second-order rate constants for the acyl transfer reactions. It is clearly demonstrated that the reactivity increases with increasing acid strengthening substituent in the acyl moiety of the substrate, and base strengthening substituent in the nucleophilic phenoxide.

For a quantitative investigation of the substituent effect

Table 2. Second-Order Rate Constants k_2 $(M^{-1}s^{-1})$ for Reactions of Substituted Phenyl Benzoates $(C_6H_5CO_2C_6H_4-Y)$ with p-Chlorophenoxide in 20 mole% $DMSO-H_2O$ Mixture at 25℃

Y	2,4-(NO₂)₂	2-NO₂-4-Cl	4-NO₂	4-CHO	3-CHO	4-CH₃CO	3-NO₂
pK_a (Y-ArOH)[a]	4.11	6.46	7.14	7.66	8.00	8.05	8.35
k_2	8.41	0.215	0.185	0.0552	0.00610	0.0236	0.0416

[a]pK_a values are taken from ref. 17

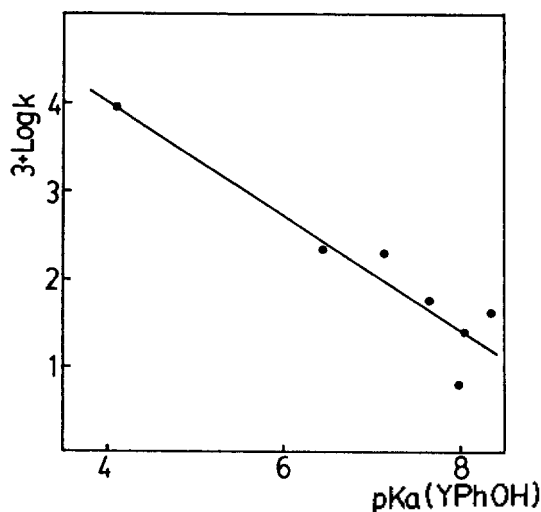408 *Bull. Korean Chem. Soc., Vol. 12, No. 4, 1991*

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Figure 2. Bronsted type plot for reactions of substituted phenyl benzoates ($C_6H_5CO_2C_6H_4$-Y) with 4-chlorophenoxide in 20 mole% DMSO-H_2O mixture at 25°C. The slope of the plot is calculated to be -0.639 ($r=0.940$).

Table 3. Summary of Bronsted Correlations for Reactions of Various Aryloxides (4-Z-$C_6H_4O^-$) with p-Nitrophenyl Substituted Benzoates (4-X-$C_6H_4CO_2C_6H_4$-4-NO_2) in 20 mole% DMSO-H_2O Mixture at 25°C

Z	4-CN	4-Cl	H	4-CH₃	4-OCH₃
pK_a (Z-ArOH)[a]	7.95	9.38	9.95	10.19	10.20
β_{acyl}	-2.06	-2.36	-2.49	-2.50	-2.55
r	0.997	0.997	0.996	0.995	0.998

[a] pK_a values are taken from ref. 17.

Figure 3. Bronsted type plots for reactions of p-nitrophenyl substituted benzoates (4-X-$C_6H_4CO_2C_6H_4$-4-NO_2) with substituted phenoxides (4-Z-$C_6H_4O^-$) in 20 mole% DMSO-H_2O mixture at 25°C. The particular substituted benzoic acid is fixed for each line as indicated.

Table 4. Summary of Bronsted Correlations for Reactions of p-Nitrophenyl Substitued Benzoates (4-X-$C_6H_4CO_2C_6H_4$-4-NO_2) with Various Aryloxides (4-Z-$C_6H_4O^-$) in 20 mole% DMSO-H_2O Mixture at 25°C

X	4-CN	4-Cl	H	4-'Bu	4-OCH₃
pK_a (X-ArCO₂H)[a]	3.55	3.99	4.20	4.40	4.47
β_{nuc}	1.15	1.13	1.02	0.99	0.96
r	0.995	0.998	0.996	0.996	0.994

[a] pK_a values are taken from ref. 17.

on reactivity, the Bronsted type plots have been constructed in Figure 1. The large negative slopes with excellent linearities shown in the plots clearly indicate that the reactivity is significantly sensitive to the electronic effect of the substituent X in the acyl moiety of the substrate for all the nucleophilic aryloxides used. Such large negative Bronsted slopes would not have been expected if the attack of nucleophile is not involved in the rate-determining step, whether the reaction proceeds *via* one or two-step pathways.

If the leaving group departure is involved in the rate-determining step, the bond rupture would be getting more difficult with increasing the electron withdrawing ability of the substituent X in the acyl moiety. Consequently, the magnitude of the Bronsted slope (β_{acyl}) would be expected to be small or even a positive slope would be expected when the leaving group departure is more important than the nucleophilic attack. Therefore, the large negative Bronsted slopes obtained here would indicate that the leaving group departure is little involved in the rate-determining step for the present reaction system.

Such a determination of reaction mechanism based on the magnitude of the sensitivity parameter has successfully been applied to the reaction of substituted benzaldehydes with semicarbazide.[10] The reactivity of substituted benzaldehydes has been reported to be significantly sensitive to the elec-
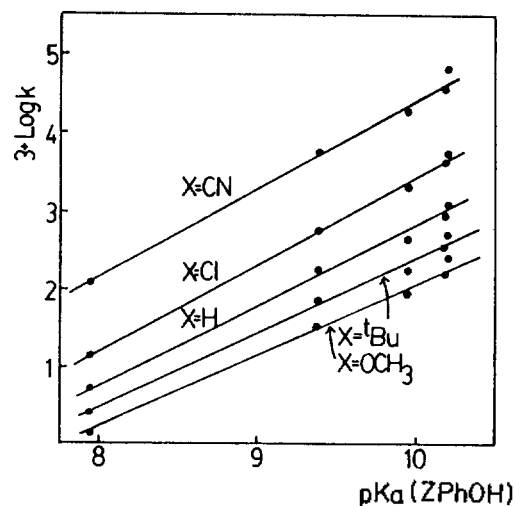
tronic nature of the substituent in an acidic medium. Thus a large Hammett ρ value has been obtained at pH 1.75 in which the addition of semicarbazide to form a carbinolamine is the rate-determining step. On the other hand, the reactivity has been reported to be little influenced upon the substituent change at pH 7.00 in which the dehydration of the carbinolamine is the rate-determining step.[10]

A further study has been performed by changing the substituent Y in the leaving phenoxide to investigate the extent of leaving group departure at the TS of the rate-determining step. Second-order rate constants for the reaction of substituted phenyl benzoates with p-chlorophenoxide are summarized in Table 2 and plotted against the basicity of the leaving phenoxide in Figure 2. Generally, the reactivity increases with increasing acid strengthening ability of the substituent Y in the leaving group. The enhanced reactivity would possibly originate from an increased leaving group ability and/or an enhanced electrophilicity of the reaction center. A careful examination, however, of Figure 2 and Table 2 reveals that the correlation of the rate constant with basicity of the leaving phenoxide is poor, *i.e.*, the reactivity is much higher for the substituent Y=3-NO_2 than Y=4-CH_3CO and 3-CHO in the leaving group although 3-NO_2 is the weakest acid strengthening substituent among them. Moreover, the reactivity

is little sensitive to the substituent change resulting in a small Bronsted β_{lg} value. This is contrary to what would have been expected if the leaving group departure is involved in the rate-determining step.

The larger β_{acyl} value compared to β_{lg} would be understood in terms of proximity effect, *i.e.*, the reacting bond being one atom closer to the acyl substituent than it is to the leaving aryloxide. However, the nature of reaction mechanism would be considered to be more responsible than the proximity effect for the significant difference in the β values. This has nicely been demonstrated in the aminolysis of substituted phenyl benzoates in which the leaving group departure has generally been known to be the rate-determining step. It has been reported that the Bronsted β_{acyl} value is much smaller (1.03) than β_{lg} value (1.73), although the former would have been expected to be larger if the proximity effect is important.[6c] Therefore, the comparison of β_{lg} with β_{acyl} values obviously lend more credence to the argument that the leaving group departure is little advanced at the TS of the rate-determining step for the present acyl transfer reaction system.

Unlike the substituent on the leaving group, the one on the nucleophilic phenoxide significantly influences the nucleophilicity resulting excellent Bronsted correlations with large slopes (β_{nuc}) as shown in Table 4 and Figure 3. Since the proximity effect for the substituent Y and Z would be same, the magnitude of β_{nuc} and β_{lg} would represent a direct extent of bond formation and bond rupture at the TS of the rate-determining step, respectively. As shown in Table 4 and Figure 3, the β_{nuc} values are much larger and better correlated than β_{lg} (Figure 2). This result indicates consistently that the nucleophilic attack would be much more advanced than the leaving group departure in the TS of the rate-determining step. Therefore, the present acyl transfer reactions are proposed to proceed *via* a step-wise mechanism in which the nucleophilic attack is the rate-determining step.

The Reactivity Selectivity Principle and TS Structure. In Tables 3 and 4 are summarized the Bronsted β values for the present acyl transfer reactions. The magnitude of β_{acyl} for the more reactive nucleophile is obtained to be larger. For example, the β_{acyl} values are -2.55 and -2.06 for 4-CH$_3$O-C$_6$H$_4$O$^-$ and 4-CN-C$_6$H$_4$O$^-$, respectively, although the former is more reactive than the latter. This result is quite unexpected based on the Leffler-Hammond postulate.[11] Such unusual β values are also observed for the β_{nuc} values. A careful examination of Tables 3 and 4 reveals a definite trend, *i.e.*, the magnitude of β increases with increasing reactivity of both the substrate and the nucleophile. Therefore, the reactivity selectivity principle[12] (RSP) is not applicable to the present acyl transfer reactions.

In Figure 4 has been constructed a schematic three-dimensional potential energy surface diagram[13] to study the transition state for the present reaction system. The reactants and products are at the bottom-left corner R and the up-right corner P, respectively. Similarly, the intermediates for the S$_N$1 pathway and the addition-elimination pathway are placed at the up-left corner O and the bottom-right corner Q, respectively.

If the reaction proceeds *via* a concerted one-step S$_N$2 like pathway, one would expect the TS would move along the diagonal RP where the attack of nucleophile occurs in the
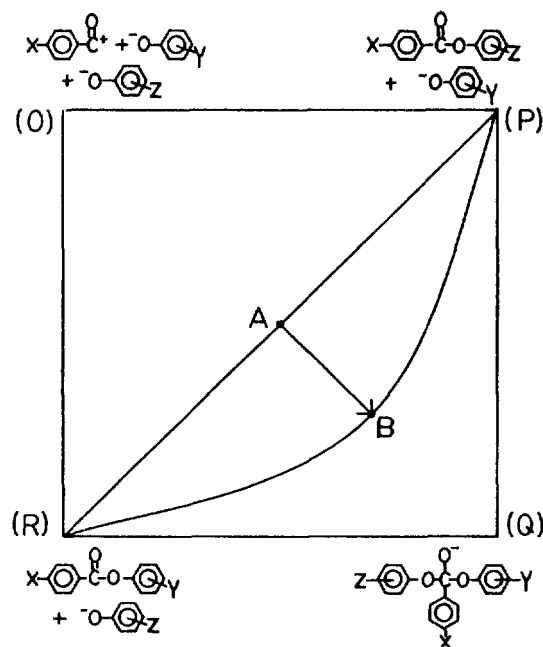

Figure 4. Schematic three-dimentional potential energy surface diagram for reactions of substituted phenyl benzoates (X-C$_6$H$_4$-CO$_2$C$_6$H$_4$-Y) with substituted phenoxides (Z-C$_6$H$_4$O$^-$).

same extent with the leaving group departure. However, based on the reaction mechanism discussed above, the position of the TS for the present system would be considered to deviate from the RP diagonal. It is, therefore, expected that the TS would move toward the bottom-right corner (A→B direction) in accord with the anti-Hammond motion, since the leaving group departure has been suggested to be little advanced at the TS of the rate-determining step. Such an anti-Hammond motion would be more significant when the substituent X in the acyl moiety becomes a stronger electron withdrawing group, since the up-left corner would be expected to be more destabilized. The shift of the TS to the A→B direction would also accompany more bond formation and less leaving group departure at the TS. Therefore, the unusual trend of β_{nuc} values for the present reaction system would be attributed to the argument that the TS structure would resemble the addition intermediate more and more as the substituent X becomes a stronger electron withdrawing group.

A similar argument could be applied to the unusual trend of β_{acyl} values. Although the β_{acyl} values can not be used as a direct measure of bond formation between the nucleophile and the substrate, it would be expected that the magnitude of the β_{acyl} conveys a relative magnitude of bond formation at the TS of the rate-determining step for the present system.

If the present reaction preceedes *via* a concerted S$_N$2-like mechanism, the position of the TS would move along the diagonal RP upon the substituent change in the nucleophile. A smaller β_{acyl} value would be expected upon changing to a more reactive nucleophile on the basis of the Leffler-Hammond postulate. The present result, however, is contrary to what would be expected, *i.e.*, the magnitude of β_{acyl} is larger for the more reactive nucleophile (Z=CH$_3$O) than the less

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reactive one (Z=CN) as shown in Table 3. To account for the present result, the TS must not move along the diagonal RP. This is consistent with the preceding argument that the TS deviates from the diagonal RP based on the reaction mechanism and on the unusual trend of β_{nuc} values.

A strong electron donating substituent in the nucleophile would destabilize both the addition intermediate and nucleophile itself, and the TS would move toward the more destabilized corner. In the present result, the β_{acyl} value increases as the substituent Z becomes a stronger electron donating group. Thus, it would be considered that the addition intermediate is more destabilized than the nucleophile on going to the stronger electron donating substituent in the nucleophile on the basis of the present result that the TS shifts toward the addition intermediate. Possibly the less destabilization of the nucleophile compared to the addition intermediate could be attributed to the solvation effect. Since phenoxide with a strong electron donating substituent would be more solvated than the one with an electron withdrawing substituent, the destabilization of the phenoxide in the gas phase would be diminished in the solution phase on going to the stronger electron donating substituent. This is in accord with the fact that the difference in free energy of ionization in the gas phase between p-CH$_3$C$_6$H$_4$OH and p-CN-C$_6$H$_4$OH is over 17 kcal/mole[14] while the one in the present solvent system is only about 4.2 kcal/mole.[5a]

Thus the TS structure variation is considered to be responsible for the failure of the RSP in the present system. Since such a TS structure variation would accompany a change in the intrinsic barriers of a series of reactions, the RSP would not be expected based on the simple Marcus theory.[15]

However, more quantitative studies would be required for a complete understanding of the present resuelt. Studies on the cross-interaction constants[16] for the present and related systems are currently underway.

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