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A Multiple Hammett Study of the Nucleophilic Substitution Reaction of α-Carbonyl Derivatives

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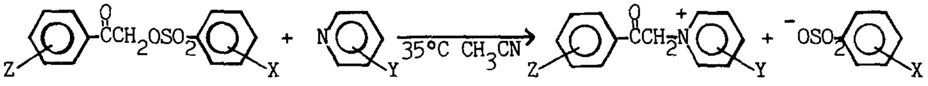
The reaction mechanism for the nucleophilic substitution reaction of substituted phenacyl benzenesulfonates with substituted pyridines in acetonitrile have been investigated by means of multiple Hammett correlation.

Although the nucleophilic substitution reactions of phenacyl halides have attracted considerable attention over several decades, opinions still differ about the precise mechanism.[1-5] The study of substituent effects provides one of the most powerful tools for probing the structure of transition state. The studies of substituent effects made until now for probing the reaction mechanism in phenacyl system have been, for the most part, toward substrate.[3,4]

We reported our results on the substituent effect of substrate, nucleophile, and leaving group for the reaction of substituted phenacyl benzenesulfonates with pyridines (1), respectively.[6]



(1)

As an extention, we have now investigated the interaction between substituents of nucleophile and those of leaving group, and the interaction between substituents of nucleophile and those of substrate, in order to clarify the nucleophilic substitution reaction mechanism of phenacyl system that is not yet clear.

Second-order rate constants for the reaction of phenacyl substituted(X) benzenesulfonates with substituted(Y) pyridines in acetonitrile at 35°C are shown in Table 1. There is an enhancement in the rate of nucleophilic substitution for a given nucleophile when electron-withdrawing substituents are present in the leaving group, and for a given leaving group when electron-donating substituents are present in the nucleophile.

The Hammett ρX and ρY values determined from linear plots of $\log(k/k_o)_X$ vs. σX and $\log(k/k_o)_Y$ vs. σY, respectively, are shown in Table 2. The ρX values increase gradually in order of 4-methylpyridine, 3-methylpyridine, pyridine, and 3-bromopyridine. In view of this result, the partial negative charge on the oxygen atom in the sulfonate group, which is developed in the transition state according to the bond cleavage between C and O, becomes large depending on the electron-withdrawing power of the substituent in the nucleophile; the bond cleavage between C and O becomes large (the reduction of bond-order between C and O). The plot of ρ_X obtained in this reaction *vs.* σ_Y (the substituent constant of nucleophile) shows a linear correlation with a slope of 0.42 ($r = 0.987$).

Table 1. Rate constants ($10^6\ k_2$ / l mol^{-1} s^{-1}) for the reactions of phenacyl X-benzenesulfonates with Y-pyridines in acetonitrile at 35°C

X	Y = 4-NH_2	3-NH_2	4-CH_3	3-CH_3	H	3-Br	3-Cl	4-CN
p-NO_2			8480	6840	3720	283		102
m-NO_2					3590			
p-Cl					1260			
p-Br			2020	1640	853	65.2		24.6
H			872	715	325	26.7		10.1
p-CH_3	8750	1222	500	371	190	16.2	15.4	9.85
p-CH_3O			363	287	139	10.7		4.17

Table 2. Reaction constants for the reactions of phenacyl X-sulfonates with Y-pyridines in acetonitrile at 35°C

X	ρ_Y (r)
p-NO_2	-2.47 (0.993)
p-Br	-2.47 (0.992)
H	-2.49 (0.992)
p-CH_3	-2.47 (0.980)

Y	ρ_X (r)
4-CH_3	1.31 (0.997)
3-CH_3	1.33 (0.996)
H	1.40 (0.985)
3-Br	1.54 (0.998)

The ρ_Y values remain unchanged, whatever substituent (*p*-NO_2, *p*-Br, H, and *p*-CH_3) may be present in the leaving group. This result can be compared with the result of the substituent effect of the leaving group obtained by varing the substituent in the nucleophile.

The rate constants for the reaction of substituted(Z) phenacyl tosylates with substituted(Y) pyridines in acetonitrile at 35°C are shown in Table 3. The substitution of a more electron-dona-

Table 3. Rate constants ($10^6\ k_2$ / l mol^{-1} s^{-1}) for the reactions of Z-phenacyl tosylates with Y-pyridines in acetonitrile at 35°C

Z	Y = 4-NH_2	3-NH_2	4-CH_3	3-CH_3	H	3-Br	3-Cl	4-CN
p-CH_3O			587	447	229			8.33
p-CH_3			595	463	238			7.96
H	8750	1220	500	371	190	16.2	15.4	9.85

ting group on the phenacyl moiety as well as on the nucleophile increase the rate of substitution reaction.

The Hammett ρ_Y and ρ_Z values obtained from linear plots of $\log(k/k_o)_Y$ *vs.* σ_Y and $\log(k/k_o)_Z$ *vs.* σ_Z, respectively, are shown in Table 4. The ρ_Y values decrease gradually in order of *p*-methoxyphenacyl tosylate, *p*-methylphenacyl tosylate, and phenacyl tosylate. This result is in contrast to the result for ρ_Y values which do not change for the various substituents in the leaving group. This shows that the induction of perturbation by the substitution of *p*-CH_3O and *p*-CH_3 group in the phenacyl moiety better accommodates the partial positive charge on the carbon atom of the reaction center than unsubstituted substrate, and thereby the bond-formation between the nitrogen atom and the carbon atom is more advanced and thus a decrease in ρ_Y is observed. The plot of ρ_Y obtained in this reaction *vs.* σ_Z gives a good linear correlation with a slope of -0.80 (r = 0.981).

Table 4. Reaction constants for the reactions of Z-phenacyl tosylates with Y-pyridines in acetonitrile at 35°C

Z	ρ_Y (r)
p-CH_3O	-2.26 (0.998)
p-CH_3	-2.30 (0.998)
H	-2.47 (0.980)

Y	ρ_Z (r)
4-CH_3	-0.28 (0.897)
3-CH_3	-0.33 (0.863)
H	-0.33 (0.859)

The ρ_Z values also have a tendency to decrease as the electron-donating power of substituent in the nucleophile decreases. The plot of ρ_Z obtained in this reaction *vs.* σ_Y gives a linear correlation with a slope of -0.31 (r = 0.912). This result indicates that ρ_Z is a function of σ_Y, and that the electronic effect of the substituent on the phenacyl moiety and that on the nucleophile affect each other.

The equation for the substituent effect of the system of three variables derived from Taylor expansion is[7] $\log k_{XYZ}/k_{000} = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_Z\sigma_Z + \rho_{XY}\sigma_X\sigma_Y + \rho_{XZ}\sigma_X\sigma_Z + \rho_{YZ}\sigma_Y\sigma_Z$

where, k_{XYZ}, k_{000} = the rate constant for compound substituted with X, Y, and Z, and that for unsubstituted compound, respectively.

ρ_{XY} = the degree of concertedness between the bond formation of nucleophile and the bond cleavage of leaving group.

ρ_{YZ} = the degree of bond formation of nucleophile with substrate.

ρ_{XZ} = the degree of bond cleavage of leaving group from substrate.

In this study, the term of interaction between X and Y, ρ_{XY} is shown to be 0.48. Therefore, the weaker the nucleophilicity of nucleophile is, the weaker the bond force between C and O becomes and the reactivity-selectivity principle is found. In contrast to this, ρ_Y and σ_X do not show such relationship ($\rho_{YX} \approx 0$). This result can be compared with the result for the reactions of benzyl substituted-benzenesulfonates with substituted N,N-dimethyl anilines[8] which proceed by synchronous S_N2 reaction and have the values of $\rho_{XY} = \rho_{YX} = 0.75$. From the rate constants for the reactions of benzyl substituted-benzenesulfonates with pyridine and with N,N-dimethyl aniline, the plot of $(\log k/k_o)_{N,N\text{-dimethyl aniline}}$ *vs.* $(\log k/k_o)_{\text{pyridine}}$ has a good linear correlation with a slope of 1.0. Therefore, if we consider the facts that the replacement of N,N-dimethyl aniline for pyridine did not change the effect of substituent in the leaving group and the substituent constants used in benzylic reactions and phenacylic reactions are identical, the reactions of phenacyl arenesulfonates can not proceed by synchronous S_N2 reaction due to carbonyl group which does not exist in benzyl arenesulfonates. In addition, the ρ_{XY} value of phenacyl system is 0.48 and is much smaller than that of benzyl system, 0.75. This result indicates that the interaction between X and Y for phenacyl system is much smaller than that for benzyl system. The result[8] that the ρ_{XY} value for benzyl system in the reaction of strong nucleophiles ($Y = p\text{-}CH_3O$, $p\text{-}CH_3$) was reduced to 0.4, while that in the reaction of weak nucleophiles ($Y = H$, $3\text{-}NO_2$) was 0.75 and thus complete concertedness was preserved, indicates that the result of this study is reasonable.

Considering the interaction between Y and Z, $\rho_Z = -0.31\,\sigma_Y$ ($\rho_{ZY} = -0.31$), while $\rho_Y = -0.80\,\sigma_Z$ ($\rho_{YZ} = -0.80$). This result indicates that the influence of Y (the substituent of nucleophile) exerted on Z (the substituent of phenacyl moiety) is not equal to that of Z exerted on Y, and can be compared with that for benzylic system which proceeds by synchronous S_N2 reaction, $\rho_{YZ} = \rho_{ZY} = 1.2$.

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