

STRUCTURE-REACTIVITY CORRELATION IN THE PYRIDINOLYSIS OF SUBSTITUTED PHENYL ACETATES

SOO-DONG YOH, JOONG-KYU KANG, and SUNG-HONG KIM

Chemistry Education, Kyungpook National University  
Taegu 635, Korea

(Received in Japan 17 September 1987)

**Abstract** - The pyridinolysis of substituted phenyl acetates in acetonitrile was investigated with an electric conductivity method. The rates of these reactions were increased with electron-donating group in pyridine and electron-withdrawing group in phenyl acetate.  $\rho_X$  (X; substituents in phenyl ring) values increase gradually according to the electron-donating ability in pyridine substituents, but the  $|\rho_Y|$  (Y; substituents in pyridine ring) values decrease with that of substituents. The  $\beta$  values increase with increasing electron-withdrawing ability of the substituents in the phenyl ring, it can be inferred that N---C bond formation increases progressively p-methyl to p-nitrophenyl acetates. This is in agreement with prediction of substituent effects for a simple  $S_N2$  displacement reaction. The sensitivity parameters,  $\beta$  and  $\rho$ , are inter-related and are themselves sensitive to the reactivity of the system. All above results are interpreted in terms of a dissociative  $S_N2$  mechanism involving a metastable tetrahedral intermediate.

Structure-Reactivity relationships in acyl transfer reactions are of interest in themselves and for the light they shed on the mechanism of the reactions. Structure-reactivity correlations for the reactions of various amines with substituted phenyl acetates<sup>1</sup> show a break from a large ( $\beta$  nuc=0.9) to a small ( $\beta$  nuc=0.2) dependence of the basicity of the attacking amine. The break has been interpreted as a consequence of a change in rate determining step from rate determining amine attack with the most basic amines ( $\beta$  nuc ~0.2) to rate-determining aryloxide expulsion from an addition intermediate with less basic amine ( $\beta$  nuc ~0.9). The value of  $\beta$  nuc are 0.15 and 0.93 for the attack of substituted pyridines on methyl chloroformate<sup>2</sup> under conditions of rate determining attack and breakdown, respectively. Most of the above reactions are amine-catalysed hydrolysis of carboxylic esters, i.e., for the reaction of pyridines with methyl chloroformate, p-nitrophenyl acetate<sup>3</sup>, 2,4-dinitrophenyl acetate<sup>3</sup>, and pyridinolysis of 2,4-dinitrophenyl p-nitrobenzoate<sup>4</sup> in aqueous solution. In pure organic solvent, however, nucleophilic displacement reactions for the reactions of carboxylic esters with t-amines and simultaneously the cross interactions of the substituents of phenyl and pyridine moiety do not seem to have been made so far.

In this paper, we report the kinetics and reaction mechanism for the reaction of substituted pyridines with substituted phenyl acetates, using activation parameters and linear free energy relationship for the Brønsted and Hammett plots.

### Experimental

All materials used were commercially available (Wako, Japan).

Pyridine was a commercial product purified by several distillation over potassium hydroxide before use. Other liquid pyridines were used without further purification, but solid pyridines were recrystallized to constant melting point. All purified pyridines were stored in brown ampoule or bottle filled with nitrogen gas. Acetonitrile was purified by distillation after standing with anhydrous potassium carbonate for three days at room temperature.

IR spectra were recorded on a Hitachi EPI-2C infrared Grating Spectrophotometer,  $^1\text{H}$  NMR spectra were taken with a Varian 60 MHz Spectrometer and conductance measurements were carried out with a Conductivity-Meter LBR (West Germany).

Phenyl acetates were prepared by a modification of a published procedures<sup>5</sup>. *p*-Nitrophenol (14 g, 0.1 mole), acetic anhydride (15 g, 0.125 mole) and a trace of pyridine were dissolved in 25 ml of dry benzene. The reaction mixture was refluxed for 4 hrs. After neutralization with saturated sodium bicarbonate solution, the benzene solution was washed with water, 5% NaOH solution, 0.1 N HCl and water, and dried over anhydrous magnesium sulfate. The benzene solution was then evaporated to dryness. The solid residue thus obtained was recrystallized from ligroin to give pale yellow crystals, mp 78–80°C (79–80°C)<sup>6</sup>, yield 80%.

Other phenyl acetates were prepared similarly and physical properties are listed in Table 1

Table 1. Physical Constants, Yields and Maximum Wavelength of Phenyl Acetates.

Sub.	b.p. °C(mmHg)(lit.6)	m.p. °C(lit.6)	$\lambda_{\text{nm}}$	Yield (%)
4-NO <sub>2</sub>		78-80 (79-80)	400	80
4-Cl	112(18) 113(18)		303	85
H	88(20) 87(20)		270	87
3-CH <sub>3</sub>	96(18) 97(18)		279	84
4-CH <sub>3</sub>	112(15) 123(15)		279	89

The product was identified as following method;

When the reaction of *p*-nitrophenyl acetate with pyridine, the *p*-nitrophenolate anion was released and the absorbance of the solution was recorded as a function of time with a Shimazu-210 spectrophotometer, the cell compartment which had been thermostated, at 400 nm wave length for the *p*-nitrophenol formed in the reaction.

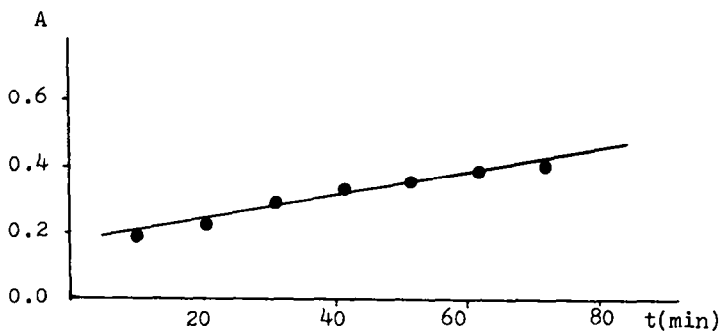
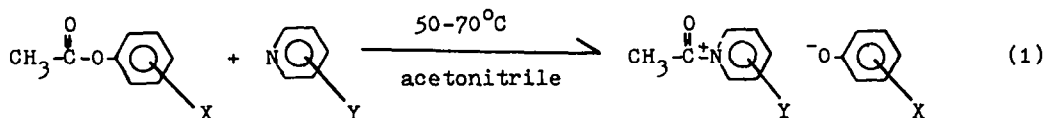


Figure 1. The relation of absorbance vs. time on the reaction of *p*-nitrophenyl acetate ( $5.0 \times 10^{-4}$  mol) with 4-aminopyridine ( $1.0 \times 10^{-2}$  mol) at 400 nm. and 60°C

Kinetic. The rate of reaction was measured by means of electric conductivity because the reaction is a kind of formation of salt in which ions are formed from electrically neutral reagents (eq.(1))



The final concentration of phenyl acetate prepared was made just 0.0075 mole/l in 15 ml volumetric flask which was filled with nitrogen gas and solvent. That of pyridine was made just 0.15 mole/l with above same. A kinetic run was initiated by placing 15 ml of pyridine solution in the conductivity cell and adding 15 ml of the phenyl acetate solution to give a reaction mixture.

All measurements were done with pyridines in large excess over phenyl acetates<sup>6</sup>. Reactions were generally run to ca 3 to 4 half-lives. Pseudo first-order rate constants were calculated from the slopes obtained from conventional plots of  $\log(C_\infty - C_t)$  against time using the least-squares method.

Second-order rate constants were calculated from the slopes of plots of the observed first-order rate constants against pyridine concentration.

#### Results and Discussion

The second-order rate constants and activation parameters for the reaction of substituted pyridines with substituted phenyl acetates in acetonitrile are summarized in Tables 2 and 3. The rate

Table 2. Kinetic Data and Activation Parameters for the Reaction of Substituted Phenyl Acetates with Substituted Pyridines.

(a)						
Y=4-NH <sub>2</sub>	10 <sup>3</sup> k <sub>2</sub> (1/mol min)			ΔH <sup>‡</sup>	-ΔS <sup>‡</sup>	
X	50°C	60°C	70°C	(Kcal/mol)	(e.u.)	
4-NO <sub>2</sub>	28.7	51.1	92.0	12.2	27.9	
4-Cl	21.7	40.2	72.1	12.6	27.3	
H	18.8	36.0	65.1	13.0	26.4	
3-CH <sub>3</sub>	18.5	35.6	64.9	13.2	25.8	
4-CH <sub>3</sub>	18.2	34.8	64.5	13.3	25.5	

(b)						
X=4-NO <sub>2</sub>	10 <sup>3</sup> k <sub>2</sub> (1/mol min)			ΔH <sup>‡</sup>	-ΔS <sup>‡</sup>	
Y	50°C	60°C	70°C	(Kcal/mol)	(e.u.)	
4-NH <sub>2</sub>	28.7	51.1	92.0	12.2	27.9	
3,4-(CH <sub>3</sub> ) <sub>2</sub>	18.9	35.2	63.7	12.7	27.3	
H	15.6	28.4	53.2	12.8	27.3	
3-COCH <sub>3</sub>	9.3	17.7	32.7	13.2	27.0	
3-Cl	8.0	16.25	28.9	13.5	26.4	

Table 3. Second-order Rate Constants for the Reaction of Substituted Phenyl Acetates with Substituted Pyridines at 60°C ( $10^3 k_2$  (l/mol min) )

Y \ X	4-NO <sub>2</sub>	4-Cl	H	3-CH <sub>3</sub>	4-CH <sub>3</sub>
4-NH <sub>2</sub>	51.1	40.2	36.0	35.6	34.8
3,4-(CH <sub>3</sub> ) <sub>2</sub>	35.2	28.4	24.7	24.5	24.4
H	28.4	22.7	20.4	20.2	20.0
3-COCH <sub>3</sub>	17.7	14.5	13.0	12.9	12.8
3-Cl	16.25	12.9	12.1	12.0	11.9

constants and  $\Delta H^\ddagger$  have shown that electron-donating substituents in the pyridines increase the rate and decrease  $\Delta H^\ddagger$ , while the substituents decrease the rate and increase  $\Delta H^\ddagger$  in the phenyl acetates.

This is as expected for nucleophilic attack of amines on the carbon atom.

The values of the activation parameters show a regular variation with substituents in the both of phenyl and pyridine ring.

A linear relationship between the enthalpies and the entropies of activation has been realized. From the slopes of the linear plot, the isokinetic temperature are calculated to be 448 K ( $r=0.992$ ) and 894 K ( $r=0.980$ ) for the reaction of the substituted phenyl acetates with 4-aminopyridine and 4-nitrophenyl acetate with substituted pyridines, respectively.

It was generally accepted that Brønsted linear relationship was shown between the rate of reaction and basicities of nucleophiles in which attacking atom is the same in S<sub>N</sub>2 reaction. The direction of the influence of the substituents in pyridine ring shows that the rate of reaction depend on the electron density of the nitrogen atom.

Good linearity of this relationship has been reported<sup>7,8</sup> on quaternization of substituted pyridines. The  $\beta$  values of these plots, though the value is very similar, increase with increasing electron-withdrawing ability of the substituents in the phenyl ring (Table 4).

Table 4.  $\beta$  and Correlation Coefficients ( $r$ ) of the Brønsted Plots (Fig. 2.) for the Reaction of Pyridines with Substituents.

X	$\sigma_X$	$\beta$	$r$
4-NO <sub>2</sub>	0.78	0.080	0.992
4-Cl	0.23	0.078	0.988
H	0.00	0.077	0.994
3-CH <sub>3</sub>	-0.07	0.076	0.992
4-CH <sub>3</sub>	-0.17	0.075	0.991

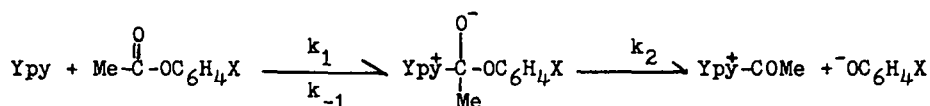
Table 5. Slopes ( $\rho_X$ ) and Correlation Coefficients ( $r$ ) of the Hammett Plots (Fig. 4.) for the Reaction of Pyridines with Phenyl Acetates.

Y	pKa	$\rho_X$	$r$
4-NH <sub>2</sub>	9.12	0.180	0.997
3,4-(CH <sub>3</sub> ) <sub>2</sub>	6.46	0.175	0.990
H	5.21	0.165	0.994
3-COCH <sub>3</sub>	3.18	0.153	0.992
3-Cl	2.84	0.148	0.988

From the  $\beta$  value, it can be inferred that N---C bond formation increases progressively from p-methyl to p-nitrophenyl acetate. This is in agreement with prediction of substituent effects for a simple S<sub>N</sub>2 displacement reaction. The large Brønsted slopes ( $\beta$ ) have been found in the nucleophilic reaction of substituted pyridines with methyl chloroformate ( $\beta$  0.93 to 0.15) and p-nitrophenyl acetate ( $\beta$  0.93), 2,4-dinitrophenyl acetate ( $\beta$  0.85), and acetic anhydride ( $\beta$  1.0). Most of the above Brønsted plots are composed of two straight lines; one in the region of low basicities of the nucleophiles and the other at high basicities and a curvature in between.

In all these reactions the occurrence of a tetrahedral intermediate in the reaction path has been proposed, and the magnitude of the higher Brønsted slope has been connected with the decomposition to products of the intermediate as being the rate-determining step. Our small  $\beta$  value, however, may be suggested that the first step of Scheme 1 is rate-determining one. The macroscopic rate constants from reactants to products of Scheme I is  $k_N$ , which

Scheme I



can be related to the microscopic rate constants of the Scheme through application of the steady state treatment to the tetrahedral intermediate (eq. (2) )

$$k_N = k_1 k_2 / (k_{-1} + k_2) \dots \dots \dots (2)$$

If the first step of Scheme I is rate determining for the present reactions, it follows that  $k_2 \gg k_{-1}$ ; equation (2) then leads to  $k_N = k_1$

It should be kept in mind that relative reactivities vary with solvent.

For example, in aqueous dioxane the relative reactivity of pyridine as compared with acetate, towards acetic anhydride drops by many powers of ten as the solvent becomes less aqueous<sup>9</sup>.

The less rate constants of these reactions are in agreement with above results.

In the case of very good leaving groups as in the acid, hydration of the carbonyl group is rate-limiting. In the case of very poor leaving groups, as in the hydrolysis of amides ( $pK \sim 35$ ), expulsion of the leaving group is rate-limiting.

The Hammett  $\rho_X$  and  $\rho_Y$  values obtained from linear plots of  $\log(k/k_0)_X$  vs  $\sigma_X$  and  $\log(k/k_0)_Y$  vs  $\sigma_Y$ , respectively are listed in Table 5 and 6. The  $\rho_X$  values increase gradually in order of 3-chloro, H, 3,4-dimethyl, and 4-amino pyridine, according to the electron-donating ability. On the other hand, the  $|\rho_Y|$  values decrease gradually in order of 4-NO<sub>2</sub>, 4-Cl, H, and 4-CH<sub>3</sub>-pyridine, according to the electron-donating ability.

The results are in agreement with prediction of substituent effects for a S<sub>N</sub>2 reaction mechanism. The  $\rho_X$  values, which decrease with decreasing reactivity of the pyridine, are linearly related to pKa of the pyridine as shown in Fig. 2, in agreement with that found in the reaction of anilines with benzenesulfonyl chlorides<sup>10</sup>. The slope of the plot of  $\rho_X$  against pKa is the same value as that of the plot of  $\beta$  against  $\sigma_X$  in which the value is 0.005 (Fig. 3). This is as expected since the various  $\rho$  and  $\beta$  values are inter-related through eq.(3)

$$\frac{\rho_1 - \rho_2}{pKa^1 - pKa^2} = \frac{\beta_1 - \beta_0}{\sigma_1} = C \dots\dots\dots (3)$$

where C is a constant<sup>11,12</sup>. As  $\rho$  is related to the extent of bond breaking relative to bond formation<sup>13</sup>. The conclusion<sup>14</sup> that stretching and charging of the C-O bond increases relative to the formation of the C-N bond, i. e., the transition state becomes more product-like, with increasingly electron-donating substituents in the nucleophile, and electron-attracting ones in leaving group is confirmed.

Thus, the transition state for these reactions may be illustrated by Scheme 2, taking no position for the moment as to whether a metastable tetrahedral addition intermediate is formed in the course of the reaction.

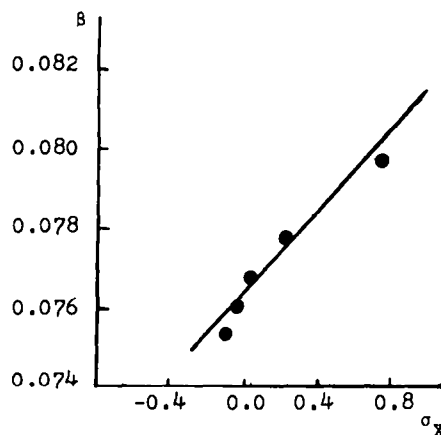
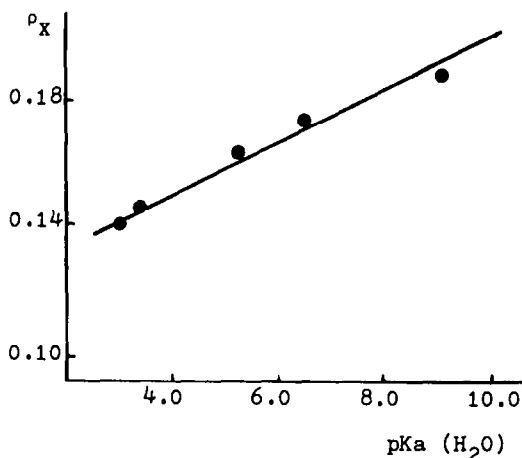


Fig. 2. Dependence of the Hammett  $\rho_X$  Values (Table 5) Upon the Basicity of the Pyridines.

Fig. 3.  $\beta$  vs.  $\sigma_X$  of the Substrates.

All above results show that concerted mechanism in which bond breaking is more advanced, involving a metastable tetrahedral intermediate for these reactions.

Scheme 2

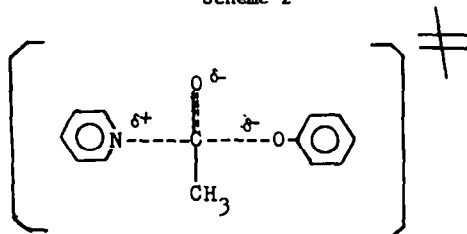


Table 6. Slopes ( $\rho_Y$ ) and Correlation Coefficients( $r$ ) of the Hammett Plots (Fig. 6) for the Reaction of Pyridines with Phenyl Acetates.

X	$\rho_Y$	r
4-NO <sub>2</sub>	-0.469	0.991
4-Cl	-0.460	0.988
H	-0.447	0.993
3-CH <sub>3</sub>	-0.445	0.993
4-CH <sub>3</sub>	-0.441	0.992

#### Acknowledgment

We are grateful to Ministry of Education, Korea, for financial support of this work.

#### References

1. C. Castro and E. A. Castro, *J. Org. Chem.*, 1981, 46, 2939
2. P. M. Bond, E. A. Castro, and R. B. Modie, *J. Chem. Soc., Perkin Trans. II*, 1983, 453
3. W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, 1967, 90, 2622
4. E. A. Castro and G. B. Steinfert, *J. Chem. Soc., Perkin Trans. II*, 1983, 453
5. M. L. Bender and K. Nakamura, *J. Am. Chem. Soc.*, 1962, 84, 2577
6. W. Takaki, D. Fukushima, T. Eiki, and Y. Tano, *J. Org. Chem.*, 1979, 44, 555
7. Soo-Dong Yoh, Kyung-A Lee, and Sung-Shik Park, *Korean Chem. Soc.*, 1982, 26(5), 333
8. Soo-Dong Yoh, Kwang-Tack Shim, and Kyung-A Lee, *ibid.*, 1981, 25(3) 110-118
9. Koskiallil. J., *Acta Chem. Scand.*, 1963, 17, 1417
10. O. Rogne, *J. Chem. Soc., (B)* 1971, 1855
11. E. H. Cordes and W. P. Jencks. *J. Am. Chem. Soc.*, 1962, 84, 4319
12. W. P. Jencks, *Progr. Phys. Org. Chem.*, 1964, 2, 63
13. C. G. Swain and W. P. Langsdorf, *J. Am. Chem. Soc.*, 1951, 73, 2813
14. P. Beltrame, P. L. Beltrame, and L. Bellotti, *J. Chem. Soc., (B)*, 1969, 932