Summary

The isotopic acyl exchange between *p*-nitrophenyl acetate and acetic acid was studied in neutral organic solvents in the presence of several kinds of bases. The kinetics showed the first order dependency of the exchange rate on the base. The exchange reaction is shown to consist of the two steps. The preliminary step produced the pyridine-acetic acid complex which participated in the true exchange step. The effect on the exchange rate of structural changes of the base was attributed to changes in base strength and steric effect, and they affected the preliminary equilibrium. Solvent effect on the exchange rate and curvature of *k* *vs*. [Base] were due mainly to effect on the true exchange step and partly to effect on the preliminary step.

(Received October 6, 1964)

[Chem. Pharm. Bull. 13(3) 361～368 (1965)]

UDC 547.564.3.07.02.14

49. **Yukio Akahori**: Studies on Isotopic Acyl Exchange. III.[*1] Acyl Exchange Reaction of Substituted Phenyl Acetates; Effect of Nuclear Substituents on the Exchange Rate.

(*Shizuoka College of Pharmacy*[*2])

In Part I,[*1] isotopic acyl exchange between *p*-nitrophenyl acetate and acetic acid in pyridine was described, and the existence of a preliminary reaction between the acid and pyridine was suggested. The preliminary reaction was studied in Part II,[*1] and it was found that the preliminary reaction was the rapid equilibrium reaction and that the effect on the exchange rate of structural changes of the base was due to the change of the equilibrium constant. The main factor which governs the exchange rate, however, may be related to the rate-determining step which is closely connected with the ester employed in the exchange reaction. The structural changes of the acyl group in the ester may act on the exchange rate in dual manner; the one is the action on the preliminary equilibrium as acyl component, and the other is the direct effect on the rate-determining step. Therefore, the structural changes of acyl group in the ester may afford complicated effects on the exchange rate. Meanwhile, the effects on the exchange rate due to structural changes of the phenol group in the ester may act only on the rate determining step, and the study of the effects may be important to elucidate the reaction mechanism. Present paper deals with the study on the relation between the exchange rate and the structure of the phenol ring in the ester.

Experimental

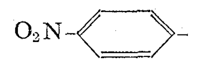
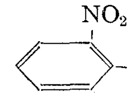
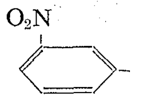
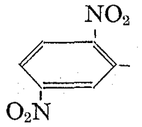
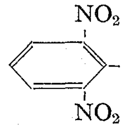
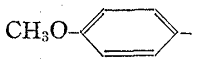
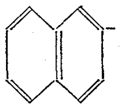
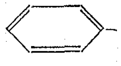
1) **Materials**——Substituted phenyl acetates: Substituted phenols were acetylated by means of Ac_2O and conc. H_2SO_4 as described in Part I,[*1] and the resulting esters were recrystallized from suitable solvents. Phenyl acetate was prepared by the same method and purified by distillation. Their properties were collected in Table I.

[*1] Part I. Y. Akahori, S. Fukushima: This Bulletin, 12, 166 (1964); Part II. Y. Akahori: *Ibid.*, 13, 352 (1965).

[*2] Oshika, Shizuoka (赤堀幸男).

Table I. Properties of Phenyl Acetates

$ROCOCH_3$

R	Cryst. form	Recryst. solvents	m.p. (found)	m.p. (lit.)	Calcd.			Found		
					C	H	N	C	H	N
	colorless needles	dil. MeOH	78~79	79~80,1) 77.5~78,2) 79.5~80,3) 76.54)						
	〃	petr. ether	38.5~39.5	39~40,5) 37.56)						
	〃	〃	54~55	55~564)						
	〃	MeOH	92		42.49	2.67	12.39	42.72	2.91	12.21
	〃	〃	109		42.49	2.67	12.39	42.78	2.67	12.28
	colorless prisms	dil. MeOH	31~32	31~327)						
	colorless needles	〃	68~69	70,8) 66.39)						
	colorless liquid		b.p. 192~193	b.p. 19510)						

Substituted phenyl acetates (carbonyl-^{14}C) : The labeled acetates were prepared by means of Ac_2O (carbonyl-^{14}C) and conc. H_2SO_4 as described above.

AcOH, pyridine, toluene and Ac_2O(carbonyl-^{14}C) were prepared by the method described in Part I.[*1]

2) **Analytical Procedure**——a) Counting was carried out by the method described in Part I.[*1]

b) Determination of kinetic rate was due to the method appeared in Part I.[*1]

c) Reaction procedure : The exchange reaction was carried out in pyridine without any kind of solvents. The general method adopted in Part I was applied to the present study. For the case of phenyl acetate, the aftertreatment was carried out as follows. The reaction mixture was poured into cold water, and the resulting solution was extracted with ether. The ethereal solution was washed with dil. HCl, dil. $NaHCO_3$ and water, successively, followed by drying over anhyd. Na_2SO_4. After removal of the solvent, the ester was dried under reduced pressure then the weight was measured. The ester was dissolved in a suitable amount of toluene, and aliquots of the solution were transferred into counting vials by using a volumetric pipette, followed by addition of toluene and scintillator solution (double strength) into the vials.

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1) O. Fernández, C. Torres : An. soc. espãn., **21**, 30 (1923); C. A., **17**, 3021 (1923).
2) M. L. Bender, B. W. Turnquest : J. Am. Chem. Soc., **79**, 1652 (1957).
3) R. S. Hartley, R. A. Kilby : Bioch. J., **56**, 288 (1954).
4) F. Arnall : J. Chem. Soc., **125**, 814 (1924); C. A., **18**, 2142 (1924).
5) N. Waljaschko : Zur. Russ. Phys. Chem. Obs., **42**, 962 (1924); Beilstein, **I**, **6**, 115 (1931).
6) J. Böseken : Rec. trav. chim., **31**, 355 (1912); Beilstein, **I**, **6**, 115 (1931).
7) Klemenc : Monatsh., **35**, 90 (1914), Beilstein, **I**, **6**, 416 (1931).
8) Miller : Ber., **14**, 1602 (1881); Graebe : Ann., **209**, 150 (1878); Beilstein. **H**, **6**, 644 (1923).
9) J. Kendall, J. E. Booge : J. Am. Chem. Soc., **38**, 1720 (1916).
10) M. Lecat : Rec. trav. chim., **46**, 245 (1927); Beilstein, **II**, **6**, 153 (1944).

d) Examination of the isolation method : Chemical and radiochemical purities of the reaction products were confirmed by the methods described in Part I,*1 and it was found that recrystallization from suitable solvents gave the pure samples enough to be subjected to kinetic examinations.

In the case of phenyl acetate, chemical purity of the reaction product was confirmed by IR spectrum. The possibility of a separation-induced exchange must be inspected, because the period required for isolation product was relatively long in this case. Treatment of the reaction-solution at time zero showed no separation-induced exchange, and the radiochemical purity of the product was confirmed by the same method.

Meanwhile, dinitrophenyl acetates were fairly unstable, and they were partly suffered by hydrolysis even in the cold aqueous pyridine solution. And the hydrolysis was observed when the reaction-solution was treated with ice-water. Fortunately, the hydrolysis was reduced by the rapid treatment, and recrystallization of the resulting crude products could remove the phenols and the acid produced by the hydrolysis. The separation-induced exchange was observed in the cases of dinitrophenyl acetates even at 0°, when the aqueous suspension was allowed to stand for a long period after the reaction-solution was poured into ice-water. Accordingly, it was required that the resulting precipitates were immediately separated from the mother liquor, and the treatment showed practically no separation-induced exchange.

In all of the other cases, no separation-induced exchange was observed as same as in the case of *p*-nitrophenyl acetate.

p-Acetylphenyl acetate could not be isolated by this separation method, and 2,4,6-tribromophenyl acetate was insoluble in the reaction-solution, and they were failed to afford the kinetic data.

e) Examination of the counting method : Dinitrophenyl acetates showed considerable quenching at higher concentration, and careful weighing and calibration for the quenching were required.

In the case of phenyl acetate, accuracy of amount of the sample taken in counting vials was inspected, and reliability of the method was proved by the experiment using the counting sample which had the known radioactivity.

f) The labeled position in the reaction product was determined by the method described in Part I,*1 and the labeled position was found to be the acyl carbon atom in the esters.

Results

For substituted phenyl acetates, the observed values of specific activities of the esters at equilibrium were identical with the values of x_∞ calculated by the McKay's formula (1).[11]

$$x_\infty = \frac{N_1 x_0 + N_2 y_0}{N_1 + N_2} \qquad (1)$$

The linearity of log $(1-F)$ *vs.* t was also found in all of these cases. The exchange rate R was calculated by the equation (2),[11] and the rate constant k was calculated by the equation (3).[11]

$$R = \frac{N_1 N_2}{N_1 + N_2} \cdot \frac{\ln 2}{t_{1/2}} \qquad (2)$$

$$R = k N_1 N_2 \qquad (3)$$

Availability of the equation (2) and (3) for the present exchange reaction was experimentally confirmed, and the values of k were collected in Table II.

1) Relation between the position of nitro group and the exchange rate.

The bulky group existing at *o*-position in the phenol ring showed no steric retardation on the exchange rate. The exchange rate of *o*-nitrophenyl acetate was nearly identical with that of *p*-nitrophenyl acetate, but the exchange reaction of *m*-nitrophenyl acetate proceeded slower than those of *p*- and *o*-nitrophenyl acetates. Their E_a values were collected in Table II, and the temperature dependency of the exchange rate was shown in Fig. 1.

2) Effect of number of nitro groups on the exchange rate.

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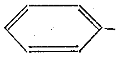
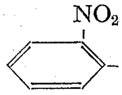
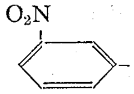
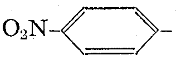
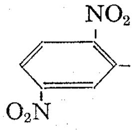
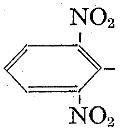
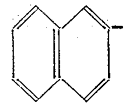
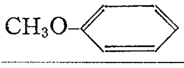
[11] H. A. C. McKay : Nature, **142**, 997 (1937).

Table II. Rates of Exchange Reactions of Substituted Phenyl Acetates with Acetic Acid in Pyridine. (C_6H_5-OAc)

C_6H_5	$10^5 k$ (L./mole/sec.)							E_a
	65.0°	55.0°	45.0°	37.0°	25.5°	25.0°	0°	(Kcal./mole)
	0.038	—	—	—	—	—	—	—
	—	—	7.25	3.87	—	1.25	—	15.3
	2.42	0.892	0.322	—	—	—	—	22.2
	—	—	6.29	3.15	1.33	—	0.144	14.7
	—	—	—	—	—	—	23.2	—
	—	—	—	—	—	—	46.4	—
	<0.003	—	—	—	—	—	—	—
	$<10^{-2}$	—	—	—	—	—	—	—

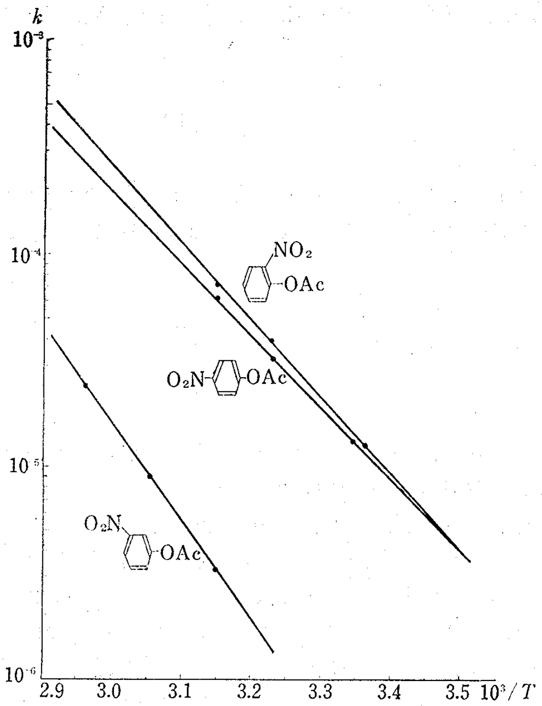
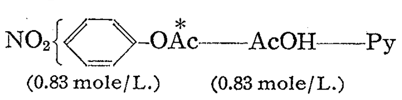


Fig. 1. Effect of Substituents



The increase of number of nitro groups in the phenol ring of the ester afforded surprising effect on the exchange rate. The exchange reactions of dinitrophenyl acetates took place quite rapidly at room temperature, and the half-exchange times $t_{1/2}$ were obtained only in the reactions undertaken at 0°. When nitro group was absent on the phenol ring, the exchange reaction proceeded quite slowly, as shown in the case of phenyl acetate. In this case, the accurate value of the half-exchange time $t_{1/2}$ could not be obtained and it was only deduced by extrapolation of $\log(1-F)$ vs. t. The same slow exchange reaction was observed in the case of β-naphthyl acetate.

3) Relation between electron-donating group on the phenol ring and the exchange rate.

The electron-attracting group on the phenol ring showed the promoting effect on the exchange rate as mentioned above, and the electron-donating group existing on the phenol ring gave the inhibiting effect on the exchange rate. *p*-Methoxyphenyl acetate showed the quite slow exchange even at 65.0°, and the value of $t_{1/2}$ was inferred to be more than 10^3 hours under this reaction condition by extending the line of log $(1-F)$ *vs.* t. Although it was difficult to compare the exchange rate of *p*-methoxyphenyl acetate with that of phenyl acetate because of the too slow reaction to get the accurate value of $t_{1/2}$, it was concluded that methoxyl group did not show any accelerating effect on the exchange rate but rather inhibiting effect.

Discussion

The exchange reaction between *p*-nitrophenyl acetate and acetic acid consists of two steps, the one is the preliminary reaction between acetic acid and pyridine as shown in the previous papers*[1] and the other is the true exchange reaction which takes place between the ester and the product of the preliminary reaction.*[1] The same reaction mechanism may be present in the cases of the other phenyl acetates. In the true exchange step, there may be three possibilities concerning the reaction center in the ester which is attacked by the product of the preliminary reaction; *i.e.*, (a) the carbonyl carbon atom in the ester, (b) the carbon atom which is present in the phenol ring and attached to the ester group, (c) the phenolic oxygen in the ester.

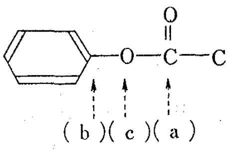
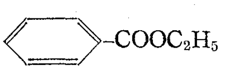
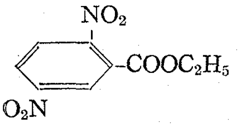
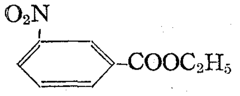
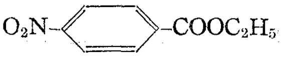


Fig. 2.

When the attack on the phenolic oxygen is assumed, there are shown several experimental evidences which are unfavorable to explain the reaction mechanism. The product of the preliminary reaction is the hydrogen-bonding complex or the ion-pair complex, as shown in Part II,*[1] when the exchange reaction is undertaken in neutral organic solvents. Although there is no proof for the presence of the complex in the exchange reaction undertaken in pyridine, it is favorable to presume the existence of the complex in this case. Accordingly, charge of the group which attacks the ester in the true exchange step may be really or potentially negative, and the reaction of the phenolic oxygen with the negatively charged group is considered to be unreasonable. Besides, the exchange reaction of the ester with acetic anhydride in pyridine showed the contribution of one-half of the radioactivity which was present in the starting anhydride, and the fact suggested no contribution of acetyl cation to the exchange reaction, as shown in Part I.*[1] These results show that the exchange reaction proceeds *via* the reaction of the negatively charged reactant with the ester. When the reactant attacks the phenolic oxygen, the reaction rate must be suffered by the steric effect of the bulky group present at *o*-position in the benzene ring. This relation was known in the case of hydrolysis of benzoates, as shown in Table III.[12] In the case of the present exchange reaction, however, no steric hindrance due to the substituent at *o*-position was observed as shown in the case of *o*-nitrophenyl acetate. And the same result is obtained in the exchange reaction of phenyl

Table III. Relative Rates of Base-Catalyzed Hydrolysis of Benzoates[12a,b,c,d)]

Compound	Relative rate[a)]
	1.00
	8.71
	69.0
	110

a) in 85% aq. EtOH.

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[12] *a*) C.K. Ingold: "Structure and Mechanism in Organic Chemistry," p. 759 (1953), Cornell Univ. Press. *b*) D.P. Evans, J.J. Gordon, H.B. Watson: J. Chem. Soc., **1937**, 1430. *c*) C.K. Ingold, W.S. Nathan: *Ibid.*, **1936**, 222. *d*) K. Kindler: Ber., **69**, 2792 (1936).

benzoates with respect to this problem, which will be described in the following paper. All of these evidences exclude the possibility (c) that the phenolic oxygen is attacked by the reactant which is produced by the preliminary reaction.

The steric effect also denies the possibility (b) that the reactant attacks the carbon atom which is present in the benzene ring and at the seat of the acetoxyl group. The bulky group present at *o*-position may afford some effects on the exchange rate, but the experimental results show no effect as described above. In the cases of dinitrophenyl acetates, their molecular structures satisfy the requirement which allows to form Meisenheimer's complex. Coloring of the reaction-solution in the cases of dinitrophenyl acetates is in accordance with the characteristic feature of Meisenheimer's complex,[13,14] and it is suggested that the exchange reaction of the dinitrophenyl acetates may proceed exclusively or partly *via* the Meisenheimer's complex. In the Meisenheimer's complex, the carbon atom at the reaction center takes sp^3 hybridization as shown in Fig. 3, and the steric course is analogous to widely known SE_2 reaction.[15] The similar mechanism was known in the case of transetherification of phenol ethers.[16] Accordingly, existence of the Meisenheimer's complex in the exchange reaction of dinitrophenyl acetates can not be excluded. In order to solve this problem, it is necessary to use ^{18}O for the exchange reaction, but the clues required for the elucidation of this point are afforded by the kinetic data obtained in the exchange reaction of dinitrophenyl benzoates, which will be discussed in the following paper.

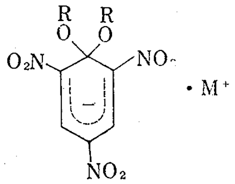
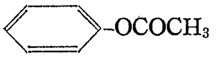
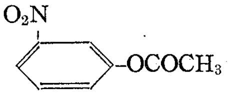
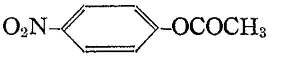


Fig. 3.

No steric effect on the exchange rate in various phenyl acetates indicates that the reaction center of the ester may be the carbonyl carbon atom (a). As shown in Table IV, the rate of hydrolysis of substituted phenyl acetates is slightly affected by the steric hindrance due to the substituents on the benzene ring. The reason may be caused by the long distance between the carbonyl carbon atom and the ring substituent even if the substituent is present at *o*-position, and the reason may also explain no steric effect on the exchange rate in the reaction of nitrophenyl acetates. The same feature is observed in the exchange reaction of dinitrophenyl benzoates, and they will be described in the following paper.

Table IV. Rates of Base-Catalyzed Hydrolysis of Phenyl Esters

Compound	$k^{a,b)}$	Relative rate
	0.576	1.00
	5.49	9.52
	8.05	14.0

a) in 60% aq. acetone, at 25°.
b) E. Tommila, C.N. Hinshelwood: J. Chem. Soc., **1938**, 1801.

Consequently, it is most probable that the carbonyl carbon atom in the ester is attacked by the reactant which is produced by the preliminary reaction between acetic acid and pyridine. The conclusion is in accordance with the results described in the previous papers.*1 The reaction mechanism is represented in Scheme 1.

The polar effect of the nuclear substituents in the ester affords remarkable changes on the exchange rate, as shown in Table II. This phenomenon means that the rate-determining step is probably the equation (1-c). When k_2 is smaller than k_{-2}, the rate-determining step is represented by the equation (1-b). In this case, however, the polar

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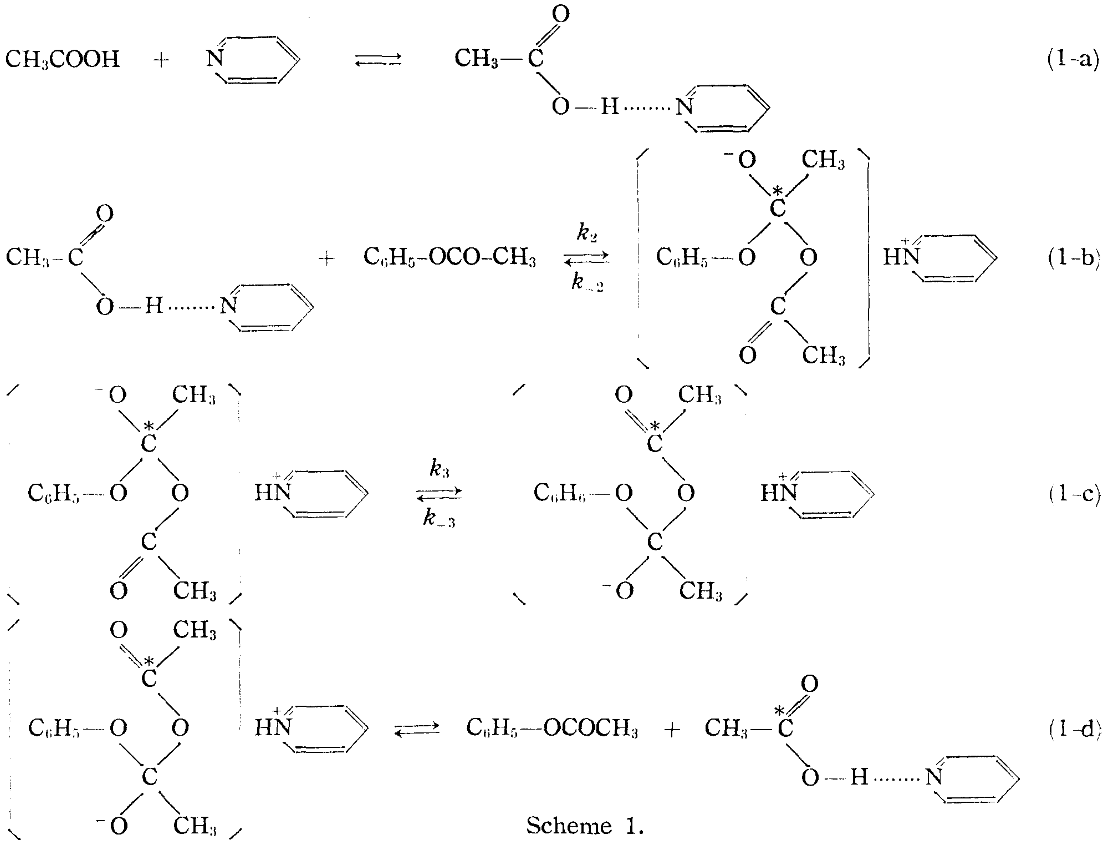
13) R.J. Pollitt, B.C. Saunders: J. Chem. Soc., **1964**, 1132.
14) L.K. Dyall: *Ibid.*, **1960**, 5160.
15) V. Gold, E.D. Hughes, C.K. Ingold, G.H. Williams: *Ibid.*, **1950**, 2441.
16) J.F. Bunnett, E. Buncel, K.V. Nahabedian: J. Am. Chem. Soc., **84**, 4136 (1962).



Scheme 1.

effect of the nuclear substituents on the exchange rate may be expected to be smaller, because the electronic effects of the nuclear substituents may be interrupted by the phenolic oxygen and resulting small change of the electropositivity of the carbonyl carbon atom affords small effect on the rate of the reaction between the carbonyl carbon atom and the nucleophilic reactant. This relation was found in the hydrolysis of phenyl acetates, as shown in Table IV. The same feature is observed in the exchange reaction of phenyl benzoates, which will be described in the following paper. These results indicate that the equation (1-b) may be unfavorable as the rate-determining step. Meanwhile, the polar effect on the exchange rate caused by nuclear substituents can be reasonably explained, when the equation (1-c) is assumed as the rate-determining step. In this case, the rate of the equation (1-c) is related to lability of the ester bond which combines the phenolic oxygen with the carbonyl carbon atom. Accordingly, it is presumed for the exchange rate to be related to *pKa* values of the corresponding phenols. Comparing the exchange rates with the *pKa* values, there is shown the reasonable relation which is obtained in the cases of phenyl benzoates, and the details will be mentioned in the following paper.

The author expresses his gratitude to Prof. K. Saito, Tohoku University, for his kind and unfailing guidance and to Prof. S. Fukushima, this College, and to Prof. T. Okamoto, Tokyo University, for their helpful advices and to Dr. T. Ukai, the President of this College, for his encouragement throughout the course of this study. Thanks are due to Miss H. Fujita and the members of the Elementary Analysis Room of this College for their technical assistances. This study was partly supported by a Grant provided by the Ministry of Education, which was gratefully acknowledged.

Summary

The isotopic acyl exchange reaction between various phenyl acetates and acetic acid was studied in pyridine solution. No steric effect on the exchange rate was

observed in the case of *o*-substituted phenyl acetate, but the polarity of the substituents existing on the benzene ring afforded remarkable effects on the exchange rate. The electron-attracting group on the benzene ring promoted the exchange reaction. Kinetic data showed that the reaction center of the ester was the carbonyl carbon atom. The nucleophilic reactant which was formed by the preliminary reaction attacked the reaction center in the ester, followed by the bond migration which was the true exchange step and was considered to be rate-determining step. The substituents on the benzene ring gave the polar effect on the rate-determining step.

(Received October 6, 1964)

[Chem. Pharm. Bull.
13(3) 368~378 (1965)]

UDC 547.581.2.07.02.14

50. **Yukio Akahori**: Studies on Isotopic Acyl Exchange. IV.[*1] Acyl Exchange Reaction of Subtituted Phenyl Benzoates and Related Compounds; Effect of Acyl Group on the Exchange Rate.

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In the previous papers,[*1, 1a,b] isotopic acyl exchange between phenyl acetates and acetic acid in pyridine was studied, and it was found that the exchange reaction consisted of the preliminary reaction and the true exchange step.[1a,b] The preliminary reaction was the rapid equilibrium reaction to which the acid and pyridine contributed, and the structural changes of the base affected the equilibrium and the change of equilibrium afforded effect on the exchange rate.[1b] The structural changes of the phenolic component in the ester gave the striking effects on the exchange rate, and the effect was due to the polarity of the substituents which was related to the rate-determining step.[*1] Thus the factors which govern the exchange rate were investigated except the effect of the structural change of acyl component in the ester. Since the structure of the ester was closely related to the rate-determining step,[*1] it is predicted that the exchange rate is affected by the structural changes of acyl group in the ester. Present paper deals with the study of effects on the exchange rate caused by structural changes of the acyl group in the ester.

Experimental

1) **Materials**——Substituted phenyl benzoates: Substituted phenols were dissolved in dry pyridine and the theoretical amounts of benzoyl chloride were added into the solutions, and the mixtures were allowed

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[*1] Part Ⅲ: This Bulletin, **13**, 361 (1965).

[*2] Oshika, Shizuoka (赤堀幸男).

1) *a*) Part I. Y. Akahori, S. Fukushima: This Bulletin, **12**, 166 (1964). *b*) Part Ⅱ. Y. Akahori: *Ibid.*, **13**, 352 (1965).

2) A. L. Bernoulli, A. St. Goar: Helv. Chim. Acta, **9**, 763 (1926).

3) Schiaparelli: Gazz. chim. ital., **11**, 74 (1881); Beilstein, **H**, **9**, 118 (1926).

4) Hubner: Ann., **210**, 386 (1881); Beilstein, **H**, **9**, 118 (1926).

5) Neumann: Ber., **18**, 3320 (1884); Beilstein, **H**, **9**, 119 (1926).

6) Kym: Ber., **32**, 1427 (1899); Beilstein, **H**, **9**, 119 (1926).

7) E. Fromm, R. Ebert: J. prak. Chem., **108**, 75 (1924); C. A., **18**, 3180 (1924).

8) E. B. Barnett, I. G. Nixon: Chem. News, **129**, 190 (1924); C. A., **19**, 260 (1925).