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23. Yukio Akahori and Seigo Fukushima: Studies on Isotopic Acyl Exchange. I. Kinetics and Mechanism of Acyl Exchange Reaction of *p*-Nitrophenyl Acetate.

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p-Nitrophenyl acetate was described as "aktivierte Ester"[1] because of its high reactivity, and the application has been extended by Schwyzer.[2] Recently *p*-nitrophenyl acetate and its homologues were practically used as the selective reagent for acylation of amino group[3] and applied for synthesis of α melanocyte-stimulating hormone.[2] The mechanism of aminolysis of *p*-nitrophenyl acetate and the related compounds was described by Jencks, *et al.*,[4] besides ammonolysis[5] and hydrolysis[6] of the ester were kinetically investigated. Concerning the substituted phenyl acetate,[7] the dimethylamino group at the end of side chain could operate as intramolecular catalyzer for hydrolysis of phenyl acetate and the mechanism was discussed as an enzyme model. However these studies were all subjected to the reactions with the other compounds and not to the properties of *p*-nitrophenyl acetate itself. The fundamental properties of this interesting ester may be elucidated by the experiments of isotope exchange.

Present paper deals with kinetics and mechanism of isotope exchange reaction between *p*-nitrophenyl acetate and acetic anhydride or acetic acid. Previously isotope exchange reaction between acetylglucose and acetic acid[8] was described but the reaction was carried out at the elevated temperature. In our study, the mild conditions which are employed in usual methods of acetylation are selected.

Experimental

1) **Materials**——AcOH: Reagent grade AcOH was mixed with $KMnO_4$ and distilled through a Widmer column, and the middle portion, boiling range 117~118°, was collected. The acid was further purified by partial freezing method, b.p. 117~118°, m.p. 16° (lit. b.p. 117.72°, m.p. 16.63°).[9]

Ac_2O: Reagent grade Ac_2O was purified by fractional distillation through a Widmer column, b.p. 139.5° (lit. b.p. 140.0°)[9]

Toluene: Reagent grade toluene was successively shaken with H_2SO_4 and aq. NaOH solution followed by drying over P_2O_5, then fractionally distilled, b.p. 110° (lit. b.p. 110.623°)[9]

Pyridine: Distilled pyridine, b.p. 115°, was dried over KOH followed by fractional distillation through a column, b.p. 115° (lit. b.p. 115.58°).[9]

Ac_2O[carbonyl-^{14}C][10]: 15 ml. of Ac_2O was added to 0.5 mc. AcONa[carbonyl-^{14}C] (9.7 mc./mmole) and allowed to stand at room temperature for 1 week. The anhydride was distilled and 10 ml. of Ac_2O was added in several portions onto the residue and distilled successively, b.p. 139.5~140°, 2.26×10^6 c.p.m./mmole. The exchange ratio was nearly quantitative.

[*1] Oshika, Shizuoka (赤堀幸男, 福島清吾).
1) R.S. Schwyzer, B. Iselin, M. Feurer: Chimia (Switz.), **8**, 264 (1954).
2) R.S. Schwyzer, A. Costopanagiotis, P. Sieber: Helv. Chim. Acta, **46**, 870 (1963).
3) R. Gllatthard, M. Matter: *Ibid.*, **46**, 795 (1963).
4) W.P. Jencks, J. Carriuolo: J. Am. Chem. Soc., **82**, 675 (1960).
5) T.C. Bruice, M.F. Mayahi: *Ibid.*, **82**, 3026 (1960).
6) J.F. Bunnett, G.T. Davis: *Ibid.*, **82**, 665 (1960).
7) T.C. Bruice, S.J. Benkovic: *Ibid.*, **85**, 1 (1963).
8) J. Swiderski: Roczniki Chem., **32**, 1121 (1958); Chem. Abstr., **53**, 7997a (1959).
9) A. Weissberger: "Technique of Organic Chemistry, Ⅶ. Organic Solvents" (1955). Interscience Publishers, Inc.
10) S. Ruben, M.B. Allen, P. Nahinsky: J. Am. Chem. Soc., **64**, 3050 (1942).

p-Nitrophenyl acetate[11]: 1.40 g. (10 mmoles) of *p*-nitrophenol was suspended in 1.12 g. (11 mmoles) of Ac_2O and 1 drop of conc. H_2SO_4 was added under swirling. The crystals were dissolved and the solution was allowed to stand at room temperature for 2 hr. After addition of 5 ml. H_2O, white crystals were separated and washed with cold H_2O. The crude product was recrystallized twice from dil. EtOH, yielding 1.75 g. of *p*-nitrophenyl acetate, nearly colorless prism, m.p. 78~79°. (lit. m.p. 79~80°,[11] 77.5~78.0°,[12] 79.5~80°[13]). (96.7% of theoretical yield). Further recrystallization gave no change on its melting point.

p-Nitrophenyl acetate[carbonyl-^{14}C]: 1.40 g. (10 mmoles) of *p*-nitrophenol was acetylated with 1.12 g. (11 mmoles) of Ac_2O[carbonyl-^{14}C] (2.26×10^6 c.p.m./mmole) by the same method as described above. 1.70 g. of *p*-nitrophenyl acetate[carbonyl-^{14}C] (1.12×10^6 c.p.m./mmole) was obtained. The recovery of radioactivity was shown to be quantitative.

2,5-Diphenyloxazole (PPO): Scintillation grade, supplied from Packard Instrument Co. Inc., U. S. A.

Toluene-^{14}C: Standard toluene-^{14}C ($4.26 \times 10^5 \pm 1.86\%$ d.p.m./ml., June 1, 1962), supplied from Packard Instrument Co.

Crushed glass: Tyston glass was crushed and washed with conc. HNO_3 followed by washing with H_2O until H_2O was free from NO_3^- ion. The glass was dried at 110° *in vacuo.*

2) **Analytical Procedure**——a) Counting: The redioactivity was measured by Tri-Carb Liquid Scintillation Spectrometer 314F (Packard Instrument Co.). The operating conditions were selected as followings: Discriminator, A-A′ 10, B 50; Gain, A 100, B 100; Voltage, 790 v. (h. v. 2.60). The temperature of the counting chamber was kept at $-5°$ throughout this study.

Scintillator solution was 0.42% PPO in toluene. Few milligram of the dried sample was weighed into a counting vial and dissolved in 10 ml. of the scintillator solution, then cooled in a refrigerator for 3 hr. prior to counting.

The efficiency of counting under the condition described above was shown to be 56% using standard toluene-^{14}C. Over the range investigated, Ac_2O showed no quenching, while slight quenching was observed for *p*-nitrophenyl acetate. The rectification of the observed counts for the ester was established by measurement of counting rate for a series of accurately weighed stable samples in the standard toluene-^{14}C, and the specific radioactivity was calculated by extrapolating at zero quenching.

b) Determination of kinetic rate: The rate of exchange *R*, was defined in equation (1).[14]

$$R = -\frac{N_1N_2}{N_1+N_2} \cdot \frac{\ln(1-F)}{t} \qquad (1)$$

N_1=concentration of *p*-nitrophenyl acetate in the reaction medium (*M*).
N_2=concentration of Ac_2O or AcOH (*M*).
F=fraction of exchange at time *t*.

$$F = \frac{x-x_0}{x_\infty - x_0} = \frac{y-y_0}{y_\infty - y_0} \qquad (2)$$

$$x_\infty = y_\infty = \frac{x_0N_1 + y_0N_2}{N_1+N_2} \qquad (3)$$

x =specific radioactivity of *p*-nitrophenyl acetate at time *t*.
y =specific radioactivity of Ac_2O or AcOH at time *t*.
x_0=initial value of x.
y_0=initial value of y.
x_∞=value of x at the equilibrated state.
y_∞=value of y at the equilibrated state.

Either x_0 or y_0 was set at zero for the practical experiments, and the fraction *F* was calculated by the equation (2) in which x_∞ and y_∞ were calculated by equation (3).

For comparison of the exchange rate, the half-exchange time $t_{1/2}$ was employed as shown in equation (4).

$$t_{1/2} = \frac{N_1N_2}{N_1+N_2} \cdot \frac{\ln 2}{R} \qquad (4)$$

c) Reaction procedures: In the general procedure adopted for determination of exchange rate *R*

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[11] O. Fernández, C. Tottres: Anales. soc. espan. fís. quím., **21**, 30 (1923); Chem. Abstr., **17**, 3021 (1923).
[12] M. L. Bender, B. W. Turnquest: J. Am. Chem. Soc., **79**, 1652 (1957).
[13] B. S. Hartley, R. A. Kilby: Biochem. J., **56**, 288 (1954); A. Kaufman: Ber., **42**, 3482 (1909).
[14] H. A. C. Mckay: Nature, **142**, 997 (1937); J. Am. Chem. Soc., **65**, 702 (1943).

the required amount of purified *p*-nitrophenyl acetate and Ac_2O or AcOH were accurately weighed into a reaction flask and the required quantity of dry pyridine was added under cooling, then the flask was tightly closed with a glass stopper. The total weight of the reagents was measured and the volume of the reaction mixture was calculated from its density which has been experimentally determined. The reaction vessel was then transfered into a thermostatically controlled bath. For the reactions at 0°, ice water bath was used instead of the mechanical thermostat. At appropriate time intervals, aliquots of the solution were taken up and poured into ice water, the crystals immediately deposited. After separation, the crystals were washed with cold H_2O followed by dring over KOH *in vacuo*. The dried crystals were purified by recrystallization from dil. EtOH and dried *in vacuo*, colorless prisms, m.p. 78~79°.

Reaction A_1: *p*-Nitrophenyl acetate and Ac_2O[carbonyl-^{14}C] were dissolved in pyridine and treated as described above.

Reaction A_2: *p*-Nitrophenyl acetate[carbonyl-^{14}C] and Ac_2O were used as the starting materials.

Reaction A_3: *p*-Nitrophenyl acetate[carbonyl-^{14}C] and AcOH were treated as described above.

Reaction B: Ac_2O[carbonyl-^{14}C] was dissolved in pyridine. After tightly closing with a glass stopper, the reaction flask was immersed in a thermostat and the temperature was kept at constant for 20 hr. Into the solution, the required amount of *p*-nitrophenyl acetate was added and the reaction was carried out in the tightly closed flask as described above.

Reaction C_1: Into the solution of reaction A_1, 0.5 g. of the crushed glass was added at time zero, then treated by the general procedure.

Reaction C_2: 0.5 g. of the crushed glass was added into the solution of the reaction A_3 at time zero, and treated as described above.

d) Examination of the isolation method: The reaction product that was isolated and purified by the general procedure showed the same melting point as that of the authentic sample of *p*-nitrophenyl acetate. Determination of mixed melting point and comparison of their IR spectra established the identity of the reaction product with the starting material. Yield of the crude product was nearly quantitative. These facts indicated that no remarkable side reaction took place in this reaction. The specific radioactivity of the product did not show any change when the reaction product was further purified by repeated recrystallization. Therefore it was excluded that the product contained small amount of strongly labeled compounds, *e.g.* radioactive AcOH.

When the reaction mixture was treated with ice H_2O at time zero, the specific radioactivity of the purified product was completely identical with that of the starting material, and the fact indicated non-existence of the induced exchange reaction throughout the isolation procedure.

These evidences confirmed that the isolation method described above was most suitable for this experiment.

e) Determination of the labeled position in the reaction product: 8 mg. of the product (8.16×10^5 c.p.m./mmole) that was obtained from the exchange reaction A_1 was hydrolyzed by warming with HCl-MeOH, and the resulted phenol was recrystallized from Et_2O-petr. ether, yielding 4 mg. of colorless rods, m.p. 113°. Admixture and IR spectra showed identity with the authentic sample of *p*-nitrophenol. Measurement of radioactivity of the compound did not show any difference from the natural count, and proved that the labeled position of the reaction product was limited to acetyl group of the ester.

Results

1) Exchange Reaction between *p*-Nitrophenyl Acetate and Acetic Anhydride

In the exchange reaction between *p*-nitrophenyl acetate and acetic anhydride[carbonyl-^{14}C] in pyridine (reaction A_1), the specific radioactivity of the product increased with reaction period and equilibrium was established after the prolonged period as shown in Fig. 1. The value of the specific radioactivity of the equilibrated product was closely identical with the calculated value which was based on one half of the specific radioactivity of acetic anhydride[carbonyl-^{14}C].

It is known that pyridine reacts with acetic anhydride to form the salt (I)[15] as shown in scheme (I-1). If it is assumed that either acetyl or acetoxyl group can be participate for the exchange reaction with *p*-nitrophenyl acetate, the experimental result can be reasonably explained.

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[15] O. Dimroth, *et al.*: Ber., **54**, 2934 (1921); *Ibid.*, **55**, 1223 (1922); R.C. Elderfield: "Heterocyclic Compounds" I. p. 481 (1959), John Wiley and Sons.

The plotting of log (1-*F*) *vs.* *t* showed slight deviation from exact linearity in reaction A_1. The perfect linearity, however, was shown in reaction B in which acetic anhydride was treated with pyridine prior to addition of *p*-nitrophenyl acetate.

In a number of reaction A_1, some of the runs showed 10 to 15% higher value of x_∞ than the calculated value based on $y_0/2$. In order to clarify the reason, several attempts were undertaken, and it was suggested that the amount of water which was contained in the reagents might have some effect on the specific radioactivity of the product at equilibrium. The effect was confirmed by the experimental result of the exchange reaction between acetic acid and *p*-nitrophenyl acetate.

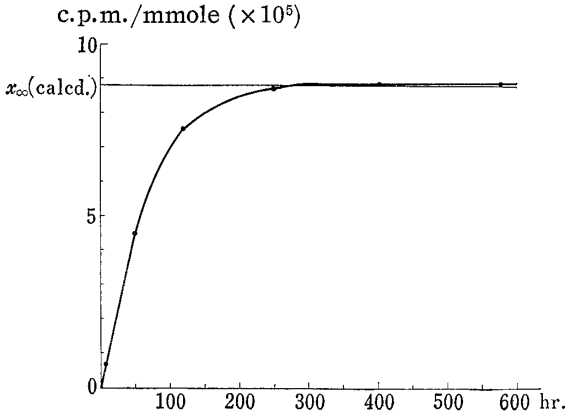

Fig. 1. Exchange Reaction between *p*-Nitrophenyl Acetate and Acetic Anhydride at 25.0°

N_1=0.486 m*M*, N_2=1.707 m*M*, $y_0=2.26\times10^5$ c.p.m./mmole
pyridine 0.485 ml. $y_0'=y_0/2$

$$x_\infty=\frac{y_0'N_2}{N_1+N_2}=\frac{y_0N_2}{2(N_1+N_2)}=8.79\times10^5 \text{ c.p.m./mmole}$$

The reaction A_2 in which the labeled *p*-nitrophenyl acetate and stable acetic anhydride were used was the same as the reaction A_1, and no difference was detectable in these two reactions.

Determination of exchange rate in presence of the crushed glass (reaction C_1) showed no change, indicating that the surface reaction did not contribute to this exchange reaction.

2) Exchange Reaction between Acetic Acid and *p*-Nitrophenyl Acetate

In pyridine solution, the exchange reaction took place between *p*-nitrophenyl acetate and acetic acid (reaction A_3), and it showed perfect linearity of log (1-*F*) *vs.* *t*. Addition of the crushed glass (reaction C_2) gave no effect on exchange rate *R*.

Generally, exchange rate *R* can be expressed as the function with respect to the concentration of the reagents as shown in equation (5).

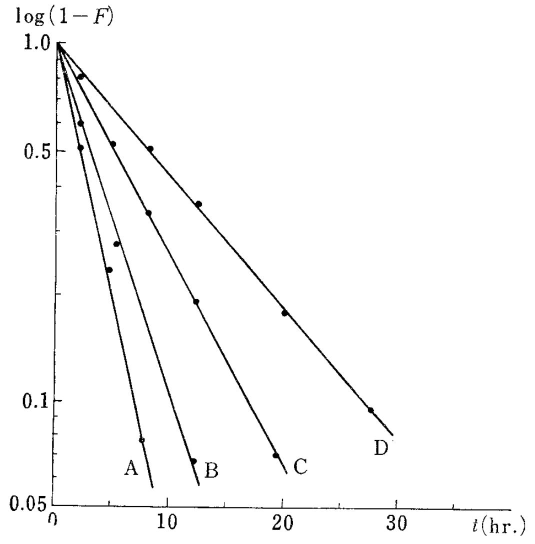

Fig. 2. Reaction A_3 at 37.0°

	$N_1(M)$	$N_2(M)$		$N_1(M)$	$N_2(M)$
A	1.330	2.638	C	0.406	0.816
B	0.762	1.528	D	0.230	0.462

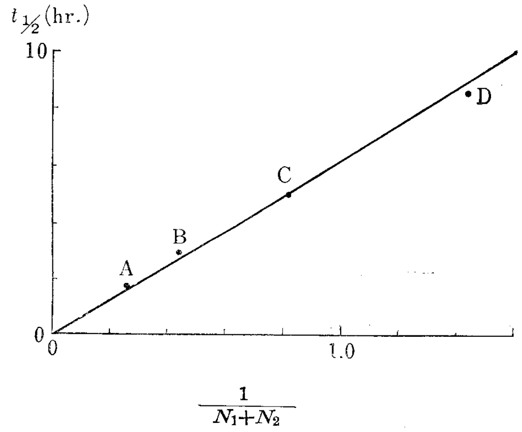

Fig. 3. Reaction A_3 at 37.0°

$$R=kN_1^{n_1}\cdot N_2^{n_2} \qquad (5)$$

In order to determine the values of n_1 and n_2, the systematic investigation on the kinetic experiments were carried out as follows.

The dependence of R on the concentration of *p*-nitrophenyl acetate and that of acetic acid was shown by changing the volume of pyridine under keeping the relative concentration of the ester and the acid at constant value (Figs. 2, 3).

When the concentration of acetic acid was changed and *p*-nitrophenyl acetate was kept at unit concentration, it was found that the exchange rate R was dependent upon the ester and the acid respectively in the first order or upon the acid alone in the same order as shown in Fig. 4, and the equation (6) was obtained.

$$R=kN_1N_2 \text{ or } kN_2 \qquad (6)$$

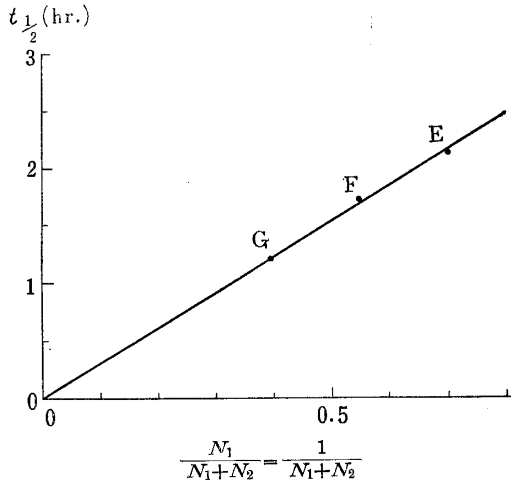

Fig. 4. Reaction A_3 at 45.0°

	$N_1(M)$	$N_2(M)$
E	1.000	0.411
F	1.000	0.810
G	1.001	1.530

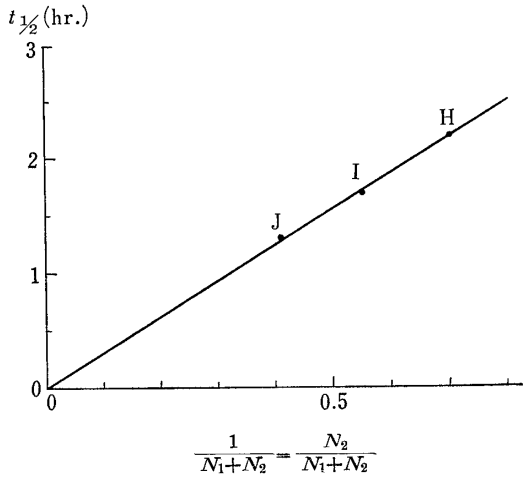

Fig. 5. Reaction A_3 at 45.0°

	$N_1(M)$	$N_2(M)$
H	0.440	0.994
I	0.824	1.005
J	1.468	0.992

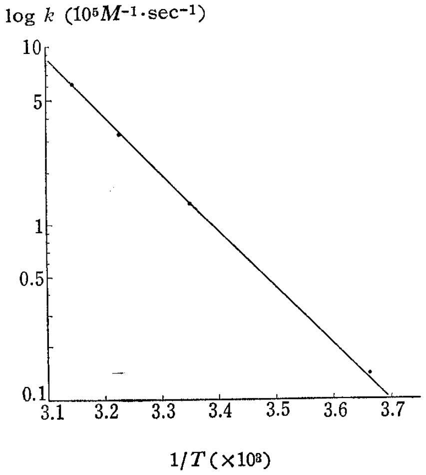

Fig. 6. Relation between Rate Constant k and $1/T$

T (°K) k ($M^{-1}\cdot$sec^{-1})

The concentration of *p*-nitrophenyl acetate was changed under keeping acetic acid at unit concentration and it was shown that exchange rate R was dependent on either concentration of both components or that of the ester alone as expressed by equation (7). (Fig. 5).

$$R=kN_1N_2 \text{ or } kN_1 \qquad (7)$$

From the equations (6) and (7), it was concluded that the dependence of exchange rate R on the concentrations was the first order with respect to the each component as shown in equation (8).

$$R=kN_1N_2 \qquad (8)$$

A number of experiments were carried out to confirm the equation (8), and the reaction rate k was calculated from the equation (9).

$$k=\frac{1}{N_1+N_2}\cdot\frac{\ln 2}{t_{1/2}} \qquad (9)$$

The results are collected in Table I.

The same experiments were carried out at 45.0°, 37.0°, 25.5°, and 0°, and Arrhenius activation energy Ea was calculated by equation (10).[10] The results are shown in Fig. 6, and 14.7kcal./mole was given for Ea.

$$k=PZe^{-E_a/RT} \qquad (10)$$

Table I. Kinetic Data of Exchange Reaction between *p*-Nitrophenyl Acetate and Acetic Acid in Pyridine (Reaction A_3)

	N_1 (M)	N_2 (M)	$t_{1/2}$ (hr.)	k ($\times 10^5$) ($M^{-1}\cdot\mathrm{sec}^{-1}$)
at 45.0°				
	0.440	0.994	2.2	6.10
	0.824	1.005	1.7	6.20
	1.468	0.992	1.3	6.01
	1.000	0.411	2.1	6.49
	1.000	0.810	1.7	6.25
	1.001	1.530	1.2	6.34
	0.442	0.883	2.3	6.31
	0.833	0.833	1.8	6.44
	0.819	0.836	1.8	6.50
	0.833	0.831	1.9	6.09
			average	6.27
at 37.0°				
	0.828	0.832	3.5	3.30
	0.837	0.454	4.4	3.39
	0.977	1.018	3.2	3.01
	0.786	1.628	2.4	3.32
	1.330	2.638	1.8	2.81
	0.762	1.528	3.0	2.80
	0.406	0.815	5.0	3.15
	0.230	0.462	8.2	3.39
			average	3.15
at 22.5°				
	0.801	0.808	8.6	1.39
	0.791	1.583	6.5	1.27
			average	1.33
at 0°				
	0.796	1.588	56	0.144

E_a=14.7 kcal./mole. log PZ=5.90

Discussion

1) Exchange Reaction between *p*-Nitrophenyl Acetate and Acetic Anhydride

According to Dimroth,[15] acetic anhydride reacts with pyridine and gives N-acetylpyridinium acetate (I). When both of the carbonyl carbon atoms in a molecule of acetic anhydride are labeled, the probabilities of bond-breaking of two C-O bonds should be exactly same. If the one carbon atom of carbonyl group is labeled and the other is not labeled, probabilities of bond-cleavage of two C-O bonds might show slight difference

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[16] S. Glasstone, K.J. Laidler, H. Eyring: "The Theory of Rate Process" p. 7 (1941), McGraw-Hill Book Co.

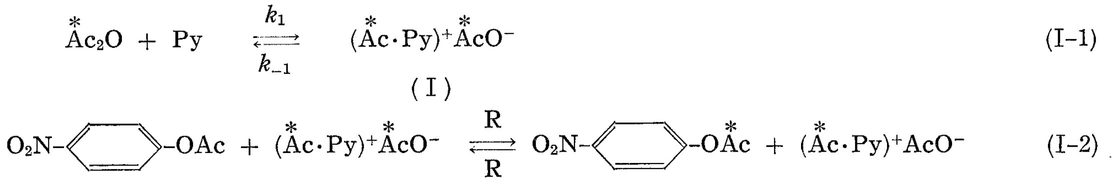
in each other since isotope effect must appear in this process. The difference, however, can be expected to be less than few percent,[17] and in this experiment it lies within the limit of experimental error. As the result, radioactivity originally present in the acetic anhydride is almost equally divided into acetyl and acetoxyl groups in the pyridinium salt (I). Therefore, it can be explained that in the exchange reaction between acetic anhydride and *p*-nitrophenyl acetate the observed value of x_∞ is identical with the calculated value based on $y_0/2$ when the followings are assumed;

i) either acetyl group or acetoxyl group in the pyridinium salt (I) can be contributed to the exchange reaction, and

ii) exchange between acetyl group and acetoxyl group in the pyridinium salt (I) is negligibly small.

The first assumption is considered to be reasonable when the exchange reaction proceeds *via* only one mechanism without accompanying the other independent routes. Whilst if the reaction is consisted of several competitive elementary reactions it may be expected that the value of x_∞ is more than the calculated value based on $y_0/2$ since participation of the acetyl and acetoxyl groups to the exchange reaction may be possible. In order to assume the interexchange between acetyl group and acetoxyl group in the pyridinium salt (I), reversibility of the reaction (I-1) must be admitted. However, the irreversibility of the reaction has been suggested by empirical evidences which were observed in synthetic procedures,[16] and further confirmed by reaction B in which exact linearity of log (1-*F*) *vs.* *t* is produced by the preliminary treatment of pyridine-acetic anhydride mixture.

Scheme I.



$$\overset{*}{Ac}_2O + Py \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (\overset{*}{Ac}\cdot Py)^+\overset{*}{Ac}O^- \quad (I\text{-}1)$$

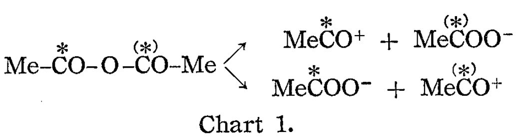
(I)

(I-2)

The result of the reaction B indicates that the exchange reaction is consisted of at least two steps (Scheme I). The first reaction is salt formation (reaction I-1) in which k_1 is larger than k_{-1}, and the second step is the typical exchange reaction (reaction I-2) which obeys McKay's rule.[14] Concerning the relative value of R and k_1, it might be considered that the rate constant k_1 is comparable with the exchange rate R, and there is no reason to neglect k_1 comparing with R because of the slight but distinct difference between reaction A_1 and reaction B.

2) Effect of Moisture

Acetic anhydride and pyridine may absorb water during experimental procedures, even though the reagents are kept under protecting from entering of moisture and treated carefully. Hydrolysis of acetic anhydride may be accelerated by water that absorbed in the reagents or on the wall of glasswares before or during the reaction, giving small amounts of acetic acid. The acetic acid reacts with pyridine and affords the salt (II) of which acetoxyl group may exchange with *p*-nitrophenyl acetate as shown in Scheme II. If the hydrolysis ratio of acetic anhydride is expressed by α, the total



$$\text{Me-}\overset{*}{C}\text{O-O-}\overset{(*)}{C}\text{O-Me} \begin{cases} \nearrow\ \text{Me}\overset{*}{C}\text{O}^+ + \text{Me}\overset{(*)}{C}\text{OO}^- \\ \searrow\ \text{Me}\overset{*}{C}\text{OO}^- + \text{Me}\overset{(*)}{C}\text{O}^+ \end{cases}$$

Chart 1.

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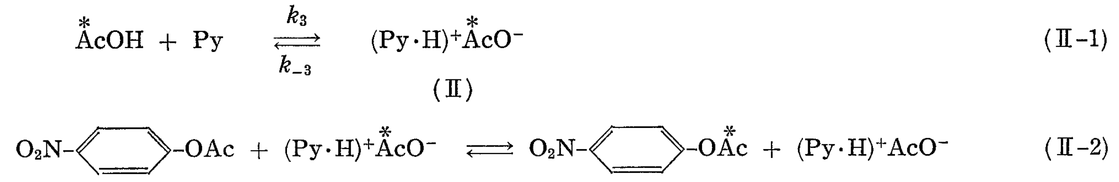
[17] G.R. Stranks, G.M. Harris: J. Am. Chem. Soc., **75**, 2015 (1953).

Scheme II.



amount of acetoxyl group that can be contributed to the exchange reaction is given by $(1\text{-}\alpha)\mathrm{I}+2\alpha\mathrm{II}$. Even if the exchange rates of the salt (I) and the salt (II) with *p*-nitrophenyl actate are not equal, the total amount of the acetoxyl group which can be employed for the exchange reaction with the ester in the equilibrated state is finally expressed by $1+\alpha$, because exchange rate does not affect the equilibrium value. By replacement of N_2 by $(1+\alpha)N_2$ in equation (3), the specific radioactivity of the ester at the equilibrated state in which hydrolysis of acetic anhydride takes place with ratio α is given by equation (11).

$$x_\infty' = \frac{x_0 N_1 + y_0(1+\alpha)N_2}{N_1 + (1+\alpha)N_2} \tag{11}$$

When x_0 is zero, change of the specific radioactivity of the ester at equilibrium is expressed by equation (12).

$$\frac{x_\infty'}{x_\infty} = 1 + \frac{\alpha N_1 N_2}{1+\alpha+N_1/N_2} \tag{12}$$

The second term in equation (12) is always positive, so that x'_∞ is larger than x_∞. This indicates that hydrolysis of acetic anhydride results in increase of the specific radioactivity of the product.

The effect of hydrolysis of acetic anhydride on exchange rate *R* can be discussed by using equation (1), when the reaction A_1 is supposed to be the complex reaction consisting of Scheme I and Scheme II. If the hydrolysis rate is comparable to or slightly smaller than rate of the other reactions which are shown in Scheme I and II, the slight deviation from linearity of log (1-*F*) *vs.* *t* in case of reaction A_1 can be reasonably explained as follows. When the hydrolysis of acetic anhydride takes place during the reaction, the concentration of the reactive acetoxyl group (N_2) gradually increases and it means increase of $\dfrac{N_1N_2}{N_1+N_2}$ in equation (1). Consequently the exchange rate *R* gradually increases and it results in the slight deviation from linearity of log (1-*F*) *vs.* *t*.

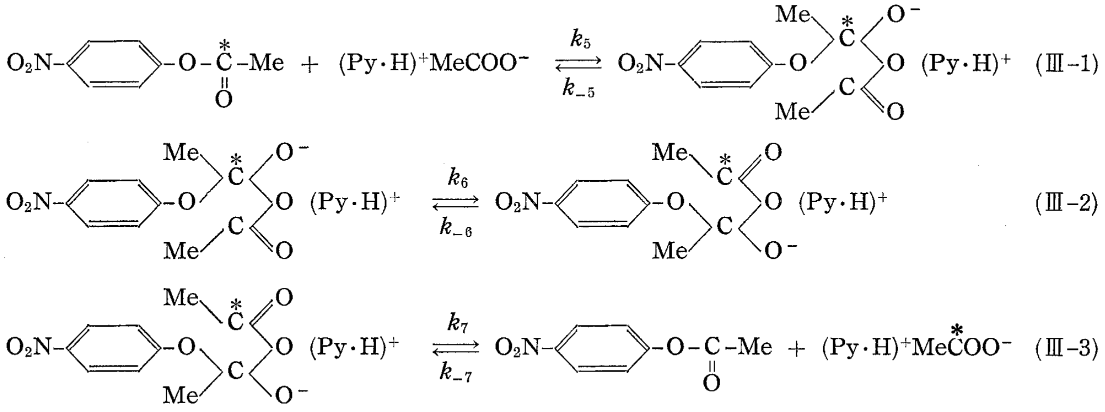
Thus the experimental evidences observed in reaction A_1 are unambiguously explained by assuming the exchange reaction between acetic acid and *p*-nitrophenyl acetate, and the assumption is confirmed by the results of reaction A_3.

3) Exchange Reaction between Acetic Acid and *p*-Nitrophenyl Acetate

The exchange rate *R* in the reaction between acetic acid and *p*-nitrophenyl acetate is shown to be dependent on the concentrations of the acid and the ester respectively in the first order as shown in equation (8). The kinetic evidence indicates that the rate-determining step is apparently related to the collision of these reactants, and the following mechanism may be proposed.

The exchange reaction is consisted of four steps as shown in Scheme II and Scheme III, where reaction (II-2) is further divided into three elementary reactions as expressed in Scheme III.

i) Acetic acid reacts with pyridine giving a pyridinium salt (II), (reaction II-1), followed by, Scheme III.



ii) nucleophilic attack of the acetoxyl group of the salt (II) to the positive center of the carbonyl group in the ester (reaction III-1),

iii) then electron displacement takes place (reaction III-2),

iv) finally acetoxyl group is eliminated (reaction III-3). Among these steps the reaction (III-1) or (III-2) might be considered as the rate-determining step. The reaction (III-1) is analogous to aminolysis,[4] ammonolysis,[5] and hydrolysis[6,12] of esters. In these cases, nucleophilic attack of amino or hydroxyl group to the carbonyl carbon atom, and *Ea* value were estimated for hydrolysis of *p*-nitrophenyl acetate under various conditions. The *Ea* value for the reaction catalyzed by base in aqueous solvents was shown as 11.1[18] and 11.0 kcal./mole,[19] and the observed value of *Ea* in this exchange reaction is 14.7 kcal./mole. According to Bender, *et al.*,[12] the hydrolysis rate of *p*-nitrophenyl ester is proportional to the basicity of the catalyzer. These relations agree with the result in this experiment.

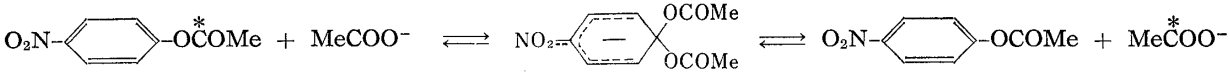
The reaction (III-3) corresponds to the last step of hydrolysis[6,12] and aminolysis[4] of esters, so that it can be deduced that k_7 is larger than k_{-7}, and k_5 is smaller than k_{-5} because reaction (III-1) and reaction (III-3) are symmetrical.

Throughout this mechanism all steps are reversible, and the fact agrees with the experimental results. If an irreversible reaction is involved in its mechanism, identity of the result of reaction A_1 with that of reaction A_2 can not be explained.

Except the problems concerning the role of catalyzer and comparison of the reaction rate k_5 and k_6, the experimental evidences are clearly explained by this mechanism.

In the mechanism discussed above, acyl-oxygen bond cleaves. When cleavage of aryl-oxygen bond is considered, the second mechanism may be proposed as shown in Scheme IV. The mechanism is analogous to transetherification which was demonstrated by azo-naphthyl ethers. Witt, *et al.*[20] found that 4-(phenylazo)-1-naphthyl methyl ether and related ethers were quite sensitive to acid-catalyzed hydrolytic cleavage, and the mineral acid-catalyzed transetherification was also described.[21] Recently Bunnett, *et al.* studied the reaction using ^{18}O, and the mechanism of aryl-oxygen fission was

Scheme IV.



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[20] O.N. Witt, C. Schmidt: Ber., **25**, 1013 (1892).

[21] O.N. Witt, H. von Helmolt: *Ibid.*, **27**, 2351 (1894).

described as shown in Chart 2.[22] In this case the protonated azo linkage strongly activates the aromatic nucleophilic substitution. Although the mechanism is similar to Scheme Ⅳ, aryl-oxygen fission mechanism may not be so probable in the case of *p*-nitrophenyl acetate, because in common case cleavage of ether linkage requires drastic conditions. There is, however, no reason to exclude the possibility of Scheme Ⅳ, and the experiment using ^{18}O is required to decide this problem.

In conclusion, Scheme Ⅲ is most probable for the mechanism of this exchange reaction, although Scheme Ⅳ can not be excluded. In the discussions, dissociation of the pyridinium salt was not considered, and it is not easy to decide at present moment whether the real form of the reactant is ion-pair or dissociated anion. And in Scheme Ⅲ, the problems concerning role of catalyzer and the ratio k_5/k_6 are left to be investigated. In order to elucidate these detailed points, studies are now proceeding and the results will be reported in future.

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Summary

Kinetic study of isotope exchange reaction between *p*-nitrophenyl acetate and acetic anhydride in pyridine showed that one half of the radioactivity of acetic anhydride was employed for the exchange reaction. The result agreed with that of exchange reaction between acetic acid and *p*-nitrophenyl acetate, and the reaction showed exact linearity of $\log(1-F)$ *vs.* t. The exchange rate N was shown to be the first order function with respect to the ester and the acid. From the experiments carried out at 45.0°, 37.0°, 25.5°, and 0°, 14.7 kcal./mole was estimated for Ea. The mechanism, nucleophilic attack of acetoxyl group to the positive center of carbonyl group in the ester followed by acyl-oxygen fission, was considered to be most probable.

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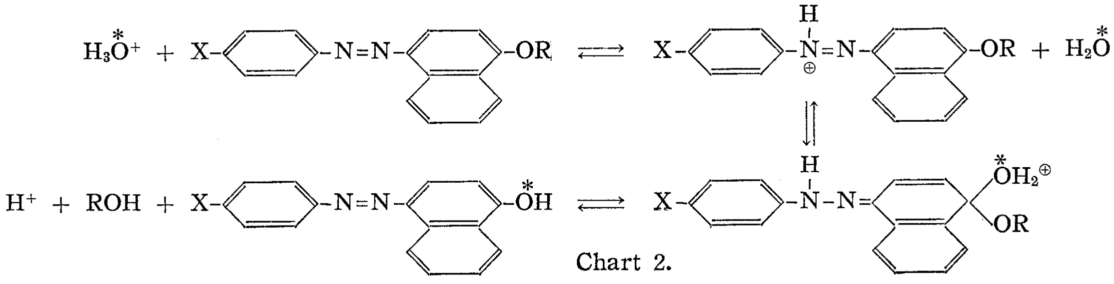

Chart 2.