Oxygen-18 Scrambling Reaction of Aroyl Alkyl Carbonates

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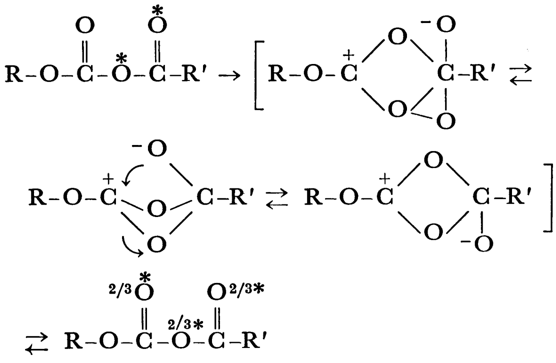
(Received August 9, 1972)

Specifically ^{18}O-labeled *p*-substituted benzoyl cyclohexyl carbonates (**1**) were prepared and heated at 45, 70 and 75 °C, and novel stepwise oxygen scrambling was found to take place in **1**. On being heated at 45 °C, the carbonic carbonyl oxygen atom and the oxygen atom sandwiched between the two carbonyl carbon atoms of **1** were found to scramble. The ^{18}O-scrambling among the above two and carboxylic carbonyl oxygen atoms of **1** was found to take place at 70 or 75 °C. A good first order kinetic dependence was observed for the first step of the scrambling at 45 °C but no substituent effect. An intramolecular mechanism involving two steps of equilibration is proposed.

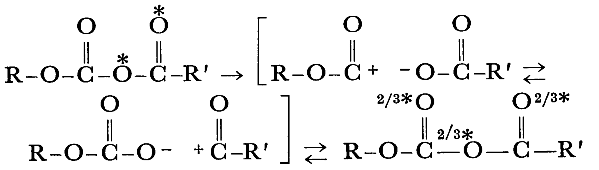
We reported on the basis of ^{18}O-tracer studies of the decomposition of several diacyl peroxides[2] that the carboxy-inversion is the major pathway for the decomposition of *sec*- and *tert*-alkylformyl peroxides, while ^{18}O-scrambling is observed not only in the original peroxide but also in the intermediate of the decomposition, *i.e.*, acyl alkyl carbonates. We extended our ^{18}O-tracer study to the ^{18}O-scrambling of the aroyl alkyl carbonates,[3] specifically ^{18}O-labeled benzoyl 1-apocamphyl carbonate being employed, and an intramolecular oxygen scrambling reaction was found. Although a zwitterion mechanism (scheme 1) has been suggested for the ^{18}O-scrambling, another intramolecular mechanism, *viz.*, an ion pair pathway is possible (scheme 2).[3] Kinetic determinations of the ^{18}O-scrambling with ^{18}O-labled substituted benzoyl 1-apocamphyl carbonates are considered to be very helpful for making choice of the two mechanisms. We have studied the reactions of *p*-substituted benzoyl alkyl carbonates having a cyclohexyl group as the alkyl moiety instead of the 1-apocamphyl group, and found an interesting stepwise scrambling of ^{18}O in these compounds. A discussion on detailed mechanism of the ^{18}O-scrambling reaction of the aroyl alkyl carbonates is given.

Zwitterion mechanism



Scheme 1.

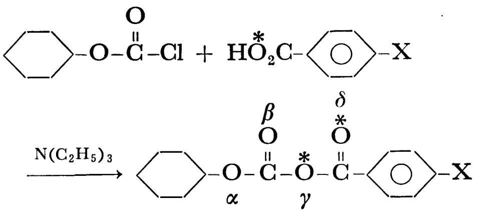
Ion pair mechanism



Scheme 2.

Results and Discussion

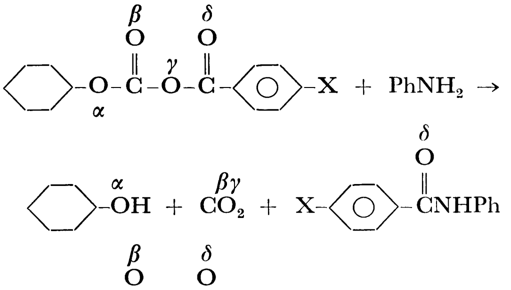
p-Substituted benzoyl cyclohexyl carbonates (**1**) specifically ^{18}O-labeled in γ- and δ-oxygen atoms were prepared as usual by the reaction of cyclohexyl chloroformate with the ^{18}O-labeled *p*-substituted benzoic acids in the presence of triethylamine in ethereal solution as in the following.[4]



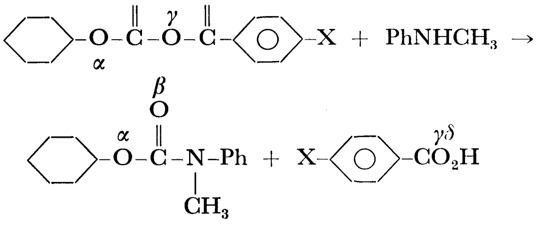
(1)

1a X=CN, **b** X=H, **c** X=CH$_3$

The aroyl carbonates (**1**) thus prepared were dissolved in CCl$_4$ (0.04 M) and heated at 45 °C for 24 hr, at 70 °C for 12 hr or at 75 °C for 24 hr. The aroyl alkyl carbonate was recovered quantitatively without decomposition. ^{18}O-Distribution in the recovered carbonate (**1**) was analyzed according to the following cleavage reactions.[3,5]



(2)



(3)

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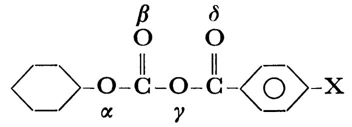
[2] a) T. Kashiwagi, S. Kozuka, and S. Oae, *Tetrahedron*, **26**, 3619 (1970). b) S. Oae, K. Fujimori, and Y. Uchida, *ibid.*, **28**, 5321 (1972).

[3] S. Oae, K. Fujimori, and S. Kozuka, *ibid.*, **28**, 5327 (1972).

[4] a) C. J. Michejda and D. S. Tarbell, *J. Amer. Chem. Soc.*, **84**, 4113 (1962). b) C. J. Michejda and D. S. Tarbell, *J. Org. Chem.*, **29**, 1168 (1964).

[5] N. A. Leister and D. S. Tarbell, *J. Org. Chem.*, **23**, 1152 (1958).

TABLE 1. ^{18}O-DISTRIBUTION IN THE AROYL ALKYL CARBONATES



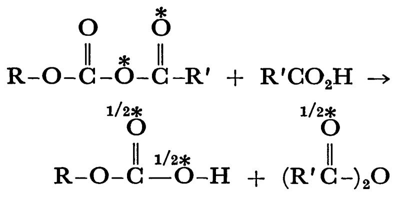
Aroyl alkyl carbonate	From starting material			^{18}O-Content (Excess atom %)[a] From recovered meterial			^{18}O-Distribution in oxygen atom (%)[b]			Reaction conditions	
	Carbamate	Acid	Anilide	Carbamate	Acid	Anilide	β[c]	γ[d]	δ[e]	Temp (°C)	Time (hr)
1a	0.00	0.84	0.81[f]	0.18	0.66	0.81[f]	21	29	50	45	24
1b	—	1.39	1.38	0.33	1.07	1.34	24	28	49	45	24
1c	0.00	1.04	1.02	0.24	0.80	0.99	23	27	49	45	25
1a	0.00	0.94	0.92	0.29	0.66	0.73	31	31	40	70	12
1b	—	1.39	1.38	0.44	0.97	1.03	32	32	37	70	12
1c	0.00	1.04	1.02	0.34	0.72	0.76	33	32	37	70	12
1a	—	0.87	0.85	0.29	0.59	0.57[g]	33	34	34	75	24

a) Estimated error ±0.005 (excess atom %). b) Based on the total amount of ^{18}O. c) Calculated from the ^{18}O-content of the carbamate. d) Estimated from the ^{18}O-content of the acid and the anilide. e) Calculated from the ^{18}O-content of the anilide. f) Carbon dioxide obtained from reaction (2) contained 0.46 excess atom % of ^{18}O. g) Carbon dioxide obtained from the reaction with aniline contained 0.57 excess atom % of ^{18}O.

The ^{18}O-analytical data and percentages of ^{18}O-distributions are summarized in Table 1. There was no ^{18}O-scrambling during the preparation of the aroyl alkyl carbonates and the α-oxygen atom remained without scrambling even after being heated at 75 °C for 24 hr. We see that nearly all the original ^{18}O-label was retained in the δ-oxygen atom after heating at 45 °C for 24 hr, while scrambling was found between β- and γ-oxygen atoms. In addition, the δ-oxygen atom participates in the oxygen scrambling reaction on heating at 70 °C for 12 hr. These results suggest a stepwise ^{18}O-scrambling for the carbonates.

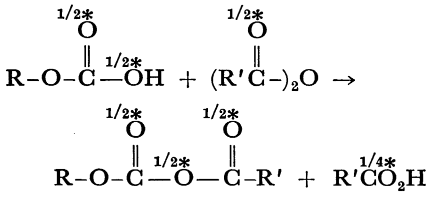
An intermolecular chain process (4)—(7) for the mechanism of ^{18}O-scrambling was ruled out on the basis of the ^{18}O-content of benzoic anhydride obtained from the reaction of ^{18}O-labeled benzoyl 1-apocamphyl carbonate with unlabeled benzoic acid.[3]

Intermolecular mechanism



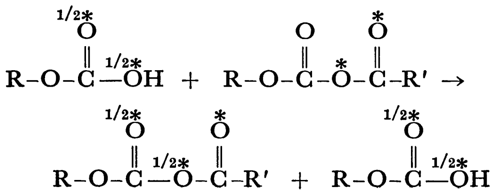
$$\mathrm{R{-}O{-}\overset{\overset{O}{\|}}{C}{-}\overset{*}{O}{-}\overset{\overset{\overset{*}{O}}{\|}}{C}{-}R' + R'CO_2H \rightarrow R{-}O{-}\overset{\overset{\overset{1/2*}{O}}{\|}}{C}{-}\overset{1/2*}{O}{-}H + (R'\overset{\overset{\overset{1/2*}{O}}{\|}}{C}{-})_2O} \quad (4)$$

$$\underset{\mathbf{2}}{}$$

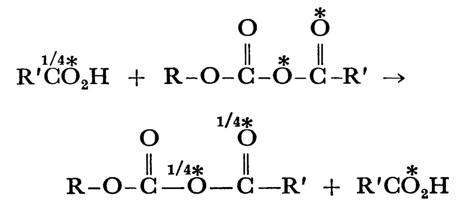


$$\mathrm{R{-}O{-}\overset{\overset{\overset{1/2*}{O}}{\|}}{C}{-}\overset{1/2*}{O}H + (R'\overset{\overset{\overset{1/2*}{O}}{\|}}{C}{-})_2O \rightarrow R{-}O{-}\overset{\overset{\overset{1/2*}{O}}{\|}}{C}{-}\overset{1/2*}{O}{-}\overset{\overset{\overset{1/2*}{O}}{\|}}{C}{-}R' + R'C\overset{1/4*}{O}_2H} \quad (5)$$

3



$$\mathrm{R{-}O{-}\overset{\overset{\overset{1/2*}{O}}{\|}}{C}{-}\overset{1/2*}{O}H + R{-}O{-}\overset{\overset{O}{\|}}{C}{-}\overset{*}{O}{-}\overset{\overset{\overset{*}{O}}{\|}}{C}{-}R' \rightarrow R{-}O{-}\overset{\overset{\overset{1/2*}{O}}{\|}}{C}{-}\overset{1/2*}{O}{-}\overset{\overset{\overset{*}{O}}{\|}}{C}{-}R' + R{-}O{-}\overset{\overset{\overset{1/2*}{O}}{\|}}{C}{-}\overset{1/2*}{O}H} \quad (6)$$



$$\mathrm{R'C\overset{1/4*}{O}_2H + R{-}O{-}\overset{\overset{O}{\|}}{C}{-}\overset{*}{O}{-}\overset{\overset{\overset{*}{O}}{\|}}{C}{-}R' \rightarrow R{-}O{-}\overset{\overset{O}{\|}}{C}{-}\overset{1/4*}{O}{-}\overset{\overset{\overset{1/4*}{O}}{\|}}{C}{-}R' + R'C\overset{*}{O}_2H} \quad (7)$$

The intermolecular mechanism can be ruled out also in the present studies involving the following crossover experiments. If the reaction proceeds with the alkyl carbonic acid (**2**) as the chain carrier (5—6), ^{18}O would be incorporated into the recovered **1a** by the crossover experiment of unlabeled **1a** and labeled **1b**. On the other hand, if the carboxylic acid (**3**) is the chain carrier as shown in (4) and (7), labeled *p*-toluic acid would be expected in the reaction of labeled **1c** with unlabeled *p*-toluic acid. An equimolar amount of unlabeled **1a** was heated with ^{18}O-labeled **1b** in the γ- and δ-oxygen atoms at 45 °C for 48 hr in CCl_4. Although a complete ^{18}O-scrambling of β- and γ-oxygen atoms was found, no excess of ^{18}O was found in the *p*-cyanobenzoic acid obtained by the treatment of the recovered **1a** with *N*-methylaniline (3). The reaction of **1c** with an equimolar amount of unlabeled *p*-toluic acid was carried out at 70 °C for 12 hr in CCl_4. *p*-Toluic acid was recovered quantitatively, no excess ^{18}O being found in the recovered acid. The results show that the mode of oxygen scrambling reaction of aroyl alkyl carbonates is quite different from that of carboxylic anhydrides.[6] Another possible ^{18}O-scrambling mechanism of the β- and γ-oxygen atoms is one involving ionic dissociation in solvent cage in view of the stepwise nature of the reaction as shown below.

If this is the case, a large negative ρ value would be expected in the kinetics of the ^{18}O-scrambling for substituted benzoyl derivatives.

The rate of scrambling between β- and γ-oxygen atoms at 45 °C can be obtained by measuring the decreasing amount of ^{18}O in the carboxylic acids ob-

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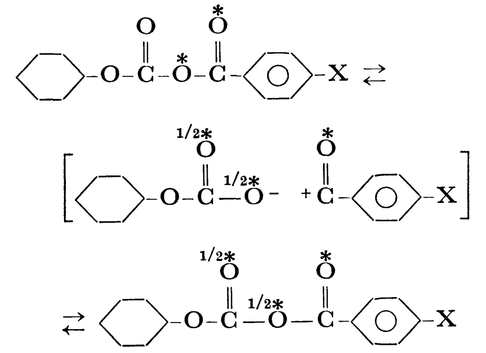
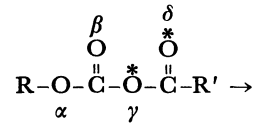
[6] L. Ponticorvo and D. Rittenberg, *J. Amer. Chem. Soc.*, **76**, 1705 (1954).



(8)

tained by treatment of the recovered carbonate with *N*-methylaniline (3). Good first-order rate constants of the ^{18}O-scrambling of β- and γ-oxygen atoms were observed: $2.42\pm0.05\times10^{-5}\,\text{sec}^{-1}$ (**1a**); $2.85\pm0.28\times10^{-5}\,\text{sec}^{-1}$ (**1b**); $2.74\pm0.02\times10^{-5}\,\text{sec}^{-1}$ (**1c**). Since there is no substituent effect, the ion pair mechanism (8) can be ruled out. A mechanism involving homolytic cleavage of the C–O bond is also unlikely since the aroyl alkyl carbonates did not decompose at all under the reaction conditions.

The only conceivable intramolecular mechanism to rationalize the observations is an intramolecular pathway involving nucleophilic attack of carbonic oxygen (β) on the carboxylic carbon as shown below.[3]



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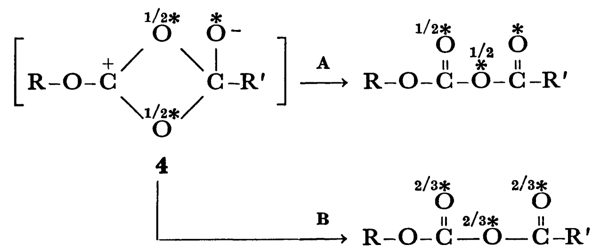
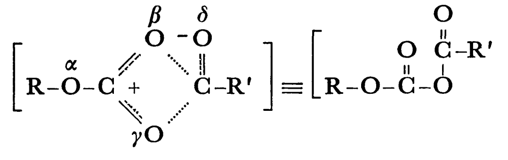
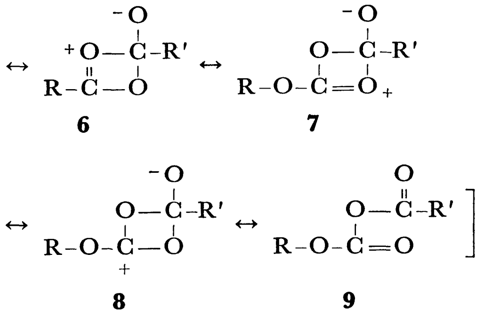


(9)

According to this mechanism, the nucleophilic attack of the β-oxygen on the carbon gives rise to the formation of an intermediate (**4**), which allows only the exchange of the β- and γ-oxygen atoms at the lower temperature (path **A**). In this process, the electron withdrawing group at the para position of the phenyl group would decrease the electron density at benzylic position of **1** and enhance the nucleophilic attack of β-oxygen atom on the carboxylic carbon atom. The structure of intermediate (**4**) is visualized as a resonance hybrid (**4′**) somewhere between the following five extremers.[7]

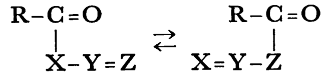


4′ **5**



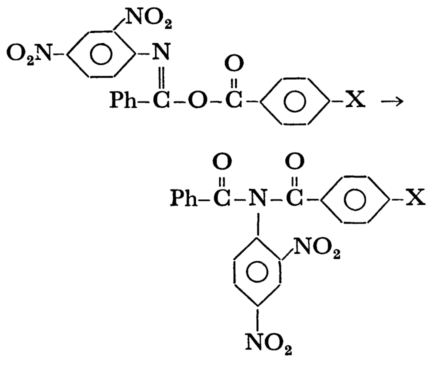
The rate of oxygen scrambling between β- and γ-oxygen atoms would therefore be determined by the stability of **4**, in which the substituent on R′ which stabllizes positive charge on β- and γ-oxygen atoms instabilizes the negative charge on δ-oxygen atom. Since β-, γ- and δ-oxygen atoms are situated in the same position with respect to R′, the opposite substituent effect would be canceled as a whole. The other possible explanation of no substituent effect of first step of oxygen scrambling is that polar canonical forms **6**, **7** and **8** hardly contribute to the structure of **4**, with respect to oxygen scrambling of acetyl peroxide (1, 3 sigmatropy) as suggested by Goldstein and Judson.[8]

The new oxygen scrambling in **1** can be regarded as an intramolecular 1, 3 acyl migration as shown by



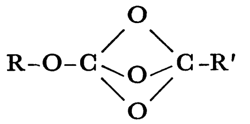
$$\begin{array}{l}\text{R-C=O}\\ \,|\\ \text{X-Y=Z}\end{array} \rightleftarrows \begin{array}{r}\text{R-C=O}\\ |\;\;\\ \text{X=Y-Z}\end{array} \qquad (10)$$

Several examples of reaction (10) are summarized in Table 2. Curtin and Miller observed the small positive ρ-value, 0.6—0.7 and proposed a similar mechanism for the *O*- to *N*-acyl migration as in the following[7]



(11)

At higher temperatures, the δ-oxygen atom in the intermediate (**4**) attacks the carbonic carbon (Scheme 1) either *via* the concerted bond formation and breaking process or *via* formation of an alternative intermediate (**5**). The three oxygen atoms of the carbonates **1** (β, γ and δ) thus scramble completely (path **B**).



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[7] D. Y. Curtin and L. L. Miller, *ibid.*, **89**, 637 (1967).

[8] M. J. Goldstein and H. A. Judson, *ibid.*, **92**, 4119 (1970).

TABLE 2. SURVEY OF SOME 1,3 ACYL MIGRATIONS

$$\begin{matrix} R-C=O \\ | \\ X-Y=Z \end{matrix} \qquad \begin{matrix} R-C=O \\ | \\ X=Y-Z \end{matrix}$$

X	Z	Y	Example	Ref.
O	O	C	Aroyl alkyl carbonates	This work, 2b
N	N	C	*N*-Acylamidines	9
N	N	N	*N*-Acyltriazenes	10
N	O	C	Isoimides	7
N	O	N	*N*-Nitrosoamides	11
S	N	C	*S*-Acylisothioureas	12

Experimental

Preparation of Cyclohexyl Chloroformate. To 45 g of phosgene cooled in an ice-bath was added 25 g of cyclohexanol, and the reaction mixture was allowed to stand overnight at room temperature. Excess phosgene was removed and cyclohexyl chloroformate was distilled under reduced pressure (90—91 °C/31 mmHg, 86%).

Preparation of ^{18}O-Labeled p-*Cyanobenzoyl Cyclohexyl Carbonate (**1a**).* In a flask equipped with a stirrer and a dropping funnel were placed 300 ml of dry ether, 10 g of ^{18}O-labeled *p*-cyanobenzoic acid and 6.8 g of triethylamine. The mixture was cooled to 0 °C with an ice-bath, 11.0 g of cyclohexyl chloroformate in 30 ml of dry ether being then added dropwise over a period of 1 hr. Stirring was continued for 4 hr. The amine hydrochloride was filtered off, and the filtrate was washed with dil HCl, dil aqueous $NaHCO_3$ and water and dried over Na_2SO_4. Evaporation of the solvent left 15.0 g of colorless crystals. Recrystallization from CCl_4–petroleum ether gave 12.6 g of **1a**, mp 54.5—55.0 °C. IR: 5.59 and 5.76 μ ($\nu_{C=O}$). Found: C, 66.08; H, 5.55; N, 5.03%. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13%.

*^{18}O-Labeled Benzoyl Cyclohexyl Carbonate (**1b**) and p-Toluyl Cyclohexyl Carbonate (**1c**)* were prepared from ^{18}O-labeled benzoic acid and *p*-toluic acid in the same way as for **1a** in 67 and 91% yields, respectively. **1b**: mp 21.0—21.5 °C resrystallized from pet. ether. IR: 5.59 and 5.76 μ ($\nu_{C=O}$). Found: C, 68.00; H, 6.32. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50% **1c**: mp 25.5—26.5 °C, IR: 5.59 and 5.76 μ ($\nu_{C=O}$). Found: C, 68.90; H, 6.76%. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92%.

^{18}O-Scrambling in the Aroyl Alkyl Carbonates. A typical run is as follows: A solution of 2.73 g of **1a** in 1 l CCl_4 was warmed at 45 °C for 24 hr. The solvent was removed under reduced pressure at room temperature and the residue was used for the following cleavage reaction, the products being subjected to ^{18}O-analysis.[2)]

Reaction of Aroyl Alkyl Carbonates with Aniline. In a typical run, 0.40 g of aniline was added 10 ml CCl_4 solution of 0.82 g of **1a** at room temperature and the mixture was allowed to stand for 1.5 hr. *p*-Cyanobenzanilide was collected by filtration and recrystallized from chloroform, mp 180—180.5 °C, and subjected to ^{18}O-analysis. The filtrate was diluted with 30 ml of ether and washed with dil HCl, dil $NaHCO_3$ and water, and dried over Na_2SO_4. Solvent was removed and the residue was chromatographed through an activated alumina column with benzene and ether as eluents. A fraction which came out in the latter was identified as cyclohexanol and subjected to ^{18}O-analysis. In order to collect carbon dioxide, the reaction was carried out as follows: The aroyl alkyl carbonate (**1**) (0.30 g) and 5 ml of CCl_4 were placed in a flask with two necks, one equipped with a bent tube charged with 0.2 g of aniline and the other connected to a vacuum line. After evacuation of the flask with cooling in a dry ice-acetone bath, it was warmed up to room temperature and aniline was added by turning the bent tube. The carbon dioxide evolved was collected in a trap cooled with liquid N_2, sublimed three times in the vacuum line and then subjected to ^{18}O-analysis.

Reaction of Aroyl Alkyl Carbonates with N-*Methylaniline.* In a typical run, 0.4 g of *N*-methylaniline was added to a solution of 0.82 g of **1a** in 10 ml CCl_4 at room temperature. The reaction was allowed to continue for 1.5 hr. Solid material was collected by filtration, recrystallized from chloroform, identified as *p*-cyanobenzoic acid, mp 219.0—219.5 °C, and subjected to ^{18}O-analysis. The filtrate was washed with dil HCl dil aqueous $NaHCO_3$ and water, then dried over Na_2SO_4. CCl_4 was removed by distillation, and the residue was chromatographed on silica gel column with benzene as an eluent. The early fraction was distilled under reduced pressure (bp 135—136 °C/3 mmHg), identified as cyclohexyl *N*-methyl-*N*-phenyl carbamate with the authentic sample and subjected to ^{18}O-analysis.

Preparation of Cyclohexyl N-*Methyl*-N-*Phenyl Carbamate.* To a mixture of 6.0 g of *N*-methylaniline and 5.0 g of triethylamine in 40 ml of dry ether was added 8.2 g of cyclohexyl chloroformate in 10 ml dry ether with stirring at 0 °C. Stirring was continued for 1 hr. Amine hydrochloride was filtrated off and the filtrate was washed with dil HCl, dil $NaHCO_3$ and water, then dried over Na_2SO_4. The ether was removed by distillation and the residue was distilled under reduced pressure to yield 8.8 g of cyclohexyl *N*-methyl-*N*-phenyl carbamate, bp 135—136 °C/3 mmHg. Found: C, 71.88; H, 8.28; N, 5.72%. Calcd for $C_{14}H_{19}O_2N$: C, 72.02; H, 8.21; N, 6.00%.

*Reaction of ^{18}O-Labeled **1c** with* p-*Toluic Aicd.* A solution of 1.31 g of **1c**, labeled with 1.04 excess atom % of ^{18}O at γ- and δ-oxygen atoms, and 0.66 g of unlabeled *p*-toluic acid in 125 ml CCl_4 was heated at 70 °C for 12 hr. After heating the free acid was extracted with aqueous $NaHCO_3$. The water layer was acidified with HCl and extracted with ether. The etheral solution was washed with water and dried over Na_2SO_4. The ether was evaporated to give 0.66 g *p*-toluic acid which was recrystallized from benzene, mp 179.0—179.5 °C and subjected to ^{18}O-analysis.

*Crossover Experiment between Unlabeled **1a** and Labeled **1b**.* A mixture of 1.36 g of unlabeled **1a** and 1.20 g of labeled **1b** (1.39 excess atom % in the γ- and δ-oxygen atom) in 250 ml of CCl_4 was heated at 45 °C for 48 hr. The solvent was removed under reduced pressure at room temperature. **1a** (0.7 g) was recovered by the fractional recrystallization of the residue from CCl_4–pet. ether. **1a** recovered was treated with *N*-methylaniline (**3**) to yield 0.17 g of *p*-cyanobenzoic acid which was subjected to ^{18}O-analysis (0.00 excess atom %).

Preparation of ^{18}O-Labeled p-*Cyanobenzoic Acid.* In a flask equipped with a stirrer and a dropping funnel were placed 33 g of *p*-cyanobenzoyl chloride, 40 g of triethylamine and 300 ml of dry dioxane to which was added dropwise

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9) H. L. Wheeler, T. B. Johnson, and D. F. McFarland, *J. Amer. Chem. Soc.*, **25**, 790 (1903).

10) a) M. O. Forsten and C. S. Garland, *J. Chem. Soc.*, **95**, 2051 (1909). b) J. D. Druliner, Ph. D. Thesis. University of Illinois, 1966.

11) K. B. Wiberg, T. M. Shryne and R. R. Kintner, *J. Amer. Chem. Soc.*, **79**, 3160 (1957).

12) R. F. Pratt and T. C. Bruice, *ibid.*, **94**, 2823 (1972).

4.0 g of ^{18}O-enriched water (1.5 atom%) in 10 ml of dry dioxane. Stirring was continued for 2 hr. The reaction mixture was filtered and the precipitate was washed with 100 ml of dioxane. The filtrate and washing solution were combined and the solvent was removed by distillation. The residue was dissolved in 300 ml of water and acidified with HCl. The precipitate was filtered, washed with water and dried. The acid was recrystallized from chloroform–acetone, mp 217.0—218.0 °C.

Kinetics of ^{18}O-Scrambling in the Aroyl Alkyl Carbonates. Kinetics of ^{18}O-scrambling between β- and γ-oxygen atoms were followed by measurement of the decreasing amount of ^{18}O in *p*-substiutted benzoic acids formed by cleavage reaction (3). The aroyl alkyl carbonates were heated at 45 °C in CCl_4 (0.04 mol/l).

^{18}O-Analysis was carried out in the same way as reported previously.[2]

We wish to thank Professor S. Okazaki for the supply of ^{18}O-water which made this work possible.