The Mechanism of Silver Perchlorate Catalyzed Solvolysis Reaction of 2-Chlorocyclohexanone-1-^{14}C

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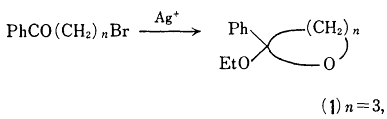
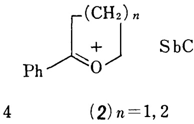
(Received July 2, 1970)

Silver perchlorate assisted solvolysis of 2-chlorocyclohexanone-1-^{14}C in ethanol-water solution gives 2-ethoxycyclohexanone-*x*-^{14}C. Successive degradation of the product reveals that the ^{14}C activity is distributed in both the carbonyl carbon and the α-carbon of ethoxyketone. The ^{14}C distribution pattern suggests that a part of the reaction proceeds *via* an epoxide intermediate which is formed by the initial attack of ethanol on the carbonyl carbon, followed by the migration of carbonyl oxygen to the α-carbon of 2-chlorocyclohexanone.

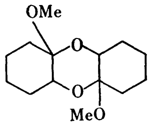
In the silver or mercury ion-catalyzed solvolytic reactions of haloketones, a carbonyl group, attached to either γ or δ position of the leaving group, is known to accelerate remarkably the rate of the reaction despite the fact that the carbonyl group is expected to retard it by its strong electron-withdrawing property. These results suggest that the carbonyl group participates in the solvolysis reaction. The rate enhancement and neighboring group participation of the carbonyl group were in fact confirmed by both kinetic study[1,2] and isolation of the products[2,3] such as **1** which undoubtedly results from the participation of carbonyl oxygen. Further, Ward and Sherman, Jr. recently isolated the intermediate **2** as a hexachloroantimonate.[4] More recently, Gassman and his coworkers demonstrated that the enol form of the ketone, which exists in a small amount in an equilibrium with the keto form, participates in the solvolysis reaction, by showing that the rate of solvolysis of anti-7-hydroxynorbornane-2-one-*p*-toluenesulfonate is 2×10^7 times larger than that of 7-hydroxynorbornane-*p*-toluenesulfonate.[5] Although participation of the carbonyl group in the solvolytic reaction has been well established in the case of halo-ketones, in which the carbonyl group is separated at least one methylene group away from the cationic center, evidence supporting the interaction of the carbonyl group with the adjacent cation center is also available. As an example of such interaction, Bergmann obtained the compound **3** from the methanolysis of 2-bromocyclohexanone.[6] The product **3** is probably formed by the dimerization of the epoxide **4**. Silver perchlorate-catalyzed solvolysis of 2-chlorocyclohexanone-1-^{14}C was carried out, to make this interaction clearer. This paper describes briefly the partial migration of carbonyl oxygen of 2-chlorocyclohexanone to the α-position of the product and the probable mechanism of the whole reaction.



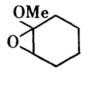
(1) $n=3,4$



(2) $n=1,2$



(**3**)



(**4**)

2-Chlorocyclohexanone-1-^{14}C was synthesized, and a series of successive degradations of the product was carried out as shown below (Fig. 1).

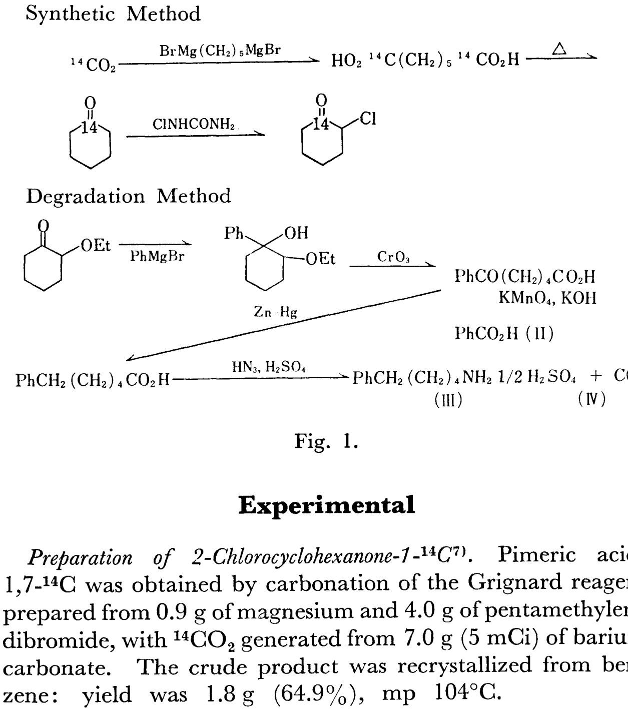


Fig. 1.

Experimental

Preparation of 2-Chlorocyclohexanone-1-^{14}C[7]. Pimeric acid-1,7-^{14}C was obtained by carbonation of the Grignard reagent prepared from 0.9 g of magnesium and 4.0 g of pentamethylene dibromide, with $^{14}CO_2$ generated from 7.0 g (5 mCi) of barium carbonate. The crude product was recrystallized from benzene: yield was 1.8 g (64.9%), mp 104°C.

A mixture of 1.8 g of pimeric acid-1,7-^{14}C and 0.1 g of barium carbonate was gradually heated in a metallic bath to about 320°C and the distillate was collected. The crude cyclohexanone-1-^{14}C (1.0 g), was diluted by adding 10 g of ordinary cyclohexanone and purified by distillation (bp 154—155.5°C). Four grams of the cyclohexanone-1-^{14}C was stirred gently overnight in a water bath at room temperature with 2 g of acetic acid and 20 m*l* of chlorourea solution, which was prepared by absorbing 35 g of chlorine in a stirred suspension of 50 g of calcium carbonate and 300 g of urea in 50 m*l* of water. The solution was then filtered with suction and the filtrate was finally diluted with water to 200 m*l*.

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1) S. Oae, *J. Amer. Chem. Soc.*, **78**, 4030 (1956).

2) G. Baddley, E. K. Baylis, B. G. Heaton, and J. W. Rasburn, *Proc. Chem. Soc.*, **1961**, 451.

3) D. J. Pasto, K. Graves, and M. M. Serve, *J. Org. Chem.*, **32**, 774 (1967).

4) H. R. Ward and P. D. Sherman, Jr., *J. Amer. Chem. Soc.*, **90**, 3812 (1968).

5) P. G. Gassman and J. L. Marshall, *ibid.*, **88**, 2599 (1966); P. G. Gassman, J. L. Marshall, and J. M. Hornback, *ibid.*, **91**, 5811 (1969); P. G. Gassman and J. M. Hornback, *ibid.*, **91**, 5817 (1969).

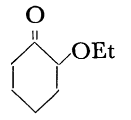
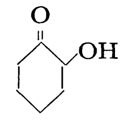
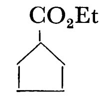
6) M. Bergmann and M. Gierth, *Ann. Chem.*, **448**, 48 (1926).

7) R. B. Loftfield, *J. Amer. Chem. Soc.*, **73**, 4707 (1951).

The reaction mixture was then extracted with benzene. The benzene solution was dried over anhydrous sodium sulfate. After removing the solvent, the residue was distilled to give 4 g of 2-chlorocyclohexanone-1-^{14}C, bp 159—159.5°C (74%).

Solvolysis of 2-Chlorocyclohexanone-1-^{14}C and Isolation of the Products. 2-Chlorocyclohexanone-1-^{14}C was solvolyzed in 12.5 m*l* of 80% aqueous ethanol containing 3.1 g of silver perchlorate at 70°C in a water bath for 18 hr. After completion of the reaction, the reaction mixture was neutralized with aqueous sodium carbonate solution. In order to determine the yield of the products by isotopic dilution method, the following non-radioactive compounds were added to the solution, *i.e.*, 1.113 g of 2-ethoxycyclohexanone, 1.086 g of 2-hydroxycyclohexanone, and 0.798 g of ethyl cyclopentanecarboxylate. After the precipitated silver chloride was filtered off, the filtrate was extracted with ether and then with methylene chloride. Both extracts were dried over sodium sulfate. The ether extract gave 2.7 g of yellow oily product (bp *ca.* 88°C/22.5 mmHg) from which 2-ethoxycyclohexanone (0.750 g) and ethyl cyclopentanecarboxylate (0.460 g) were identified and separated with gas liquid chromatography. 2-Hydroxycyclohexanone (0.340 g) was obtained from the methylene chloride extract by removing the solvent and keeping the residue in an ice-box for a few days, mp 110—113°C. The products thus obtained were identified by comparing their NMR, IR spectra and melting points with those of the authentic samples. The yield of the products is shown in Table 1.

TABLE 1. YIELD OF PRODUCTS[a)]

		
31%	23%	1%

a) The yields were determined by the isotopic dilution method.

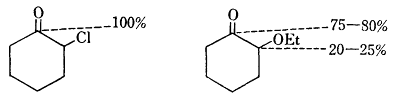
Degradation of 2-ethoxycyclohexanone-x-^{14}C. 2-Ethoxycyclohexanone-*x*-^{14}C (0.75 g) was mixed with 2.00 g of ordinary 2-ethoxycyclohexanone and dissolved in 30 m*l* of dry ether. This etheral solution was added with stirring to the Grignard reagent prepared from 4.13 g of bromobenzene and 0.64 g of magnesium in 30 m*l* of dry ether. The solution was kept at room temperature overnight, and then acidified with dilute hydrochloric acid. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extract was washed with aqueous sodium bisulfite solution, neutralized with aqueous sodium carbonate solution, washed with water, and finally dried over sodium sulfate. After removal of ether, 3.8 g, of crude 1-phenyl-2-ethoxycyclohexanol was obtained in 70% yield (bp 114.5—116.0°C/1.5 mmHg). Found: C, 76.07; H, 9.03%. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%.

A mixture of crude 1-phenyl-2-ethoxycyclohexanol-*x*-^{14}C (3.8 g) and chromic acid (1 g) was vigorously stirred. When the temperature reached 25°C, another 9 g of chromic acid was added during a period of one hour keeping the temperature at around 30°C. After the addition of chromic acid, the mixture was diluted with an equal amount of water and was extracted with ether several times. The ether extract was washed with water. The etheral solution was extracted with 300 m*l* of aqueous 5% sodium hydroxide solution. The alkali extract was warmed on a water bath to remove excess ether. After cooling, the solution was acidified with 100 m*l* of concentrated hydrochloric acid. The precipitates were filtered and recrystallized from benzene-*n*-hexane. Thus, 5-benzoylvaleric acid (1.01 g) was obtained in 31% yield; mp 75—76°C. A mixture of 0.35 g of 5-benzoylvaleric acid-*x*-^{14}C, 2.8 g of potassium permanganate, and 1.45 g of potassium hydroxide was dissolved in 50 m*l* of water and refluxed for 4 hr. After the reaction, the precipitates were filtered off and washed with *ca.* 100 m*l* of boiling water. The filtrate was bubbled with sulfur dioxide, acidified with dilute hydrochloric acid and then extracted with ether. The extract was dried over sodium sulfate. After removal of ether, benzoic acid was obtained in 71% yield, mp 120—121°C (recrystallized from *n*-hexane). 5-Benzoylvaleric acid-*x*-^{14}C (1.38 g) was reduced by Martin and Clemmensen's method.[8)] Thus, 6-phenylcaproic acid-*x*-^{14}C (0.81 g) was obtained in 62% yield, bp 150—151.5°C, mp 16—21°C. 6-Phenylcaproic acid-*x*-^{14}C (0.81 g), dissolved in 1.7 m*l* of concentrated sulfuric acid, was decarboxylated with 6.5 m*l* of 1.6 N hydrazoic acid in chloroform solution and the carbon dioxide generated was trapped with

TABLE 2. THE ^{14}C COUNTING DATA

Run	Method of[a)] Measurement	$PhCO(CH_2)_4CO_2H$ (I)	$PhCO_2H$ (II)	$Ph(CH_2)_5NH_2 1/2H_2SO_4$ (III)	CO_2[b)] (IV)
I	(A) cpm/mmol	2.84×10^5	2.10×10^5		
	(B) cpm	11388			2855
(^{14}C distribution)		(100 %)	(74.9 %)		(25.1 %)
II	(B) cpm	5170		4182	1122
(^{14}C distribution)		(100 %)		(80.9 %)	(21.7 %)

a) (A) liquid scintillation counter, (B) G. M. Counter (Van Slyke method)
b) Counted as barium carbonate.
All runs were repeated at least twice.



^{14}C-Distribution

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8) "Organic Reaction," Vol. 1, John Wiley & Sons, New York, p. 155; L. D. Freedman and G. O. Doak, *J. Amer. Chem. Soc.*, **71**, 779 (1949).

9) S. Oae, N. Furukawa, M. Kise, and M. Kawanishi, This Bulletin, **39**, 1212 (1966).

0.25 N aqueous barium hydroxide solution. After completion of the reaction, chloroform and excess hydrazoic acid were removed *in vacuo*. The residue, to which a small amount of water was added, was filtered, washed with acetone-ether, and recrystallized from water. 5-Phenylamylamine-x-^{14}C 1/2 H_2SO_4 (0.673 g) was thus obtained in 75.2% yield, mp 325—330°C (decompd.).

Measurement of the Activities. The activities of the samples were measured both with a 2π-gas flow G.M. counter using Q gas and with a liquid scintillation counter using POP and POPOP as scintillators in toluene solution. 5-Benzoylvaleric acid-x-^{14}C was used as the standard sample of the total activity. The activity measurement with 2π-gas flow G.M. counter was described precisely in a previous paper.[9] An aliquot of each sample was thoroughly oxidized by the Van Slyke-Folch method, and all the carbon dioxide formed was converted to a barium carbonate tablet which was then subjected to measurement of its ^{14}C activity. The results are shown in Table 2.

Results and Discussion

The products were isolated and identified by the ordinary method and their yields were determined by isotope dilution technique. The result is shown in Table 1. The usual synthetic procedures were used for the ^{14}C compounds. Degradation of 2-ethoxy cyclohexanone was also carried out by a well-known procedure involving no skeltal rearrangement. 5-Benzoylvaleric acid was used as the standard sample of the total activity. The ^{14}C total activities and those of the respective degradative products were calculated from the specific activities of the corresponding samples. The result of the degradation is listed in Table 2. We see that 5-benzoylvaleric acid carries 75—80% of the total activity in carbonyl carbon and the rest is found in carboxylic carbon. This means that 75—80% of the total ^{14}C activity is in the carbonyl carbon atom and 20—25% is in the carbon atom bearing ethoxy group in 2-ethoxycyclohexanone. Namely, around 25% carbonyl oxygen migrates to the α-carbon attached to chlorine. The product analysis seems to rule out both the Wagner Meerwein type rearrangement mechanism, in which the carbon-carbon bond migrates to the cation center as in the case of the deamination of 2-amino cyclohexanone[10] and the Favorskii type mechanism[11] involving the initial formation of cyclopropanone *via* the participation of enolizable carbon-carbon double bond. If the reaction proceeds through one of these routes, cyclopentanecarboxylic acid derivatives would be the major products. Thus, both product analysis and ^{14}C tracer experiments suggest the following mechanism (Fig. 2). Namely, silver ion assists the abstraction of chlorine anion following the migration of carbonyl oxygen to the α carbon atom bearing chlorine atom.

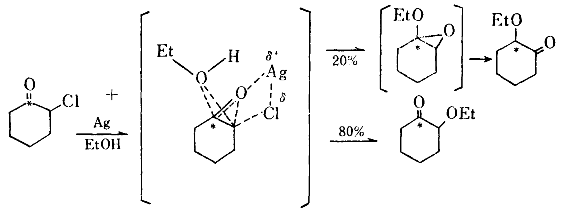

Fig. 2. Mechanism of the reaction.

The authors wish to express their appreciation to Dr. M. Hamada of the Radiation Center of Osaka Prefecture for the measurement of ^{14}C activities.

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[10] M. Nakai, N. Furukawa, and S. Oae, This Bulletin, **42**, 2917 (1969).

[11] R. B. Loftfield, *J. Amer. Chem. Soc.*, **72**, 632 (1950).