Chemistry

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1962

SovietRxiv

Abstract

Full Text

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ON THE MECHANISM OF THE DEMJANOV REACTION

On the basis of a study of the isomerization of alkyl cations with migration of hydride ions ($^{1-3}$), we earlier (^{2}) put forward the supposition that in molecules of cyclohexanol, formed by the action of nitrous acid on cyclohexylamine, the hydroxyl group is bonded not only to the carbon atom to which the amino group was bonded in the initial cyclohexylamine molecule.

In the present work we have confirmed this supposition experimentally. Labeled cyclohexylamine, in which C^{14} is bonded to nitrogen*, was synthesized according to the following scheme:

$$\mathrm{Br(CH_2)_5Br} \xrightarrow[\text{(2) hydrolysis}]{\text{(1) } KC^{14}N} \mathrm{HOOC^{14}(CH_2)_5C^{14}OOH} \xrightarrow[\text{heating}]{\mathrm{BaCO_3}} {}^{14}\mathrm{O{=}cyclohexanone}$$

$$\xrightarrow[\text{skeleton Ni}]{\mathrm{HCONH_2},\ \mathrm{HCOOH}} {}^{14}\text{cyclohexyl—}\mathrm{NH_2}$$

The interaction of cyclohexylamine perchlorate, in which C^{14} is bonded to the amino group, with nitrous acid leads to the formation of a mixture of cyclohexanol and cyclopentylcarbinol

$${}^{14}\text{cyclohexyl—}\mathrm{NH_2}\cdot\mathrm{HClO_4} \xrightarrow{\mathrm{HNO_2}} \text{cyclohexanol} + \text{cyclopentyl—}\mathrm{CH_2OH}$$

To establish the position of the radiocarbon C^{14} in the cyclohexanol molecule, the latter was subjected to the following degradation:

$$\text{cyclohexanol} \xrightarrow{\mathrm{O}} \text{cyclohexanone} \xrightarrow{\mathrm{HN_3}} \mathrm{HOOC(CH_2)_5NH_2} \xrightarrow{\mathrm{HN_3}} \mathrm{H_2N(CH_2)_5NH_2{+}C^{14}O_2} \quad \text{radioactive}$$

Pentamethylenediamine proved to be radioactive** ($3.7 \pm 0.3\%$ of the activity of cyclohexanone). This means that in some molecules of cyclohexanol the hydroxyl is bonded not to the carbon atom to which the amino group was bonded in the initial cyclohexylamine molecule.

* In order to make certain that cyclohexylamine was labeled with C^{14} only at the carbon bonded to nitrogen, the following degradation was carried out: cyclohexylamine was oxidized to cyclohexanone; the latter, under the action of hydrazoic acid, was converted into δ-amino-*n*-caproic acid and then into pentamethylenediamine, which proved to be nonradioactive

$$^{14}\text{cyclohexyl—NH}_2 \xrightarrow{\text{O}} {}^{14}\text{cyclohexanone} \xrightarrow{\text{HN}_3} \text{HOOC}^{14}(\text{CH}_2)_5\text{NH}_2 \xrightarrow{\text{HN}_3} \text{H}_2\text{N}(\text{CH}_2)_5\text{NH}_2 + \text{C}^{14}\text{O}_2.$$

nonradioactive

** The low percentage of rearrangement of the cyclohexyl cation is possibly explained by the fact that it reacts very rapidly with the solvent, giving cyclohexanol. An analogous explanation is given by Streitwieser and Coverdale ([4]) for the fact that in the reaction of cis-cyclohexylamine-2-D perchlorate with nitrous acid, not less than 94% cis-cyclohexanol-2-D is formed.

Thus, the cyclohexyl cation undergoes isomerization analogous to the isomerization of the propyl cation ([2]):

$$\begin{tikzcd}
\text{cyclohexyl-1-}^{14}\text{C amine perchlorate} \arrow[r, "\text{HNO}_2"] \arrow[d, "\text{OH}^-"] & \text{cyclohexyl-1-}^{14}\text{C cation} \arrow[r, phantom, "\rightleftarrows"] \arrow[d, "\text{OH}^-"] & [^{14}\text{CH}_2\text{C}_5\text{H}_9]^+ \\
\text{cyclohexanol-1-}^{14}\text{C} & \text{C}^{14}\text{H}_2\text{C}_5\text{H}_9\text{OH} &
\end{tikzcd}$$

The results of the present work show that the mechanism of the Demyanov reaction for the interconversion of alicycles is more complex than is usually assumed. It is complicated by isomerizations resulting from hydride-ion transfer.

Experimental Part

I. Synthesis of cyclohexylamine-1-C^{14}.

1. Preparation of pimelic-1,7-C^{14} acid ([5]). From 2.86 g (0.044 mole) of $KC^{14}N$ (total activity 55 mCi) and 4.6 g (0.040 mole) of pentamethylene dibromide, 2.84 g (81% of theory) of pimelic-1,7-C^{14} acid was obtained.
2. Preparation of cyclohexanone-1-C^{14} ([5]). On heating a mixture of 3.0 g (0.019 mole) of pimelic-1,7-C^{14} acid and 0.1 g (0.005 mole) of barium carbonate, 1.7 g (79% of theory) of cyclohexanone-1-C^{14} was obtained, n_D^{20} 1.4498, m.p. of the 2,4-dinitrophenylhydrazone 161–162°. Literature data ([6]): n_D^{20} 1.4503, m.p. of the 2,4-dinitrophenylhydrazone 162°.

3. Preparation of cyclohexylamine-1-C^{14} (7). From 50 g (1 mole) of a formamide-formate mixture, 50 g (1 mole) of 85% formic acid, 0.5 g of Raney nickel, and 24 g (0.25 mole) of cyclohexanone-1-C^{14}, 16.08 g (50% of theory) of cyclohexylamine was obtained in the form of the perchlorate.

II. Reaction of cyclohexylamine-1-C^{14} perchlorate with nitrous acid (analogously to (4)).

To 15.7 g (0.08 mole) of cyclohexylamine-1-C^{14} perchlorate in 50 ml of water, cooled with ice water, were added 7 ml of 60% perchloric acid and, dropwise, a solution of 6.5 g (0.09 mole) of sodium nitrite in 30 ml of water. After stirring for 6 hours at 0°, 1 g (0.014 mole) of sodium nitrite was added to the mixture. The reaction mixture was left for 18 hours at 0–2°, then for 24 hours at 20°. The upper layer of cyclohexanol-C^{14} and cyclopentylcarbinol-C^{14} was separated; the lower layer was saturated with sodium chloride and extracted with ether. The ether extracts and the layer of alcohols were washed with 10% sulfuric acid and with water, and dried over ignited sodium sulfate. After distillation of the ether, 1 g of cyclohexanol carrier was added to the residue and the fraction 159–161°/752 mm was collected. Weight 2.88 g. Literature data (8,9): b.p. of cyclohexanol 160.5°, of cyclopentylcarbinol 162.5–163.5°.

III. Determination of the position of carbon C^{14} in cyclohexanol-C^{14}.

1. Oxidation of cyclohexanol-C^{14} and cyclopentylcarbinol-C^{14} (analogously to (10)). To 2.88 g of the mixture of alcohols in 15 ml of water and 1.8 ml of conc. H_2SO_4, 2.2 g (0.022 mole) of CrO_3 in 50 ml of water was added dropwise, and the mixture was left overnight at 20°. About 20 ml of distillate was distilled from the reaction mixture; after saturation of the distillate with anhydrous potassium carbonate, the separated layer of cyclohexanone-C^{14} and cyclopentylaldehyde-C^{14} was extracted with ether. The ether solution was evaporated; the residue in 20 ml of water was boiled for 1.5 hours with an excess of freshly precipitated silver oxide. Cyclohexanone-C^{14} was distilled from the reaction mixture with water; after saturation of the solution with anhydrous potassium carbonate, cyclohexanone-C^{14} was separated (1.8 g). To the aqueous layer was added 0.5 g of carrier—cyclohexanone; the mixture was shaken vigorously, after which cyclohexanone was again separated (weight 0.45 g). To the combined layers of cyclohexanone-C^{14}, 14 ml of 36% sodium bisulfite was added, and the mixture was left overnight at 0–2°. The bisulfite compound of cyclohexanone-C^{14}

filtered off and washed with ether. Cyclohexanone-C^14 was isolated from the bisulfite compound by adding the latter to 20 ml of a boiling saturated solution of potassium carbonate. After the mixture had cooled, the cyclohexanone-C^14 layer was separated (weight 1.16 g). For additional isolation of cyclohexanone-C^14, 0.5 g of carrier—cyclohexanone—was again added. An additional 0.28 g of cyclohexanone was isolated. Total weight 1.44 g. For measurement of radioactivity, cyclohexanone-C^14 was converted into the 2,4-dinitrophenylhydrazone, m.p. 161-162°. The 2,4-dinitrophenylhydrazone was recrystallized from alcohol, m.p. 161-162°. The radioactivity is given in Table 1.

Table 1

Distribution of radioactivity in the reaction products (imp/min · mmole)

	Deamination of cyclohexylamine-1-C^14	Oxidation of cyclohexylamine-1-C^14
Cyclohexanone (as the 2,4-dinitrophenylhydrazone)	$355 \cdot 10^3$	$405 \cdot 10^3$
Pentamethylenediamine (as the picrate)	$13.2 \cdot 10^{3}$*	0.0
Percent rearrangement	3.7$±$0.3	0.0

* Average value of the results of two parallel experiments of the reaction of cyclohexanone with hydrazoic acid.

2. Reaction of cyclohexanone-C^14 with hydrazoic acid (11). From 1.39 g (0.014 mole) of cyclohexanone-C^14, in the reaction with hydrazoic acid, 1.93 g (81% of theory) of δ-amino-*n*-caproic-C^14 acid was obtained as the hydrochloride.

3. Reaction of δ-amino-*n*-caproic-C^14 acid with hydrazoic acid (11). From 0.80 g (0.006 mole) of δ-amino-*n*-caproic-C^14 acid hydrochloride, in the reaction with hydrazoic acid, 0.51 g of pentamethylenediamine hydrochloride was obtained. For measurement of radioactivity the pentamethylenediamine hydrochloride was converted into the picrate, m.p. 226-228°. The picrate was recrystallized twice from alcohol, m.p. 228-229°. Literature data (12): m.p. 225-230°. The results of the radioactivity measurements are given in Table 1.

IV. Experiments proving that cyclohexylamine is labeled with C^14 only at the carbon bonded to the amino group.

1. Oxidation of cyclohexylamine-1-C^14 (13). A solution of 10.4 g (0.05 mole) of cyclohexylamine-1-C^14 perchlorate in 30 ml of water was added to 200 ml of 5% potassium permanganate; the mixture was made alkaline with 40% NaOH to pH 8, and then a further 4 ml of 0.5N NaOH was added. The reaction mixture was heated at 90-100° for 30 min. From the acidified solution, cyclohexanone-1-C^14 was distilled off with water; the distillate was saturated with potassium carbonate and cyclohexanone-1-C^14 was separated. Weight 1.5 g (32% of theory), n_D^{16} 1.4495, m.p. of the 2,4-dinitrophenylhydrazone 160-161°.

2. Determination of the position of the C^14 carbon in cyclohexanone-1-C^14 was carried out as in III, Nos. 2, 3. The results of the radioactivity measurements are given in Table 1.

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Received
25 X 1961

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