Reports of the Academy of Sciences of the USSR

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1964

SovietRxiv

Abstract

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Reports of the Academy of Sciences of the USSR

1964. Volume 154, No. 1

CHEMISTRY

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ON THE CONVERSION OF 1,6-ANHYDROALDOHEXOSES INTO PHENOLS UNDER THE ACTION OF METALLIC SODIUM IN LIQUID AMMONIA

(Presented by Academician B. A. Kazanskii on 31 VII 1963)

The results of our published works ($^{1-5}$) on the study of the reaction of trimethyl ethers of 1,6-anhydrides of *D*-hexoses (see Table 1) with a solution of metallic sodium in liquid ammonia showed that in all cases a mixture of phenols of identical composition is formed: a monohydric phenol and dihydric phenols—pyrocatechol, resorcinol, and the monomethyl

Table 1

Yields of phenols for various 2,3,4-tri-*O*-methyl-1,6-anhydrohexoses

Starting substance	Yield of phenol, %	Yield of dihydric phenols, %	Literature source
2,3,4-Tri-*O*-methyl-1,6-anhydro-*D*-glucopyranose	50—56	15	(1,2)
2,3,4-Tri-*O*-methyl-1,6-anhydro-*D*-galactopyranose	27—34	20	(3)
2,3,4-Tri-*O*-methyl-1,6-anhydro-*D*-mannopyranose	15—17	20	(4)
2,3,4-Tri-*O*-methyl-1,6-anhydro-*D*-gulopyranose	45—49	20	(5)

Scheme 1: reaction scheme showing the conversion of a trimethyl 1,6-anhydrohexose derivative under the action of RNa/Na to sodium phenoxide

Figure 1: Scheme 1: reaction scheme showing the conversion of a trimethyl 1,6-anhydrohexose derivative under the action of RNa/Na to sodium phenoxide

Starting substance	Yield of phenol, %	Yield of dihydric phenols, %	Literature source
2,3,4-Tri-*O*-methyl-1,6-anhydro-*D*-idopyranose	49	25	(5)

ether of resorcinol. Although the amount of the monohydric phenol formed varies from 56% to 15%, depending on the nature of the sugar, this reaction is common to trimethyl ethers of 1,6-anhydrides of *D*-aldohexoses.

P. P. Shorygin and one of us, who were the first to discover in 1939 the conversion of trimethyllevoglucosan into phenol (^{1}), proposed a scheme for this reaction (Scheme 1).

Scheme 1

This scheme assumes that the first act of the reaction is the cleavage of the C_1—O—C_5 and C_1—O—C_6 acetal bonds with simultaneous closure of the carbocycle. The C_1—O—C_5 acetal bond is cleaved under the action of sodium, and the C_1—O—C_6 bond by addition of RNa, organometallic sodium compounds formed during the reaction, for example CH_3Na. The cyclitol formed in this process is then converted into phenol with the elimination of two moles of alkali and one mole of methyl alcohol. The proposed reaction pathway is in principle logical, but it had not been proved. Therefore we undertook investigations with the aim of refining this scheme.

First of all, we showed that cleavage of the acetal bonds, without which carbocyclization is impossible, becomes feasible only after preliminary activation of the molecule. It turned out that levoglucosan reacts with metallic sodium in liquid ammonia only with the formation of

alkoxide. The behavior of different ethers of levoglucosan under identical conditions is different and depends on the nature of the ether group. Thus, the triethyl ether of levoglucosan reacts with sodium in liquid ammonia analogously to the trimethyl ether, with formation of a mixture of phenolic substances: phenol (yield 48%), pyrocatechol, and resorcinol. The tribenzyl ether of levoglucosan, in contrast to the trimethyl and triethyl ethers, gives no phenols under these conditions; instead, simple reductive cleavage of the ether bond occurs, as a result of which levoglucosan is regenerated (^{6}).

These data indicate the high stability of the $C_1—O—C_5$ and $C_1—O—C_6$ acetal bonds toward the action of the reagent studied, while in the case of different ethers of levoglucosan the stability of these bonds is determined by the direction of cleavage of the ether bond. Only such a direction of cleavage as in the case of the trimethyl and triethyl ethers makes possible cleavage of the acetal bonds.

Theoretically, two directions of cleavage of the ether bond may be represented:

$$> C—O—R \quad \begin{array}{lll} \nearrow^{\text{Na}} & > C—ONa + RNa & (a) \\ \searrow_{\text{Na}} & > CNa + RONa & (b) \end{array}$$

or, from the now generally accepted electronic point of view of reductive cleavage by sodium in liquid ammonia (^{7}),

$$> C—O—R \quad \begin{array}{lll} \nearrow^{e} & > C—O^- + R\cdot \overset{e}{\to} > C—O^- + R^- & (a) \\ \searrow_{e} & > C\cdot + RO^- \overset{e}{\to} > C^- + RO^- & (b) \end{array}$$

Following this scheme, for the tribenzyl ether of levoglucosan we must adopt the direction of cleavage (a), in which the oxygen of the ether group remains bound to the carbohydrate molecule. In the case of the trimethyl and triethyl ethers, the second direction (b) is probable, in which an alcohol and a carbohydrate carbanion are formed. The formation of gaseous products under these conditions could not be expected.

Experimental data confirmed this direction of cleavage of the ether group. In the reaction of trimethyllevoglucosan with sodium in liquid ammonia, neither methane nor other gaseous products were detected. It was possible to isolate and quantitatively determine methyl alcohol by the method of Fischer and Schmidt (^{8}), based on the fact that methyl alcohol forms methyl nitrite with nitrous acid, which is absorbed in a receiver containing acidified KI solution, liberating an equivalent amount of iodine. The methyl alcohol was distilled off from the aqueous solution of the reaction products first from alkaline medium in order to separate it from phenols, and then was distilled a second time from the acidified distillate in order to separate it from amines. The results of the determination are summarized in Table 2.

In Table 2 the number of moles of methanol was calculated on the assumption of 100% cleavage of all three methoxy groups in trimethyllevoglucosan with formation of methanol. If, however, it is taken into account that a monomethyl ether of resorcinol was found among the reaction products and that conversion of the starting molecule into phenols proceeds to 70%, then the yield of methyl alcohol amounts to about three moles per mole of trimethyllevoglucosan converted into phenols.

It is interesting to note the fact that in all the experiments carried out, the formation of a bright-red coloration was observed, which, as is known from the literature, is characteristic of organometallic compounds dissociated in liquid ammonia.

Determination of methyl alcohol

Table 2

Sample of trimethyllevoglucosan, mol	Total volume of methyl alcohol solution, ml	Volume of the solution analyzed, ml	Volume of 0.1 N $Na_2S_2O_3$, ml —for titration	Volume of 0.1 N $Na_2S_2O_3$, ml —in blank experiment	Methanol obtained, mol/mol of trimethyllevoglucosan
0.015	110	10 ml of solution, diluted 1 : 25	1.37	0.17	2.2
0.015	110	2	5.77	0.17	2.0
0.01	100	2	4.15	0.17	2.0

organic compounds. Probably, in the course of the reaction organometallic compounds are formed in which sodium is bonded to the carbon of the carbohydrate, since methylsodium is gray in color. Cleavage of a simple ether bond in trimethyllevoglucosan with formation of a carbohydrate carbanion and an alcohol is the first stage of this reaction. Such cleavage evidently affects only one of the three ether groups, since otherwise it would be impossible to explain the formation of an aromatic compound from the resulting cyclitol. Most probably, cleavage occurs at C_2 or C_4, where a lowered electron density is possible owing to the influence of the acetal oxygens (Scheme 2). Formation of a carbanion upon cleavage of a simple ether bond makes possible the removal of the second methoxyl group at C_3, by analogy with the β-elimination reaction of ethers. As a result, a double bond is formed in the β-position to the acetal bonds, which weakens these bonds.

We believe that cleavage of the C_1—O—C_5 and C_1—O—C_6 acetal bonds by sodium in liquid ammonia occurs analogously to cleavage of a simple ether bond, i.e., by electron addition. With simultaneous addition of electrons to the cyclic acetal bonds, a bianion-biradical is formed, for which cyclization is more probable than polymerization or addition of a second electron. As a result, a cyclitol is formed as an intermediate product of the transformation under study. The directions of cleavage of the acetal bonds are indicated in the scheme:

Scheme 2

arbitrarily, but these directions are the most probable. We were unable to isolate intermediate reaction products. In experiments with three gram-atoms of sodium per 1 mole of starting substance, unreacted trimethyllevoglucosan was

Scheme 2: reaction scheme showing cleavage and rearrangement of trimethyllevoglucosan under sodium/liquid ammonia to cyclitol intermediates and sodium salts

Figure 2: Scheme 2: reaction scheme showing cleavage and rearrangement of trimethyllevoglucosan under sodium/liquid ammonia to cyclitol intermediates and sodium salts

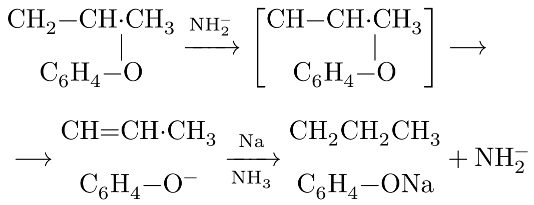
isolated, and the yield of phenol amounted to 50% based on the trimethyllevoglucosan that had reacted. This fact made it possible to suppose that the rate of phenol formation is limited by the formation of the carbocycle. Indirectly this supposition was proved experimentally.

When sodium in liquid ammonia acts on the hexamethyl ether of mesoinositol, even at −33°, a mixture of phenolic substances is formed containing monohydric phenol. This gives grounds for asserting that the formation of intermedi-

of an exact carbocyclic compound readily converted into phenolic substances, is quite probable under the conditions of our reaction. The ease of conversion of cyclic alcohols and their derivatives into aromatic compounds is well known from the literature; however, the mechanism of these transformations has not been studied.

In the scheme of P. P. Shorygin (Scheme 1), the formation of double bonds in the intermediate ring was explained by elimination of a molecule of alcohol and two molecules of NaOH. In organic chemistry many examples are known of elimination reactions with formation of an olefin under the action of various reagents; however, reactions of this type under the action of sodium in liquid ammonia have scarcely been investigated. The mechanism of β-elimination of ethers under the action of sodium in liquid ammonia was first proposed by Hurd and Oliver (9) to explain the behavior of phenylphenethyl ether and methylcoumaran in this system. The authors consider amide ions, traces of which are possible in the sodium—liquid ammonia system, to be responsible for this reaction. A scheme of these reactions is given below:

1. $$C_6H_5CH_2CH_2{-}O{-}C_6H_5 \xrightarrow{NH_2^-} [C_6H_5\dot{C}H{-}CH_2{-}O{-}C_6H_5] \longrightarrow$$
$$\longrightarrow C_6H_5CH{=}CH_2 + C_6H_5O^- \xrightarrow[NH_3]{Na} C_6H_5CH_2CH_3 + C_6H_5ONa + NH_2^-$$

2.

$$\begin{array}{c} CH_2{-}CH{\cdot}CH_3 \\ | \\ C_6H_4{-}O \end{array} \xrightarrow{NH_2^-} \left[\begin{array}{c} CH{-}CH{\cdot}CH_3 \\ | \\ C_6H_4{-}O \end{array}\right] \longrightarrow$$
$$\longrightarrow \begin{array}{c} CH{=}CH{\cdot}CH_3 \\ C_6H_4{-}O^- \end{array} \xrightarrow[NH_3]{Na} \begin{array}{c} CH_2CH_2CH_3 \\ C_6H_4{-}ONa \end{array} + NH_2^-$$

Accepting the possibility of a β-elimination reaction under our conditions, we propose the following scheme for the reaction of formation of phenol from the cyclitol:

$$\text{[cyclitol intermediate with NaO, } CH_3O\text{, H, NaO, and numbered ring atoms 1–6]} \longrightarrow C_6H_5ONa$$

The literature notes the very high stereospecificity of elimination reactions under the action of various reagents (^{10}). For elimination, a biaxial arrangement of the substituents is necessary, in which coplanarity of the four atomic centers involved in the reaction is present (^{11}).

At present we find it difficult to predict the conformation of the intermediate cyclitol, and therefore it is impossible to draw a more definite conclusion about the influence of the steric factor in this reaction. However, it is quite probable that the stereospecificity of the elimination is an important factor influencing the yield of phenols for different stereoisomers of 1,6-anhydrohexoses (see Table 1).

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Received
8 VII 1963

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Note: Figure translations are in progress. See original paper for figures.

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