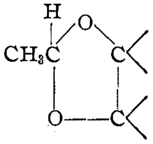
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

STUDIES ON REACTIONS RELATING TO CARBOHYDRATES AND POLYSACCHARIDES. VI. RELATIVE EASE OF FORMATION OF FIVE- AND SIX-MEMBERED HETEROCYCLIC CARBON-OXYGEN CONFIGURATIONS

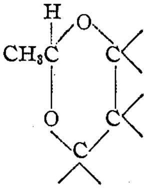
BY HAROLD S. HILL[1] AND HAROLD HIBBERT

RECEIVED OCTOBER 16, 1923

There is probably no more general characteristic of all varieties of sugars and polysaccharides than the recurrence in one form or another of heterocyclic, carbon-oxygen configurations. At the present time, however, the greatest confusion exists concerning the relative stability and ease of formation of the different cyclic structures encountered, so that any evidence of a general character which can be brought forward regarding either of these factors is of importance from both theoretical and practical standpoints. A large amount of work will have to be done before the solution of such a complicated problem may be hoped for, and it is obvious that at the present early stage of the investigation it is desirable first to ascertain the relationships existing between the simplest possible derivatives. The present research is concerned mainly with supplying evidence concerning the relative ease of formation of the ring systems A and B, using for this purpose "partition experiments" by the new acetylene method for the synthesis of cyclic acetals described in the preceding communication,[2] (Part V). This consists essentially in passing acetylene into a glycol mixed with a small amount of concd. sulfuric acid and mercuric sulfate, the latter acting as a catalyst.



A



B

The "partition principle,"[3] as applied to this reaction, is based on the assumption that, when one molecular weight of acetylene is passed into a mixture of one molecular weight of each of two different glycols, the gas will react preferentially, and consequently the amounts of the two cyclic acetals formed will be a relative measure of their ease of formation. The reaction would appear to be admirably suited for such a study since, (1) only traces of by-products are formed; in other words, the acetylene

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[1] Antoine Chiris Co. Research Fellow.

[2] THIS JOURNAL, **45**, 3108 (1923).

[3] Michael, *J. prakt. Chem.*, N. F., **60**, 341 (1899); *Ber.*, **39**, 2138, 2143, 2149, 2153, 2157, 2569, 2785, 2789 (1906); **40**, 140 (1907).

reacts only to form cyclic acetals; (2) there is practically no hydrolysis of the acetals to acetaldehyde and glycol, only traces of water being present throughout the reaction; there was also little, or no darkening, indicating the absence of free aldehyde; (3) there is no reverse reaction; (4) the acetylene is supplied only as fast as it reacts.

The objection might be raised that different solubility relationships between the two glycols and their respective acetals might bring about a preferential reaction with the acetylene. Against this view is the fact that, in the experiments on which the conclusions of this paper are based, the materials used, and the products formed, were either all mutually soluble, thereby insuring the presence of one phase throughout, or else their solubilities were so nearly identical as to render it unlikely that a given reaction would be appreciably favored by this factor.

Discussion of Experimental Results

In reviewing the evidence it is well to bear in mind the three main factors governing the ease of ring formation in this type of reaction.[4]

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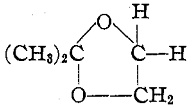
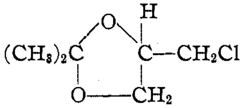
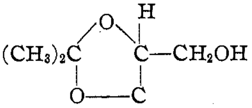
[4] In this connection mention should be made of the investigations of Boeseken in which he attempts to show that the ease of formation of cyclic structures by the interaction of an aldehyde or acetone with a polyhydroxy derivative is dependent largely on the relative spatial positions of the hydroxyl groups about the carbon axis. Such a reaction, it is claimed, takes place readily only when the two hydroxyls involved are on adjacent carbon atoms, and on the same side of the chain. He had previously shown [*Ber.*, **46**, 2612 (1913)] that compounds having this configuration, when added to a solution of boric acid, increase its conductivity, and from the results of experiments using this method, concluded that in the simple glycols, such as ethylene, trimethylene and tetramethylene glycol, pinacol, etc., the two hydroxyls are on opposite sides of the chain, while in glycerol and many other polyhydroxy compounds there are two on the same side. He then determined [*Rec. trav. chim.*, **40**, 525 (1921)] the equilibrium constants for the reaction of acetone with ethylene glycol, chlorohydrin and glycerol, and found values of K equal to 0.28, 0.14 and 0.77, respectively, thus proving, in his opinion, the marked influence exerted on the ease of ring formation by the spatial position occupied by the hydroxyl groups. A serious objection must be raised to such evidence in that Boeseken, in drawing conclusions from his determinations of equilibrium constants, has apparently disregarded the fact of the widely different energy relationships of the groups H, Cl, and CH_2OH, which must in themselves be potent factors in influencing the extent to which the cyclic ketals are formed, and hydrolyzed. It seems rather improbable that the compounds,





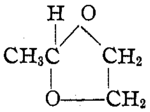


would be formed and hydrolyzed with the same ease, regardless of the position of the hydroxyl groups in the free glycol or glycerol. A further objection to Boeseken's view is the ease with which a wide variety of aldehydes react with all the simple glycols, as well as with glycerol and the more complex polyhydroxy compounds. In view of such conflicting evidence, it is considered doubtful that the spatial configuration of the hydroxyl groups in the *simple* 1,2 and 1,3 diol derivatives exerts an appreciable influence on the ease of formation of their cyclic acetals.

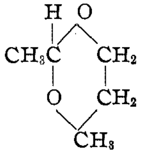
These are (1) the number of atoms in the ring; (2) the nature of the atoms in the ring; (3) the nature of the atoms or groups attached to the ring atoms.

Influence on Ring Formation Exerted by the Number of Atoms in the Ring

An experiment involving a partition of acetylene between ethylene glycol and trimethylene glycol showed that the 6-membered cyclic structure, II, is formed in marked preference to that containing 5 ring atoms, I, the ratio being approximately 2: 1.

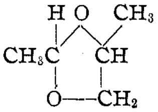


I

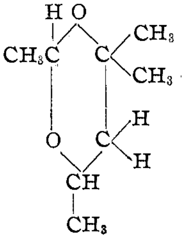


II

A similar experiment using the isomers, 1,2-propylene and trimethylene glycols, gave almost the same ratio, favoring II over III.



III



IV

The partition experiment between 2-methyl-2,4-pentanediol and ethylene glycol yielded five times as much of the 6-membered cyclic derivative, IV, as of ethylidene ethylene glycol, I, while when the same experiment was repeated using trimethylene glycol instead of ethylene glycol, the ratio of configuration, IV to that of II, was found to be only about 2: 1. The results of these two experiments, therefore, supply indirect, yet clearly confirmatory evidence that it is primarily the structure (size) of the ring itself which determines the greater ease of formation of II over I.[5]

The Influence of Groups Attached to the Ring Atoms

Partition experiments, using the acetylene method for the synthesis of cyclic acetals, appear to establish the fact that where formation of similar rings is concerned the presence of methyl groups attached to the glycol carbon atoms favors cyclization. Thus, IV is formed in preference to II

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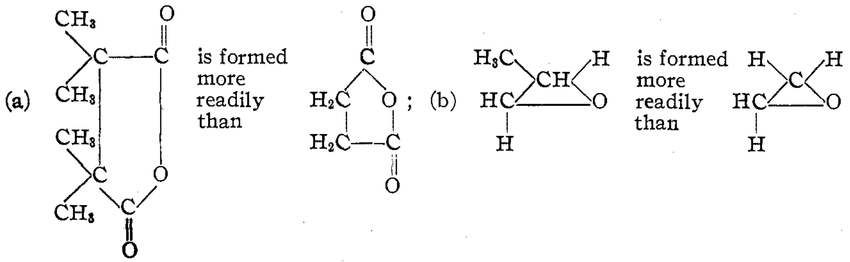
[5] This is in agreement with the earlier work carried out in this Laboratory by Dr. John A. Timm (not yet published), on the "partition ratios" obtained when using one molecular equivalent of an aldehyde with one equivalent each of a 1, 2, and a 1, 3 glycol and a small amount of sulfuric acid (40%) as a catalyst.

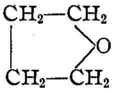
in the ratio of 2:1. Formation of cyclic acetal IV takes place five times as easily as I, while with II and I, which involve the same rings except for the absence in the former of methyl groups, the ratio is only 2:1.

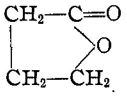
In harmony with such evidence are the observations of Meyer,[6] Hjelt[7] and others,[8] that (a) tetramethyl- and other alkylated succinic acids form cyclic anhydrides with markedly greater ease than succinic acid itself, and that (b) by Evans,[9] that methylated cyclic oxides are prepared more readily than those having no methyl groups attached to the ring atoms.

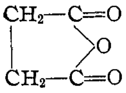


On the other hand, cyclic acetal formation is apparently hindered by the introduction of a second methyl group on the ring carbon of the acetaldehyde residue. The compound V, for example, could not be prepared by the earlier methods for the synthesis of such derivatives,[10] although Boeseken, Schaefer and Hermans[11] have recently isolated it.[12]

It is well known that the replacement of two hydrogen atoms by oxygen in a carbon-oxygen heterocyclic structure causes a great decrease in stability of the ring.


Stable


Less stable


Least stable

A replacement of hydrogen by hydroxyl appears to bring about a similar change.

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[6] Auwers and Meyer, *Ber.*, **23**, 101 (1890).

[7] Hjelt, *Ber.*, **26**, 1925 (1897).

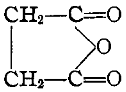
[8] Manasse and Rupe, *Ber.*, **27**, 1822 (1894). Auwers, *Ber.*, **31**, 2112 (1898). Von Bischoff, *Ber.*, **23**, 620 (1890). Zelinsky, *Ber.*, **24**, 3997 (1891).

[9] Evans, *Z. physik. Chem.*, **7**, 337 (1891). See Petrenko-Kritschenko and Konschin, *Ann.*, **342**, 51 (1905).

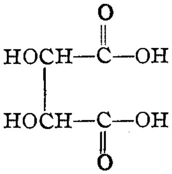
[10] Fischer and Pfähler, *Ber.*, **53**, 1606 (1920).

[11] Boeseken, Schaefer and Hermans, *Rec. trav. chim.*, **41**, 722 (1922).

[12] It would be interesting to ascertain whether this product V could be prepared by passing allylene ($CH_3—C\equiv CH$) into trimethylene glycol in the presence of a mercuric salt. If a positive result were obtained, an experiment employing equimolecular quantities of allylene, acetylene and this glycol should give a partition between V and II, the extent of which would provide definite evidence as to the influence on ease of formation of methyl groups attached to a carbon between two ring oxygens.



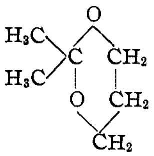
Easily formed from acid



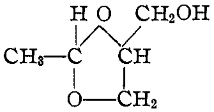
Does not form a cyclic anhydride

The Structure of Ethylidene Glycerol

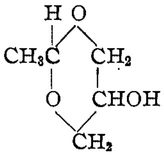
The greater ease of formation of 6-membered over 5-membered cyclic acetals, in the partition of acetylene between a mixture of 1,2 and 1,3 glycols leads to interesting speculations as to the probable structure of ethylidene glycerol. It has been shown[2] that this cyclic acetal may be obtained with a yield of 63% by means of the acetylene method, the product boiling within the range 189–196°. From the results of partition experiments already mentioned, there is no apparent reason why, in the preparation of the glycerol derivative, there should not be an *intra*molecular partition leading to the formation of configurations VI and VII, with the latter predominating.



V



VI



VII

With a view to obtaining additional data bearing on this problem, experiments were carried out involving a partition of acetylene between glycerol and ethylene glycol, which gave yields of [VI or VII] and I in a ratio of about 2: 1. Using trimethylene glycol and glycerol, the ratio of [VI or VII] to II was a little less than 1: 2, and a similar experiment with glycerol and 1,2-propylene glycol showed a marked preference in favor of [VI or VII] over III.

Correlating these results as to their bearing on the configuration of ethylidene glycerol, we find:

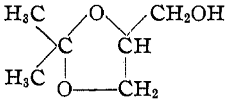
A. If the 5-membered cyclic structure, VI, predominates, it follows from the results of partition experiments that (1) the ease of formation of VI is greater than that of VII; (2) VI than I; (3) VI than III; and (4) that of VI is less than that of II.

B. If the 6-membered ring, VII, predominates (1′) the ease of formation of VII is greater than that of VI; (2′) VII than I; (3′) VII than III; and (4′) that of VII is less than that of II.

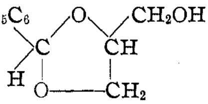
Alternative B appears to have the greater weight of supporting evidence. 1′, 2′ and 3′ follow from the generalization that in all the cases investigated, a 6-membered cyclic ethylidene derivative is formed in preference to a 5-, and 4′ is in harmony with the observation that replacement of hydrogen on a ring carbon by hydroxyl causes a decrease in tendency towards cyclization. On the other hand, in A there is no particular evidence favoring 1, 2 and 3.

The conclusion to be drawn from partition experiments, therefore, is that ethylidene glycerol is probably a mixture of VI and VII, with the latter predominating.[13]

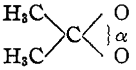
It should be borne in mind, however, that *iso*propylidene and benzylidene glycerols, have been shown by Irvine and his pupils[14] as well as by Fischer[15] to possess the 5-membered cyclic structures,



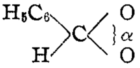
and



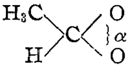
Just why these two acetals should have a ring configuration different from that of ethylidene glycerol is not clear, but an explanation may possibly be found in the light of the theory developed by Ingold and Thorpe,[16] namely, that each group attached to a carbon atom influences the direction of the remaining valence bonds, or forces—the larger groups requiring more space. From this it would follow that the angle α would be less in VIII and IX than in X, thus accounting for the marked tendency of



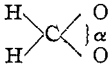
VIII



IX



X



XI

acetaldehyde to form the larger ring structure, and also for the fact that acetone does not react readily with trimethylene glycol to give the 6-membered *iso*propylidene derivative, V, while the 5-membered *iso*propylidene ethylene glycol can be readily obtained.

With a methylene group attached to two oxygen atoms, XI, the angle α would be still larger and, as a matter of fact, methylene glycerol exists in two isomeric forms.[17]

Experimental Part

In each of the following experiments the glycol or glycerol used was pure and dry.

Expt. I. Partition of Acetylene between Ethylene Glycol and Trimethylene Glycol.—A mixture of 93 g. of ethylene glycol and 114 g. of trimethylene glycol was treated

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[13] If this is the case, it is possible that the two acetals may hydrolyze at different rates, which fact would make itself known in the properties of the non-hydrolyzed material. The matter is to be investigated further from this standpoint.

[14] Irvine, Macdonald and Soutar, *J. Chem. Soc.*, **107**, 337, 815 (1915).

[15] Fischer, *Ber.*, **27**, 1536 (1894); **28**, 1167, 2496 (1895).

[16] Ingold and Thorpe, *J. Chem. Soc.*, **107**, 1080 (1915); **115**, 320 (1919).

[17] Schulz and Tollens, *Ann.*, **289**, 29 (1896).

with 33.6 liters of acetylene in the presence of 6 g. of mercuric sulfate and 6 cc. of concd. sulfuric acid. The apparatus and method of procedure were the same as that described in the previous communication.[2] Special care was exercised in securing as exact a measurement of the gas as possible, and the temperature during absorption was not allowed to rise higher than 60°. The final product was extracted with ether immediately after the required amount of acetylene had reacted, the resulting lower layer being treated several times with this solvent. The ether solution was washed with a small amount of 10% aqueous potassium carbonate, the latter extracted with ether, and the combined ether solutions were dried over solid potassium carbonate and carefully fractionated using a 30cm. bead column. The product was found to consist almost entirely of ether, ethylidene ethylene glycol (b. p., 82–85°), and ethylidene trimethylene glycol (b. p., 107–111°), the yields of these two acetals being 40 g. and 91 g., respectively. Calculating the percentage yields on the basis of the total possible amounts of each, it was found that the yield of the ethylene derivative was 30%, and that of the trimethylene derivative was 60%.

It is not claimed that this ratio is more than an approximate measure of the relative amounts of the two cyclic configurations formed by this method, due to the difficulty in this case of separating the cyclic acetals completely.

Expt. II. Partition of Acetylene between Ethylene Glycol and 1,2-Propylene Glycol.—A mixture of 93 g. of ethylene glycol and 114 g. of 1,2-propylene glycol when treated exactly as in Expt. 1, yielded 100 g. of a mixture of the two corresponding cyclic acetals, boiling within the range 85–91°. It was not possible to separate this mixture into its components which boil at 83° and 92°, respectively.

Expt. III. Partition of Acetylene between Trimethylene Glycol and 1,2-Propylene Glycol.—From a reaction mixture of 66 g. each of trimethylene glycol, 1,2-propylene glycol and 19 liters of acetylene, involving the same quantities of catalyst as in Expts. I and II and operating under the same experimental conditions, by careful fractionation 45 g. (51%) of ethylidene trimethylene glycol (b. p., 107–111°) and 20 g. (23%) of ethylidene 1,2-propylene glycol (b. p., 92–97°) were obtained.

Expt. IV. Partition of Acetylene between Ethylene Glycol and 2-Methyl-2,4-pentanediol.—A mixture of 29 g. of the pentane derivative and 15.5 g. of ethylene glycol was allowed to react with 5.6 liters of acetylene in the presence of 1.5 g. of mercuric sulfate and 1.5 cc. of concd. sulfuric acid. The temperature was kept at 20°. Fractionation of the extracted products gave approximately 3 g. (13%) of ethylidene ethylene glycol (b. p., 80–90°) and 22 g. (61%) of ethylidene 2-methyl-2,4-pentanediol, (b. p., 138–140°).

Expt. V. Partition of Acetylene between Trimethylene Glycol and 2-Methyl-2,4-pentanediol.—A mixture of 29 g. of the pentane derivative and 19 g. of trimethylene glycol with 5.6 liters of acetylene yielded about 6 g. (24%) and 16 g. (44%) of their respective cyclic acetals (b. p., 108–115°, and 138–140°). The amounts of catalyst used were the same as in Expt. IV.

Expt. VI. Partition of Acetylene between Ethylene Glycol and Glycerol.—A mixture of 78 g. of glycerol, 53 g. of ethylene glycol and 19 liters of acetylene with 4 g. of mercuric sulfate and 4 cc. of concd. sulfuric acid gave 52 g. (51%) of ethylidene glycerol (b. p., 189–197°) and 19 g. (25%) of ethylidene ethylene glycol (b. p., 80–90°).

Expt. VII. Partition of Acetylene between Trimethylene Glycol and Glycerol.—A mixture of 79 g. of glycerol, 66 g. of trimethylene glycol and 19 liters of acetylene yielded 27 g. (26%) and 41 g. (47%) of their respective cyclic acetals (b. p., 185–197°, and 106–111°). The quantity of catalyst used was the same as in Expt. VI.

Expt. VIII. Partition of Acetylene between 1,2-Propylene Glycol and Glycerol.—A mixture of 79 g. of glycerol, 66 g. of 1,2-propylene glycol and 19 liters of acetylene, gave 42 g. (40%) of ethylidene glycerol (b. p., 189–196°) and 22 g. (25%) of ethylidene-

1,2-propylene glycol (b. p., 91–96°). There was some difficulty in obtaining a complete separation of the acetals from the unchanged glycols, owing to the mutual solubility of 1,2 propylene glycol and ethylidene glycerol in both ether and the aqueous solution of potassium carbonate used in washing the product. In order to ensure the removal of the unchanged glycol and glycerol, it was necessary to wash the extracted product once with water. This wash liquor undoubtedly contained a certain amount of the soluble ethylidene glycerol so that the actual yield of the glycerol derivative was probably somewhat greater than the amount isolated. There is no doubt, therefore, of the preponderance in this reaction of the formation of this acetal over that of ethylidene-1,2-propylene glycol.

Summary

1. "Partition experiments" on the formation of cyclic acetals by the action of 1 molecular equivalent of acetylene on a mixture of one equivalent of a 1,2-glycol and one of a 1,3-glycol, indicate that the 6-membered ring forms with considerably greater ease than the 5-membered ring.

2. The presence of methyl groups attached to the glycol carbon atoms increases the tendency towards ring formation.

3. It seems probable that ethylidene glycerol, as prepared by the acetylene method from glycerol, represents a mixture of a 5- and a 6-membered cyclic acetal, the latter predominating. The product thus represents the final result of an "*intra*molecular partition reaction."

New Haven, Connecticut

[Contribution from the Department of Chemistry, Yale University]

STUDIES ON REACTIONS RELATING TO CARBOHYDRATES AND POLYSACCHARIDES. VII. THE EASE OF FORMATION AND NATURE OF CERTAIN SIX, SEVEN, AND LARGER CARBON-OXYGEN CYCLIC STRUCTURES

By Harold S. Hill[1] and Harold Hibbert

Received October 16, 1923

In the preceding communication (Part VI), the question of the relative ease of formation of certain 5- and 6-membered heterocyclic compounds was considered, and evidence submitted showing that cyclic acetals obtained from acetaldehyde and containing 6 ring atoms are formed in marked preference to those having only 5. The present investigation is an extension of this study to derivatives containing more than 6 atoms in the ring.

The importance of further experimental evidence on this subject is at once apparent from a review of the theories which have recently been advanced regarding the molecular configurations of various polysaccharides. Cellulose, for example, is regarded by Karrer[2] as being a polymerized form of a hypothetical anhydro cellobiose. The latter compound

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[1] Antoine Chiris Co. Research Fellow.

[2] Karrer, *Helvetica chim. Acta*, **5**, 187 (1922).