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."

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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).

contains a 13-membered cyclic structure having 11 carbon and 2 oxygen ring atoms. The same investigator assigns to diamylose, and its polymer starch, a similar, 14-membered cyclic configuration. On the other hand, Irvine[3] believes that the known facts regarding cellulose are best interpreted on the basis of its complex molecule being derived from an anhydrotriose unit,[4] consisting of an 18-membered cyclic structure having 15 carbon and 3 oxygen atoms in the ring. Except for these assumptions, there exists at the present time no knowledge regarding the existence of carbon-oxygen rings of this size, much less with respect to their properties and the conditions under which they are formed. In fact, examples of simple, carbon-oxygen heterocyclic structures containing even as high as 7 ring atoms are very rare, the most prominent of these being ethylidene tetramethylene glycol prepared recently by the action of acetylene on tetramethylene glycol.[5]

Before taking up the interpretation of the experimental evidence, a brief discussion is necessary of the more important factors involved in the formation of large, cyclic configurations. The problem is obviously complicated by questions such as whether an atom can rotate *freely* on the axis of a single bond, and whether there is a force which tends to keep the atom of a cyclic structure in the same plane. The great influence of these factors on the configuration of a large ring may be illustrated by the use of suitable wire models.[6]

The universal existence and ease of formation of 5- and 6-membered rings would seem in itself to be strong evidence that there is a mutual attraction between all the atoms in a chain, and that it is this force which causes "cyclization." Thus in a given hypothetical case, where the assumption is made of a constant angle of valence forces of approximately 120°, a chain of 3 atoms exists in a configuration illustrated by 1–3; a chain of 4 atoms as 1–4, rather than 1–4′; one with 5 atoms 1–5 instead of 1–5′, etc., and in a 6-membered chain the systematic structure 1–6 rather than one of the large number of possible 1–6′ groupings.

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[3] Irvine, *J. Chem. Soc.*, **123**, 525 (1923).

[4] It is of interest that Bertrand has recently succeeded in isolating such a triose complex.

[5] Hill and Hibbert, THIS JOURNAL, **45**, 3108 (1923).

[6] These can be made by taking a piece of stout iron or brass wire, measuring off, for example, 3 cm., then bending this to form a given angle, say 120°; again measuring off the same distance and bending to form a second similar angle. This typifies the union of 4 atoms. By continuing, a ring may be built up of any number of atoms. It will be noticed, however, that with a larger number of atoms (7, or more) there is a considerable strain on the ring, which is the greater, the larger the number of atoms present. When this strain reaches a certain limit it is relieved by the collapsing of the simple, large ring, to give a more complex, but more stable, spiral configuration such as is indicated in II or III of Fig. 2.

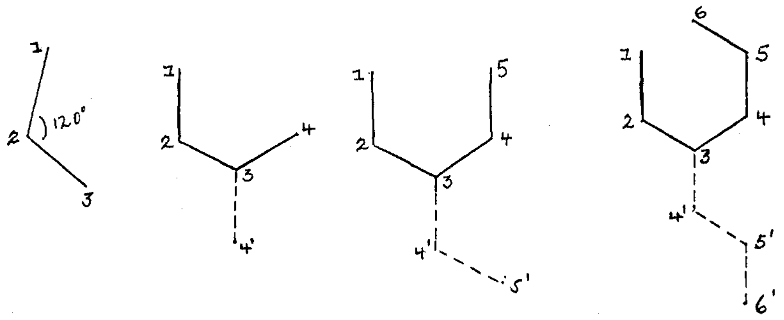

Fig. 1

In other words, a mutual attraction tends to keep the atoms of a chain in one plane and at the same time prevents in some measure free rotation about a single valence linking. The absence of any directing force would allow free rotation on the axis of a single bond with the consequent displacement of the atoms from a plane so that 6′ might be located at almost any point in space about 1 within the maximum length of the chain. It is believed that a systematic arrangement, 1–6, is more in harmony with our existing knowledge, than an indefinite zigzag structure[7] represented by 1–6′. It should be noted that the relative positions of 1 and 6 would be influenced by groups attached to any of the atoms.

If the foregoing conception of the structure of an atomic chain, the atoms of which possess a constant angle of valence forces of 120°, is correct, it follows that a 7-, 8-, 9-, or higher-membered chain would exist in Form I, the positions of 7, 8, 9, etc., being held near to 1, 2, 3, etc., respectively, by the same mutual forces which determined the configuration of the original ring. The actual forms, therefore, of closed chains containing as high as 12 and 18 ring atoms would resemble the spiral configurations indicated by II and III. In other words, cyclization in atomic chains might be expected to be a periodic function of their length, *the period depending on the angles between the valence bonds, or forces, joining the atoms.*[8]

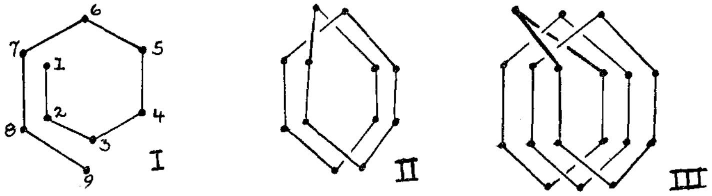

Fig. 2

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[7] This point is to be discussed by one of us (Hibbert) in a forthcoming paper dealing with the "Mechanism of Organic Reactions."

[8] The theory would appear to derive some support from the fact that, while tetra- and pentamethylene glycols readily dehydrate to give cyclic oxides, the 1–6, 1–7 and 1–8 diols do not show this property. 1–10-Decamethylene glycol, however, may be

The higher periods would be less sharply defined than the first, since the greater the number of atoms in a closed chain, the less would be the strain produced by the addition or subtraction of a single atom.

The possibility of spiral ring formation was suggested by Frankland[9] and has been emphasized by Pickard, Kenyon and co-workers,[10] in their interesting researches on the dependence of rotatory power on chemical constitution. The latter show[11] that "in a series of normal esters of secondary alcohols exhibiting optical activity we may expect irregularities in the rotatory power....and that these irregularities are due to the fact that the ester chain of carbon atoms assumes a spiral form with about five atoms in one complete turn, entire turns being completed at the point of irregularity."

Relative Ease of Formation of 5-, 6- and 7-Membered Cyclic Acetals

It was of primary importance to establish definitely the existence of the first period in the tendency towards ring closure. Consequently, the relative ease of formation of 5-, 6- and 7-membered cyclic acetals resulting from the action of acetylene, in the presence of a catalyst, on ethylene glycol, trimethylene glycol and tetramethylene glycol, respectively, was first investigated. It has already been shown in the last communication[12] that it is possible to apply the "partition principle" to this reaction, and that one mole of acetylene, when caused to react with a mixture of one mole of ethylene glycol, and one mole of trimethylene glycol, combines more readily with the latter, the ratio of the 6-membered cyclic structure to the 5, being approximately two to one. A similar experiment involving a partition of one mole of acetylene between one mole each of ethylene glycol and tetramethylene glycol now shows that the penta-atomic ring is formed three times as readily as the acetal containing 7 ring atoms. The existence of an optimum in the ease of ring formation with this series of compounds is therefore clearly demonstrated.

Attempts to Prepare Cyclic Acetals Containing More than Seven Ring Atoms

The rapid decrease in the ease of ring closure in hepta-atomic configurations renders it difficult to account for the formation and stability of the much larger ring systems which are assumed to exist in the polysaccharides

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converted into a cyclic oxide, indicating a second period in the tendency toward cyclization. Some doubt exists as to the actual configuration of decamethylene oxide, so that the evidence is not conclusive. This product is to be investigated as well as the higher members of the glycol and polyglycol series and their cyclic acetals.

[9] Frankland, *J. Chem. Soc.*, **75**, 368 (1899).

[10] Pickard, Kenyon and others, *ibid.*, (a) **99**, 45 (1911); (b) **100**, 620, 1427 (1912); (c) **103**, 1923 (1913); (d) **123**, 1 (1923).

[11] Ref. 10d, p. 7.

[12] This series, Part V, THIS JOURNAL, **45**, 3108 (1923).

except on the ground that, with sufficient lengthening of a chain, there is a recurrence of the tendency towards "cyclization." Estimating that the second "period" of ring formation in this series of cyclic acetals would occur in structures having from 11 to 13 ring atoms, an attempt was made to prepare the cyclic ethylidene derivatives of octa- and decamethylene glycols. The method used was that in which a mixture of a glycol and paracetaldehyde is heated in the presence of a trace of 40% sulfuric acid as a catalyst. Both octa- and decamethylene glycol yielded heavy, sirupy, odorless acetals which had very high and indefinite boiling points, the latter property indicating that polymerization had probably occurred, since the simpler cyclic acetals containing 5, 6, and 7 ring atoms are limpid, volatile liquids, possessing a characteristic odor. It has not yet been possible to prove definitely whether the sirups obtained from the higher glycols are cyclic structures or open-chain derivatives of indefinite size resulting from successive glycol-acetaldehyde condensations, such as $HO—(CH_2)_9—CH_2—O—CH(CH_3)—O—CH_2—(CH_2)_9—O—CH(CH_3)—O—CH_2—(CH_2)_9OH$, etc. Analysis for carbon and hydrogen gave values reasonably close to those calculated for the cyclic acetal, which are somewhat below the percentages of carbon and hydrogen in an open chain of the type mentioned above. In view of other possible configurations, however, it is not considered possible to differentiate by analysis alone between the cyclic and open-chain alternatives.

If our conception of large atomic rings as closed spirals (II and III) is correct, the different physical properties of the ethylidene compounds of octa- and decamethylene glycols from those of the lower homologs cannot be considered as evidence against the existence of the former in cyclic form. It is to be expected that a change of molecular structure from a simple ring to a dicyclic, closed spiral would give rise to compounds having totally different physical properties.[13]

[13] In this connection it is interesting to note that in the homologous series of cyclic anhydrides of dibasic acids there is a sharply marked break in physical properties [Auger, *Ann. chim. phys.*, [6] 22, 362 (1891). Etaix, *ibid.*, [7] 9, 370, 387, 398, 404 (1896). Michael, *J. prakt. Chem.*, [2] 60, 337 (1899). Voerman, *Rec. trav. chim.*, **23**, 265 (1904). Einhorn and von Diesbach, *Ber.*, **39**, 1222 (1906). Einhorn, *Ann.*, **359**, 150, 158 (1908). Staudinger and Ott, *Ber.*, **41**, 2208, 3829 (1908). Staudinger and Bereza, *Ber.*, **41**, 4462 (1908). Diels and Lalin, *Ber.*, **41**, 3429 (1908)] between succinic and glutaric anhydrides on the one hand, and adipic and the higher members on the other. The two former derivatives contain 5- and 6-membered heterocyclic configurations and closely resemble each other in their properties, being characterized by their tendency to form large crystals, and their ready solubility in solvents. Adipic anhydride differs from glutaric from a chemical standpoint only in the addition of another CH_2 group, yet this compound and the higher homologs have practically no crystalline form and are insoluble in many solvents. More important, still, is the fact that the 7- and higher-membered cyclic anhydrides exist for the most part only in a polymerized condition, while succinic and glutaric anhydrides do not polymerize. These

The suggestion is offered that "cyclization" of long chains to give closed spiral configurations is closely connected with the phenomenon of polymerization. It is difficult to explain this change in the case of polysaccharides in any other way.[14] For example, Karrer's diamylose (anhydro maltose) differs from maltose itself only in that: (1) a new half-acetal type of linkage is introduced by the dehydration, and (2) a closed chain of 14 atoms has been formed. Since there are already three analogous linkages in maltose, the introduction of a fourth group of this inert type could scarcely be expected to produce any great change in properties. It is probable, therefore, that the formation of the 14-membered ring is alone responsible for the tendency of diamylose to polymerize. Furthermore, since most of the known examples of simple, cyclic structures do not polymerize, it is unlikely that merely increasing the number of ring atoms to form simple large rings would cause this property to appear. The conclusion is reached that the longer closed chains exist in the alternative, closed-spiral configurations, and that it is the greatly increased complexity of the latter which in some way (possibly an interlocking as suggested by Robinson)[15] brings about polymerization.

Similar reasoning may be applied to the polymerization of the 18-membered cyclic structure of the anhydro-triose suggested by Irvine as the unit on which the cellulose complex is built up.

On the whole it appears probable that the acetal sirups obtained from the action of acetaldehyde on octa- and decamethylene glycols are polymerized forms of 11-, and 13-membered ring structures.

The present investigation was rendered difficult by the laborious processes necessary for the preparation of the higher glycols. The three which have been tried with the acetal reaction were made only in small

facts would seem to indicate that the addition of a CH_2 group into the molecule of glutaric anhydride does not give rise merely to an increase in size of a simple ring, but that the 7-membered closed chain assumes an entirely different molecular configuration. A logical explanation is that simple atomic rings above a certain size become strained to a point where the structure collapses to a more stable but more complex form, the *valence bonds remaining intact.* This would account for the sharp change in physical properties without a corresponding break in the chemical nature of members of a homologous series.

[14] The phenomenon of polymerization is one of the most important with which chemists have to deal, and at the same time, one of the least understood. It plays a leading role in animal metabolism, plant life, and industrial processes and in fact, penetrates to the roots of our very existence. It seems useless, however, to expect an understanding of the nature of the more complicated, polymerized products, such as cellulose, starch, etc., and of the factors giving rise to their formation, until the simpler cases, such as the polymerization of ethylene oxide, have been examined, and an explanation furnished. An investigation of these simpler derivatives is in progress. (Hibbert.)

[15] Robinson, *J. Soc. Chem. Ind.*, 42, 953 (1923).

amounts. It is proposed to synthesize a series of glycols, trimethylene to decamethylene, and higher if possible, as well as polyglycols, and to make a more exhaustive study of the heterocyclic structures which may be derived from them.

Experimental Part

Preparation of 1,4-Tetramethylene Glycol

Tetramethylene glycol was synthesized from trimethylene glycol, by first converting it into tetramethylene bromide by the method of Marvel and Tanenbaum.[16] The reduction of the ester was the most troublesome step, but after the technical difficulties had been overcome, the method gave a yield of 60–72%. Efficient stirring appears to be of the greatest importance.

The tetramethylene bromide was converted into the diacetate by means of the procedure given by Henry[17] for the similar synthesis of trimethylene diacetate. A mixture of 100 g. of tetramethylene bromide, 125 g. of potassium acetate and 225 cc. of 90% ethyl alcohol was heated for 14 hours on a steam-bath. The cooled solution was filtered from the solid potassium bromide, and the greater part of the alcohol distilled. Two layers separated, the lower of which was extracted with ether and the latter solution added to the upper layer which was then distilled under diminished pressure. After the last of the alcohol had been removed, a certain amount of potassium acetate separated. The distillation was stopped, ether added, the mixture filtered, and the ether removed. Fractionation of the solution under diminished pressure yielded 76 g. of tetramethylene acetate, b. p., 106–112°, representing a 95% yield of fairly pure material.

The diacetate was converted into tetramethylene glycol by heating with powdered potassium hydroxide[17] and distilling the resulting glycol directly from the reaction mixture, under diminished pressure. The yields were poor, 34 g. of diacetate with 24 g. of potassium hydroxide giving only 9.5 g. of purified glycol, and representing a 50% yield. Calcium or barium hydroxide, in place of potassium hydroxide gave no better results.

Preparation of Ethylidene Tetramethylene Glycol.—This cyclic acetal has already been prepared from the glycol by means of acetylene and a trace of mercuric sulfate and concd. sulfuric acid.[18] It may also be obtained by the following method. A mixture of 11.6 g. of tetramethylene glycol, 10 g. of paraldehyde (added from time to time) and one drop of 40% sulfuric acid was heated for 10 hours on the water-bath. The product was extracted with ether, washed with a small amount of 10% sodium carbonate solution, dried over solid potassium carbonate and fractionated. There was obtained 4 g. of ethylidene tetramethylene glycol; b. p., 125–127°; yield, 27%. There was about an equal amount of a sirup left in the flask which could not be distilled, but which was an acetal of some kind, since it was readily hydrolyzed by dilute acids into acetaldehyde and tetramethylene glycol.

Partition of Acetylene between Ethylene Glycol and 1, 4-Tetramethylene Glycol.—The procedure employed for this experiment was identical with that already described in a similar determination of the "partition value" between ethylene glycol and trimethylene glycol.[19]

A mixture of 18 g. of tetramethylene glycol, 12.4 g. of ethylene glycol and 4.4 liters of acetylene (the calculated amount) with 1 g. of mercuric sulfate and 1 cc. of concd. sulfuric acid as catalyst, gave 4.6 g. (b. p., 80–90°) and 2 g. (b. p., 120–130°) of the

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[16] Marvel and Tanenbaum, THIS JOURNAL, **44**, 2645 (1922).

[17] Henry, *Rec. trav. chim.*, **18**, 224 (1898).

[18] Ref. 12, p. 3115.

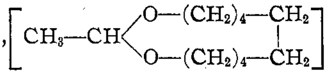
[19] This series, Part VI, THIS JOURNAL, **45**, 3117 (1923).

respective cyclic acetals, representing yields of 26.0% and 8.5% of the 5- and 7-membered ring derivatives, respectively. It is not claimed that these yields are more than approximations, although there is no doubt of the preponderance of the smaller cyclic ring derivative.

Preparation of Decamethylene Glycol.—Dimethyl sebacate was prepared by heating a mixture of 5 parts by weight of sebacic acid, 2 parts of methyl alcohol and 4 parts of concd. sulfuric acid for 15 hours. The product was poured into an excess of water, extracted with ether, and distilled under diminished pressure; yield of pure dimethyl ester, 90–95%; b. p., 167–168° (15 mm.).

It was found that Marvel and Tanenbaum's modification[16] of the reduction method developed by Levene and Allen[20] may be applied, satisfactorily to the reduction of dibasic esters. Ninety g. of dimethyl sebacate was reduced with 138 g. of sodium, 320 cc. of toluene and 780 cc. of absolute ethyl alcohol. The yield of decamethylene glycol, m. p., 72°, was 41 g. or 60%. The procedure followed was approximately that given by Marvel and Tanenbaum for the reduction of ethyl phenoxybutyrate.[16] After the distillation of alcohol and toluene from the reaction mixture, 600 cc. of water was added and the crude solution extracted five times with ether. Evaporation of the solvent left crude decamethylene glycol which was recrystallized from a mixture of ligroin and benzene.

Preparation of Ethylidene Decamethylene Glycol,



$$\left[CH_3{-}CH\begin{matrix}\diagup O{-}(CH_2)_4{-}CH_2\\ \qquad\qquad\qquad\quad |\\ \diagdown O{-}(CH_2)_4{-}CH_2\end{matrix}\right]_x$$

?. —Eighteen g. of decamethylene glycol, 15 g. of paracetaldehyde and 4 drops of 40% sulfuric acid were heated together for 12 hours under a reflux condenser. More paracetaldehyde (10 g.) was then added to replace loss by volatilization and the heating continued for another 12 hours. The product was treated with ether, the solution washed with a small amount of 10% sodium carbonate solution and dried over solid potassium carbonate. Removal of the solvent left a viscous, colorless sirup which was fractionated under diminished pressure. The small first fraction, boiling at 138–140°, was found to be unchanged glycol. At 230° (0.5 mm.) a sirup began to distil, and the temperature rose steadily to 320° (0.5 mm.) at which point the distillation was stopped. The greater part of the product still remained in the flask as a colorless sirup. There had been no apparent decomposition, although the product was somewhat more viscous than at the start of the distillation. This fact, together with the rise in boiling point would seem to indicate that a polymerization of the product had been brought about by heating.

Analyses [distilled sirup, b. p., 230–320° (0.5 mm.)]. Calc. for ethylidene decamethylene glycol, $C_{12}H_{24}O_2$: C, 72.00; H, 12.0. Found: C, 71.16; H, 11.8. Sirupy residue. Found: C, 71.41; H, 11.9.

Both sirups were readily hydrolyzed to acetaldehyde and decamethylene glycol by treatment with dilute acids.

Preparation of Octamethylene Glycol.—Suberic acid was obtained from castor oil by oxidizing this with nitric acid according to the method given by Markownikoff.[21] The yield of pure acid was only about 5–6% of the weight of oil used, although earlier investigators record a higher yield.

A mixture of 115 g. of pure suberic acid (m. p., 141°) with 230 g. of methyl alcohol and 75 g. of concd. sulfuric acid was heated for six hours under a reflux condenser. The yield of dimethyl suberate, [b. p., 136–138° (14 mm.)] was 87 g., or 62%.

Dimethyl suberate was converted into octamethylene glycol by the same method

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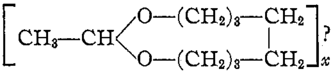
[20] Levene and Allen, *J. Biol. Chem.*, **27**, 435, 443 (1916); **33**, 509 (1918).

[21] Markownikoff, *Ber.*, **26**, II, 3090 (1893).

and procedure as followed in the reduction of dimethyl sebacate ester; 80 g. of dimethyl suberate, on reduction with 138 g. of sodium, 780 cc. of absolute ethyl alcohol and 320 cc. of toluene, gave 33 g. of pure octamethylene glycol; b. p., 167–168° (15 mm.); m. p., 63°; yield, 55%. Because of the greater solubility of this glycol in water, eight extractions with ether were necessary in order to remove it completely from the crude, aqueous salt solution. Prior to this extraction only the minimum amount of water necessary to dissolve part of the solid products had been added to the residue left after removal of the alcohol and toluene.

Preparation of Ethylidene Octamethylene Glycol,



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—A mixture of 19 g. of octamethylene glycol, an excess of paraldehyde (25 g.) added from time to time, and 6 drops of 40% sulfuric acid was heated for 12 hours under a reflux condenser. Extraction with ether, as in the preparation of the decamethylene derivative, yielded similar products, namely, a small amount of unchanged glycol, and a sirup having an indefinite, very high boiling point. The latter material was not analyzed, but appeared to be analogous to the sirup obtained from the reaction of acetaldehyde with decamethylene glycol, being readily hydrolyzed to the free aldehyde and glycol by means of dilute acids.

The authors desire to express their thanks to the Antoine Chiris Company, through whose generosity the work described in Parts V, VI and VII, was rendered possible. They also wish to express their gratitude to the Committee of the Warren Fund, National Academy of Sciences, for the grant made to them for the purchase of chemicals used in the course of these investigations.

Summary

1. A discussion is given of ring formation and of the properties of cyclic acetals derived from high-membered glycols (1:4; 1:8; 1:10).

2. It is shown that the ease of formation increases from the 5- to the 6-membered rings and then diminishes again with the 7-.

3. It is suggested that due to the strain involved in the structures of higher-membered cyclic acetal rings, these collapse, and assume a "spiral ring formation." The tendency of atomic chains to assume the latter is probably a periodic function of the number of atoms in the chain. The properties of the individual atoms in such spiral ring formations probably vary in a "periodic manner."

4. The "tendency towards polymerization" and "that of long chains to undergo cyclization to give closed-spiral configurations" probably stand in intimate connection with each other.

5. It is considered probable that the condensation products derived from acetaldehyde and octa- and decamethylene glycol, respectively, represent polymerized cyclic acetals of the "closed-spiral type."

6. The possibility of the existence of starch, cellulose, etc., as polymerized, closed-spiral configurations may serve to account for the stability of such ring complexes.

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