# CYCLIC MODIFICATIONS OF THE DIALDEHYDE FROM PERIODATE OXIDATION OF METHYL α-D-GLUCOPYRANOSIDE

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In 1928 Malaprade (1) demonstrated that periodic acid reacted with ethylene glycol to produce iodic acid and formaldehyde. Higher polyhydric alcohols behaved similarly, the two terminal CH_2OH groups appearing as formaldehyde and each connecting CHOH group appearing as formic acid. Criegee (2) reported that lead tetraacetate cleaved 1,2-diols in a similar manner. The reaction with periodic acid was adapted with marked success by Jackson and Hudson (3) in 1937 as a means of investigating carbohydrate structure, especially as regards ring size and the α,β-relationships in glycosides.

Jackson and Hudson isolated the dialdehyde (I) from methyl α-D-glucopyranoside, as well as from the galactoside, guloside, and mannoside. It was a sirup, characterized by positive rotation and by oxidation with bromine water in the presence of barium carbonate to the barium salt of the dicarboxylic acid. They gave it the name D'-methoxy-D-(hydroxymethyl)diglycolaldehyde.
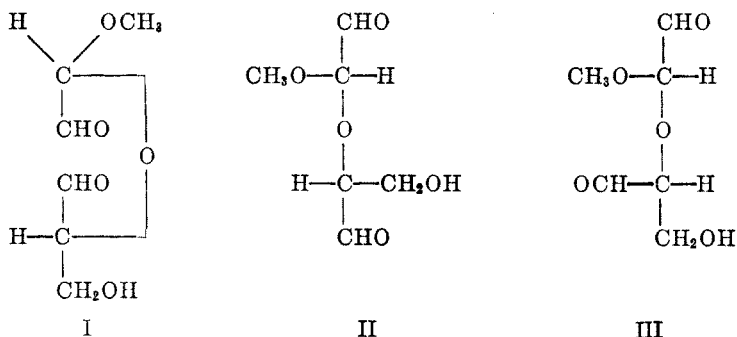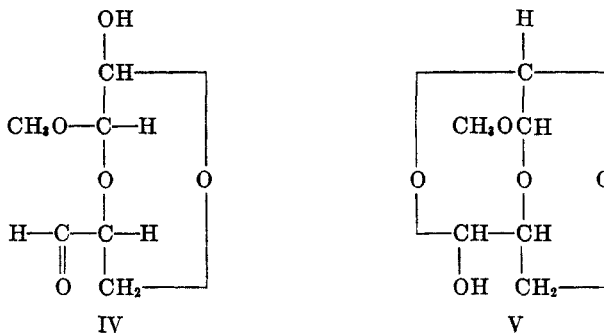

The D' and D refer to the configuration of atoms 1 and 5, respectively, in the original glucoside molecule rather than to the configuration of the asymmetric atoms in the diglycolaldehyde molecule. If one selects diglycolaldehyde as the principal skeleton for naming purposes rewriting I as II reveals it to have a D-relationship for the hydroxymethyl group on position 4 and an L-relationship for methoxy at 2. As a derivative of diglycolaldehyde therefore, the name should be 4D-hydroxymethyl-2L-methoxy-diglycolaldehyde.
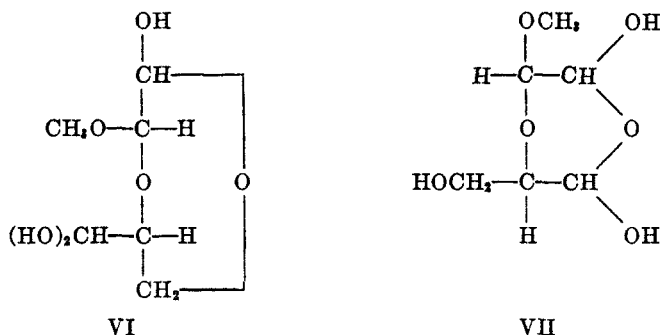
In view of the known ease of cyclization of γ- and δ-hydroxy aldehydes it seemed reasonable to regard this compound as cyclic, not acyclic (4). This is more readily appreciated if II is rewritten as III; then the "pyranose" form

would be IV, a cyclic hemiacetal. IV also is a δ-hydroxy aldehyde and if it cyclizes further it would give rise to the hemialdal V. The hydrate of V is VI, and this is included since some of the data fit this structure rather well.

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        OH                                    H
        |                                     |
        CH————                      ————————C————————
        |          |                |         |         |
  CH₃O—C—H         |                |   CH₃OCH          |
        |          |                |         |         |
        O          O                O         O         O
        |          |                |         |         |
   H—C—C—H         |                └——CH———CH          |
       ‖  |        |                    |      |         |
       O  CH₂—————                     OH     CH₂————————
        IV                                    V
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An isomer of VI is VII. It is also a hemialdal. We are grateful to a referee for suggesting that it should be considered also.

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        OH                            OCH₃      OH
        |                              |        /
        CH————                    H—C—CH
        |          |                   |        \
  CH₃O—C—H         |                   O         O
        |          |                  /          /
        O          O           HOCH₂—C—CH
        |          |                   |         \
  (HO)₂CH—C—H      |                   H          OH
        |          |
        CH₂—————
        VI                             VII
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Lewis and coworkers (5) recently postulated structure IV to explain their observation that one of the two aldehyde groups of this substance could be selectively hydrogenated in the presence of a palladium catalyst, whereas both were reduced at 120° if a Raney nickel catalyst was used.

Our findings support this suggestion. Our strongest evidence that the substance cannot represent the unmodified acyclic form is based on ultraviolet absorption spectra. In a study of the ring-chain tautomerism of several hydroxy aldehydes, Hurd and Saunders (6) compared the extinction coefficients of 5-methoxy- and 5-hydroxy-pentanal, and thereby established 6.1% of free aldehyde form in the latter at equilibrium. 4-Hydroxybutanal also was predominantly cyclic (11% free aldehyde), but for $HO(CH_2)_nCHO$ wherein n = 5, 7, 8 the free aldehyde form existed to the extent of 85–91% at 25°.

In contrast, the ultraviolet absorption spectra of the present compound in dioxane or water (Fig. 1) showed only continuous absorption with no maxima in the carbonyl region. This would mean the absence of free aldehyde group, but would not decide between a hemiacetal, aldehyde hydrate, or hemialdal.

Kuhn (7) studied the infrared spectrum of (I) and reported that it contained

a moderately strong band at 6.2 μ, which he attributed to the aldehydic carbonyl. This assignment seems questionable in view of the fact that absorption due to this group generally occurs (8) at considerably shorter wavelengths, around 5.8–5.9 μ.

Weak bands in the 6.0–6.2 μ region were observed (9) in a number of carbohydrates and their derivatives, including periodate-oxidized cellulose, and it has been suggested that they arise from hydrate formation. Treatment of methyl 4,6-benzylidene-α-D-glycopyranoside with periodic acid yields a dialdehyde which is isolated as the crystalline dihydrate. The infrared spectrum of this product contains a weak band at 6.1 μ which is also present in the parent
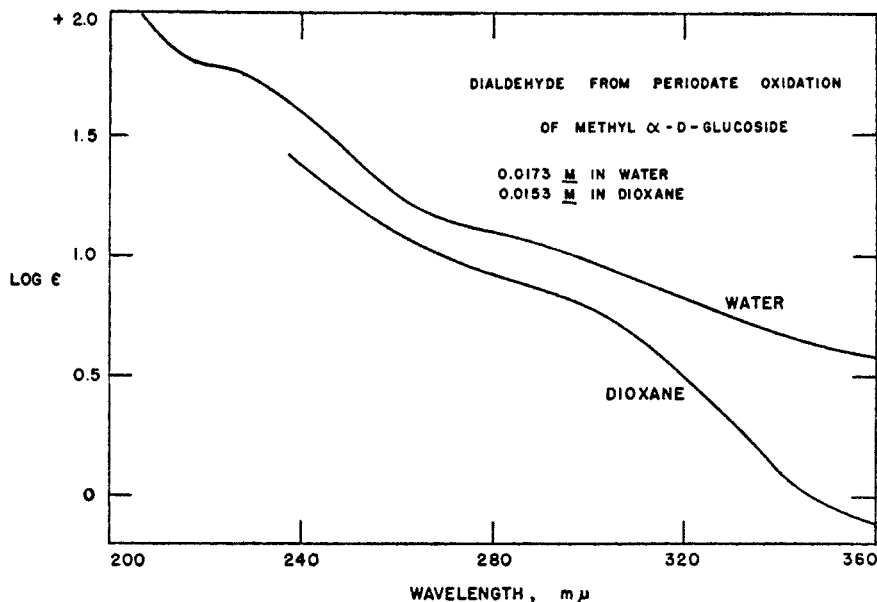

FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF THE DIALDEHYDE

compound, plus a strong band in the 3.0 μ region attributable to the hydroxy group. The absence of carbonyl absorption along with the strong hydroxy absorption suggests that the water of hydration is combined directly with the carbonyl groups.

Another physical method, namely, polarography, also gave evidence against the presence of any free aldehyde group. No polarographic wave was observed at the dropping mercury electrode.

Several new chemical reactions of the dialdehyde were developed in the course of this investigation. They are included not because of any bearing they have on the structure for they do not contribute in any decisive manner on the question of acyclic vs. cyclic forms. The reactions are of interest, however, in connection with the chemistry of the dialdehyde.

One such reaction, mentioned above, is hydrogenation. This experiment is fair evidence for IV (or VI). The dialdehyde itself is a thick sirup whose methoxy

analysis agrees fairly well with a hydrated form, VI or VII, and this water of hydration was not removed by prolonged storage over calcium chloride.

Acetylation of the dialdehyde with ketene gave a yellowish sirup possessing 20.6% acetyl which is satisfactory for a monoacetate of I, IV, or V. The C, H values would not distinguish between this formula, $C_8H_{12}O_6$, and the triacetate of VI or VII since both are C, 47.1 and H, 5.9%. Considerable tarring of the product occurred on vacuum distillation, but a 25% yield of volatile product was obtained with C, H values close to these figures.

Treatment of the dialdehyde with methanol and hydrogen chloride yielded a hygroscopic, reducing sirup, whose analysis for C and H was satisfactory for $C_9H_{20}O_7$. This could represent

$$CH_3OCHCHOCH(OCH_3)CH(OCH_3)_2$$
$$\quad | \quad\quad |$$
$$\quad HO \quad CH_2OH$$
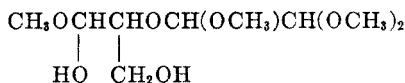
which is derivable from VI or VII.

Reaction with p-nitrophenylhydrazine gave glyoxal bis-p-nitrophenylhydrazone. This could be interpreted as simple hydrolysis of I, the open chain dialdehyde, but a good case may be made also for cyclic structure IV which is related to dioxane, since 2,5-dioxanediol (glycolaldehyde dimer) also is known (10) to yield glyoxal bis-p-nitrophenylhydrazone on reaction with p-nitrophenylhydrazine.

That the sirupy oxidation product was indeed the desired dialdehyde was established by oxidation to the known dicarboxylic acid.

EXPERIMENTAL

Oxidation of methyl α-D-glucoside. Methyl α-D-glucoside was supplied by Corn Products Refining Company. Oxidation with periodic acid followed the directions of Jackson and Hudson (3), with the modification below for larger scale runs.

To an aqueous solution of 25 g. of the glucoside, cooled to 0°, was added 60 g. of paraperiodic acid (H_5IO_6) in 750 ml. of water. The mixture was diluted to one liter and was divided into ten 100-ml. portions, each of which was stoppered and left at 20–25° overnight. Much better yields were obtained by processing the ten small fractions than one large batch. Barium hydroxide and barium carbonate were used as recommended by Jackson and Hudson. The final yield of viscid, water-soluble, pale yellow dialdehyde was 18.5 g.; $[\alpha]_D^{27}$ +110.2° (c, 7.13 in water). The reported rotation is +121° (c, 0.825 in water).

The air-dried sample gradually lost weight in a vacuum desiccator over calcium chloride (3.37 g. to 2.81 g. in 40 days, to 2.76 g. in 54 days, and no further change in 75 days), but Zeisel analysis pointed to one mole of bound water.

Anal. Calc'd for $C_6H_{10}O_5$ and $C_6H_{10}O_5 \cdot H_2O$: CH_3O, 19.1; 17.2. Found: CH_3O, 17.6, 18.0, 17.4.

Methylation. A mixture containing 10 g. of the dialdehyde, 150 ml. of pure methanol, and 1.2 g. of hydrogen chloride was kept at 20–25° for one week. Then 4 g. of anhydrous sodium carbonate was added and the mixture was evaporated (without filtering) at 50°. The oil (10.8 g.), separated from the salts by ether extraction, was distilled at 2 mm.: 1.5 g. at 40–110°; 4.4 g. at 110–118°; 0.4 g. at 117–120°; 1.0 g. of black tarry-residue; and 2.9 g. in a trap at −78°. All the trap liquid and the first two fractions possessed an aldehyde odor. Fractions 2, 3 were viscous, pale yellow liquids. Redistillation of fraction 2 gave 4.1 g. of pale, straw-colored, viscous liquid at 112–115° (2 mm.); n_D^{20} 1.4425, d 1.176 g./ml., $[\alpha]_D^{25}$ +96° (c, 7.45 in water). The material reduced Tollens reagent. It was hygroscopic and picked up weight rapidly in air.

Anal. (by M. Ledyard) Calc'd for $C_9H_{20}O_7$: C, 45.0; H, 8.38.
    Found: C, 44.4; H, 8.57.

Acetylation by ketene. The dialdehyde (3 g.) was suspended in 50 ml. of acetone and ketene was passed in until all the suspension dissolved. The heat of reaction caused boiling and a yellow coloration. After cooling, 50 ml. of chloroform was added and the mixture was washed twice with water, once with dilute sodium carbonate solution, twice with water, dried (Na_2CO_3), and evaporated. The 1.5 g. of yellow syrupy residue was soluble in chloroform, insoluble in water: $[\alpha]_D^{20}$ +101° (in chloroform). Its acetyl content was 20.57% (Calc'd for $C_6H_9O_5 \cdot COCH_3$: $COCH_3$, 21.08). About half of this material was distillable at 100–145° (2 mm.) but there was extensive formation of red-black tar. A fraction collected at 135–145°, $[\alpha]_D^{24}$ +100° (*c*, 2.0 in chloroform), contained 48.0% C and 6.49% H.

Reaction with p-nitrophenylhydrazine. Addition of 0.4 g. of the dialdehyde to a solution of 1 g. of *p*-nitrophenylhydrazine hydrochloride in 100 g. of water caused an immediate color change to bright red and formation of a copious flocculent precipitate of glyoxal bis-*p*-nitrophenylhydrazone, m.p. and mixture m.p. 305–306°.

To a solution of 0.2 g. of the acetylated dialdehyde in alcohol, water was added to turbidity, then 1 ml. of phenylhydrazine and one drop of acetic acid. This mixture was heated on a steam-bath for a few minutes then cooled to 0°. Yellow crystals of glyoxal bisphenylhydrazone separated which, after crystallization from 50% alcohol, melted at 160–162°. A known sample supplied by L. K. Rochen melted at 161–164°. The mixture of these melted at 160–162°. The recorded m.p. (11) is 169–170°, or 179° after repeated crystallizations.

Oxidation of the dialdehyde. A mixture of 3 ml. of bromine, 1.44 g. of the dialdehyde, 250 ml. of water, and 20 g. of strontium carbonate was oxidized using a procedure closely adapted from that of Jackson and Hudson (3). After removal of bromide ions by silver carbonate, and silver ions by hydrogen sulfide, the mixture was aerated, concentrated to 35 ml., decolorized with Norit A, and then concentrated at reduced pressure to a colorless sirup. This was taken up with 7 ml. of hot water and alcohol was added until incipient turbidity. On cooling, a white solid separated. It was recrystallized twice more in this manner, then once from water containing 20% alcohol. After heating at 100° and 15 mm. for six hours 1.4 g. (54%) of white crystals resulted: $[\alpha]_D^{25}$ −48° (*c*, 0.6 in water). Jackson and Hudson reported the specific rotation of −52.9° and a yield of 65–70% of the strontium methoxy(hydroxymethyl)diglycolate.

The free acid was liberated by dissolving 0.202 g. of the salt in 15.0 ml. of 0.10 *N* hydrochloric acid. This solution was diluted to 20.0 ml. The acid content should have been 0.140 g. The angular rotation at 24° (*c*, 0.70) was 0.33°, hence the specific rotation was 24°. Jackson and Hudson reported 26°.

Polarographic analysis. Both the Heyrovsky polarograph, model XI of E. H. Sargent and Co., and the Leeds-Northrup polarograph with the Micromax recorder were used in this work. The reductions of the dialdehyde in water were run at several concentrations (0.02 *M* to 0.0001 *M*) at the natural pH of 7.1 or at a buffered pH of 7.2 or 7.4. The electrolyte was 0.025 *M* potassium chloride. Plotting of the current *vs.* potential (negative voltage) revealed no wave between values for E of −0.3 to −1.8 volts. Instead, there was a steady rise in current beyond −1.1 or −1.2 volts. Under comparable conditions, furfural gave a well-defined wave, $E\frac{1}{2}$ −1.37 v.

The acetate of the dialdehyde, dissolved in a 1:1 mixture of 2-propanol and water (0.02 to 0.0001 *M*), behaved analogously. No wave was indicated.

Ultraviolet absorption. A Beckman DU spectrophotometer was used, with the hydrogen lamp as a source of light. Solutions were contained in 1-cm. quartz cells. The result is shown in Fig. 1.

SUMMARY

The sirupy dialdehyde obtained by oxidation of methyl α-D-glucoside contains a molecule of water of hydration which is not removed by prolonged

desiccation. Methanol and hydrogen chloride yielded a syrupy derivative, $C_9H_{20}O_7$, which still reduced Tollens reagent. The dialdehyde and ketene yielded a monoacetate. p-Nitrophenylhydrazine caused cleavage into glyoxal bis-p-nitrophenylhydrazone.

That the dialdehyde contained no more than traces of free CHO groups was established by demonstrating that no polarographic waves were obtained at the dropping mercury electrode, and by showing that its ultraviolet absorption spectra possessed only continuous absorption with no maxima in the carbonyl region. The facts seem best explained by assuming that the dialdehyde is a hydrate of the hemiacetal form, VI.

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