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1,4-DIOXANE-2,6-DIOL FROM ANHYDROALDITOLS: SOLVENT EFFECTS ON ITS FORMATION AND CONFORMATION*

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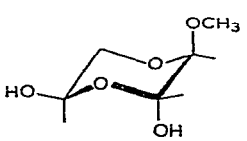
ABSTRACT

The dialdehyde produced by oxidative glycol-cleavage of 1,5-anhydropentitols exists in a variety of forms, the proportions of which vary widely with changing conditions. As a syrup, it is largely a polymer, which decomposes in deuterium oxide to a mixture of a hydrated acyclic form (30%) and two cyclic hemialdals, namely, *cis*(*e*,*e*)- and *trans*(*a*,*e*)-1,4-dioxane-2,6-diol (22% and 48%, respectively). With acetone, pyridine, or methyl sulfoxide as solvent, the equilibrium is shifted almost exclusively in favor of the cyclic species and, in contrast to the behavior of sugars, the proportion of the diequatorial conformation increases. At elevated temperatures, however, the proportion of the latter species is lowered and the acyclic form is preponderant. These equilibria also are markedly sensitive to mixed solvents.

INTRODUCTION

Derivatives of 1,4-dioxane-2,6-diol (*e.g.*, **1**) may be prepared by glycol-cleavage oxidation of glycosides, because the dialdehydes initially formed undergo hydration and intramolecular cyclization[1–3]. Depending on the structure of the dialdehyde, other kinds of intramolecularly cyclized forms are possible, as well as intermolecular hemicetals[1]. P.m.r. spectroscopy shows that, in deuterium oxide, diol **1** is in equilibrium with an equimolar proportion of the hydrated dialdehyde and exists in this solvent and also in methyl sulfoxide almost entirely in the conformation shown, *i.e.*,



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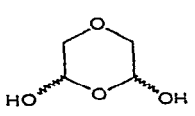

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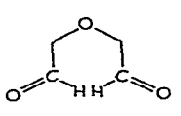
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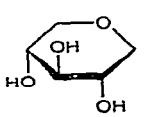

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*Dedicated to Dr. Horace S. Isbell, in honour of his 75th birthday.
†Postdoctoral fellow (1966–67) at the National Research Council Laboratory, Saskatoon, Canada, where part of this study took place. A preliminary account was presented (by H.R.G.) to the South African Chemical Institute Convention, Durban, South Africa, July 1967.

with the 2-methoxyl and 3-hydroxyl groups axial, and the 5-hydroxyl group equatorial[4]. The tendency for electronegative substituents, especially halogen, on the 1,4-dioxane ring to assume an axial orientation is very marked[5], as for sugars[6,7]. This is seen also in **1**, and presumably the equatorial disposition of HO-5 is favored because the axial alternative would involve an unfavorable interaction[4] with HO-3.

The current study deals with the parent compound in this series, namely, 1,4-dioxane-2,6-diol (**2**). By analogy with the information given above, **2** should be

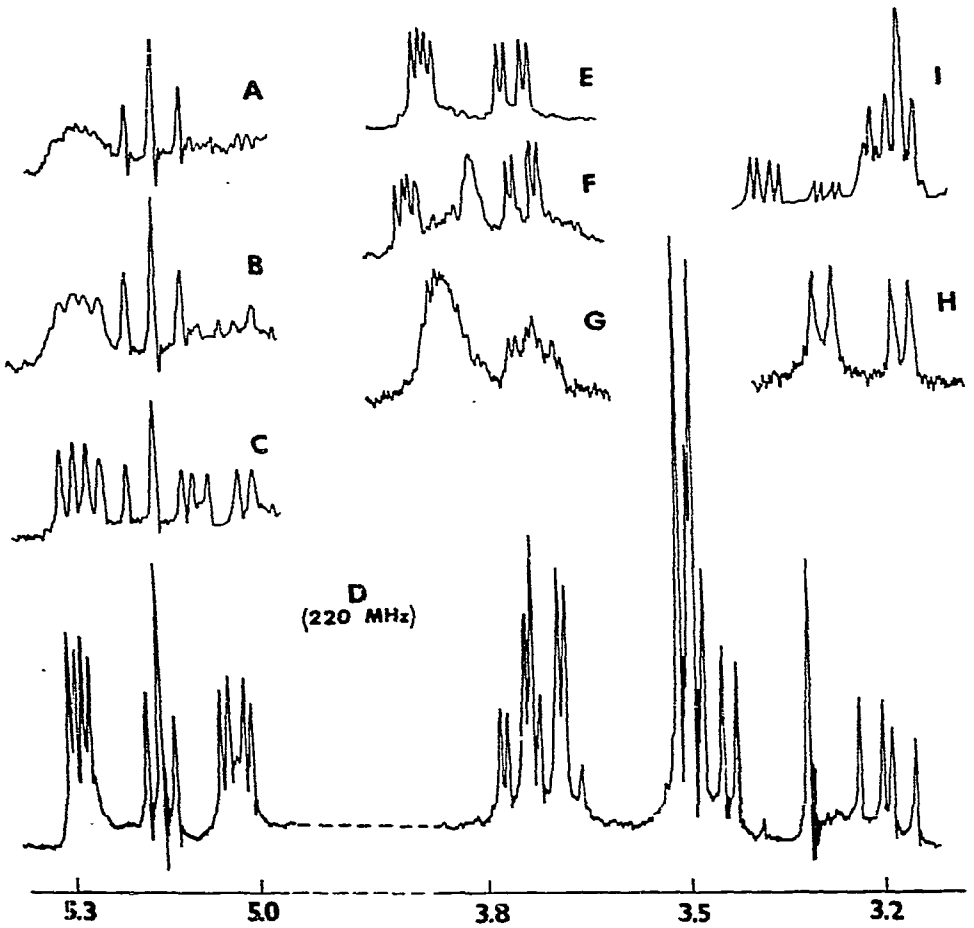
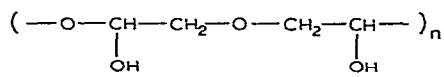


Fig. 1. P.m.r. spectroscopy of the product formed in the periodate oxidation of 1,5-anhydropentitols or 1,4-anhydroerythritol. Partial spectrum (100 MHz, 5.0–5.3 p.p.m. range, 500-Hz sweep-width) of A, the syrupy product freshly dissolved in deuterium oxide (35°); B, the same solution at 70° after equilibration (10 h); C, the equilibrated solution at 35°; D, spectrum of the equilibrated deuterium oxide solution at 220 MHz (1000-Hz sweep-width) (23°). Partial spectrum (100 MHz, 500-Hz sweep-width, 35°) of the oxidation product: E, at equilibrium in acetone-d_6 (4.7–5.8 p.p.m.); F, during equilibration in pyridine-d_5 (5.2–6.0 p.p.m.); G and H, at equilibrium in methyl sulfoxide-d_6 (4.9–5.6 and 6.6–7.2 p.p.m. regions, respectively); I, at equilibrium in methanol-*d* (2.3–3.8 p.p.m., using the solvent CH_3 as lock).

formed *via* diglycolaldehyde* (3) by scission of the diol group of a 1,4-anhydrotetritol or the 2,3,4-triol groups of a 1,5-anhydropentitol. The periodate-oxidation product of 1,5-anhydroxylitol (4) (1,5-anhydro-L-arabinitol and 1,4-anhydroerythritol were also used for this preparation) was a syrup, which could not be characterized either as a *p*-nitrobenzoate or 2,4-dinitrophenylhydrazone but, on reduction with sodium borohydride, furnished the expected ether, namely, bis(2-hydroxyethyl) ether (diethylene glycol).

When this syrupy oxidation-product is freshly dissolved in deuterium oxide, it gives an overall, poorly resolved 100-MHz p.m.r. spectrum (Fig. 1A). Aside from the spin-coupled triplet at 5.15 p.p.m. (and a doublet at 3.55 p.p.m. which can be seen in spectrum 1D), signals are ill-defined and are largely merged with the baseline. However, as the solution is stored, other well-resolved groups of signals appear. Fig. 1C shows the corresponding region of the spectrum after equilibrium has been reached, and Fig. 1D the complete spectrum recorded at 220 MHz. The quartet (doublet of doublets) centered at 5.30 p.p.m. is associated with two others upfield, centered at 3.70 and 3.45 p.p.m., respectively, and the quartet at 5.05 p.p.m. with those at 3.75 and 3.20 p.p.m., respectively; these associations are evident from the observed spacings and have been confirmed by spin decoupling. Hence, at least three distinct species are present in admixture in this solution, two being generated slowly from the syrupy oxidation-product. Probably, the latter consists largely of polymeric material (*e.g.*, 5), which would account for the overall weakness of spectrum 1A. The triplet and doublet present are ascribed to the aldehydic and methylene protons, respectively, of the hydrated dialdehyde 6, hydration being evidenced by location of the triplet in a region characteristic of hydrated aldehydes[9]. In a freshly prepared deuterium oxide solution, then, the first discernible species is the acyclic form 6.



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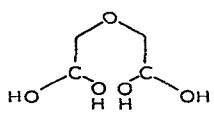

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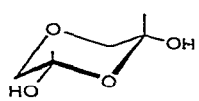

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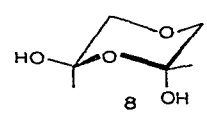

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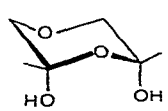

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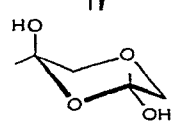

*Diglycolaldehyde (3), described as a superior hardening-agent for gelatin, has been prepared[8] by ozonolysis of 2,5-dihydrofuran, and assumed to exist in aqueous solution in equilibrium with 1,4-dioxane-2,6-diol.

The two groups of three quartets (Fig. 1D) are each taken to represent the ABX protons of the hemiacetal and methylene protons of two isomers (**7** and **8**) of 1,4-dioxane-2,6-diol formed by cyclization of **6**. Because of the relatively large, chemical-shift differences observed within each group, these spectra may be classified as approximately of the AMX type and, in fact, the spacings are virtually the same at 220 MHz as at 100 MHz. Accordingly, the low-field quartet clearly exhibits both gauche (2.5 Hz) and diaxial (8.0 Hz) vicinal couplings characteristic of 1,4-dioxane[10]. This requires that HO-2 and HO-6 are equatorial, and therefore that this quartet and associated quartets represent a diequatorial isomer of the diol **7**, accepting that these are chair conformers (see below). Because of the magnitude of these couplings, it is unlikely that the *cis* diol exists to an appreciable extent in the diaxial conformation **9**, which would be characterized by small spacings.

Characteristics of the second group of three quartets are indicative of the presence of interconverting chains in which one hydroxyl is equatorial and the other axial (**8**). This is suggested particularly by the overall width of the signal at 5.25 p.p.m., *i.e.*, the observed width of 7.2 Hz (both at 100 and 220 MHz) is intermediate in size relative to the sum of the gauche and diaxial couplings given above.

Chemical shifts provide supporting evidence for the assigned structures, **7** and **8**. Thus, of the two low-field quartets (Fig. 1C and 1D), that ascribed to the axial 2 and 6 protons of **7** are, as would be expected, at higher field than the axial–equatorial average value for the corresponding protons in **8**. Similarly, the methylene-proton quartets of **8** are intermediate in shift between those of the low- (equatorial) and high-field (axial) signals of the methylene protons of **7** (Fig. 1D).

Carbon-13 chemical shifts also are consistent with these conclusions. Six signals are accounted for in the proton-decoupled spectrum of the mixture (Table I), two each for **6**, **7**, and **8**. The resonances produced by **6** were readily assigned by comparing the spectrum of the aqueous solution with that in methyl sulfoxide: as shown below, the proportion of **6** in the latter solvent is greatly diminished. Signals for **7** and **8** were then differentiated by analogy with data available for *cis* and *trans* isomers of the cyclohexanediols[11] and for sugars[12,13], which show that the relative order of chemical shifts of ^{13}C nuclei and appended protons are reversed. Accordingly C-2 and C-6 of **7** are less shielded than the corresponding carbon atoms of **8**, and by

TABLE I

^{13}C CHEMICAL SHIFTS (P.P.M.)[a]

Compound	*C-2, C-6 Δδ*	*C-3, C-5 Δδ*
e,a (**7**)	103.5 } 1.8 (2.1)[b]	123.7 } 0.4 (0.9)[b]
e,e (**8**)	101.7 }	123.3 }
acyclic (**6**)	103.5 (C-1, C-5)	117.0 (C-2, C-4)

[a]From downfield CS_2. [b]Difference in chemical shift between *e,a* and *e,e* isomers of cyclohexane-1,3-diol.

almost the same amount (1.8 p.p.m.) as the difference (2.1 p.p.m.) between the carbinol ^{13}C signals of *trans* (*e,e*) and *cis* (*e,a*) cyclohexane-1,3-diols (Table I). The signals of the methylene carbon atoms differ little in chemical shift, which is true also of the corresponding signals (C-4 and C-6) of the cyclohexanediol analogue. Accepting that cyclohexanediols exist essentially in a chair conformation, these data suggest that the 1,4-dioxanediols are similarly constituted.

The proportions of **6**, **7**, and **8** in equilibrium are highly sensitive to a change in temperature or solvent. In aqueous solution at 23° (Fig. 1D), the ratios **6**:**7**:**8** are 1:1.3:1.8. The acyclic form is more favored, and the diequatorial isomer (**7**) less favored, by a rise in temperature; *i.e.*, at 35°, the ratios are 1:0.8:1.5 (Fig. 1C), and at 70°, 1:0.5:1.3 (Fig. 1B). Organic solvents produce the opposite effect. In acetone, for example, the acyclic species is no longer detectable, and **7** and **8** are now present in closer to equimolar proportions (Fig. 1E).

With pyridine as the solvent, a group of broad p.m.r. signals is obtained initially. Well-resolved quartets characteristic of **7** and **8** emerge with time, accompanied by the disappearance of a diffuse band (Fig. 1F shows a late stage in the overall process). At equilibrium, the spectrum in this region is closely similar to that depicted in Fig. 1E, except that **7** produces the relatively stronger signal (1.1:1). Presumably, the poorly resolved, central band in Fig. 1F depicts the acyclic species **6** in the process of slow, partial dehydration by the solvent.

In methyl sulfoxide also, the syrupy product of periodate oxidation at first affords a poorly resolved spectrum; after a period of three days, the spectrum appears as shown partially in Figs. 1G and 1H. The doublets at 6.75 (*J* 6.3 Hz) and 7.0 p.p.m. (*J* 7.0 Hz) are due to the hydroxyl protons, the downfield doublet being spin-coupled with the upfield multiplet in Fig. 1G. On addition of deuterium oxide, not only is coupling with the hydroxyl protons eliminated but the overall resolution gradually improves markedly. Once again, a spectrum similar to that depicted in Fig. 1E is recorded in this region, showing that the acyclic species is absent and that **7** and **8** exist at equilibrium in a ratio of 1.2:1.

The characteristics found with methanol as solvent are distinctly different from those observed in the other media, and are sufficiently complex that only a preliminary comment is offered. By far the largest signal in the downfield region (Fig. 1I) is a triplet (*J* 5.0 Hz). Since the latter corresponds to the triplet produced by **6**, it is probably due to solvated dialdehyde, *i.e.*, the 1,5-dimethyl acetal of **6**. The other major signal, the low-field quartet, possesses almost the same spacings as the quartet of **7**, and is attributed tentatively to a mono-*O*-methyl derivative of diequatorial isomer **7**. However, there are no signals that suggest the presence of a corresponding derivative of the *a,e* stereoisomer.

Methanol aside, the changes in solvent have only a moderate effect on the relative stabilities of the *cis* and *trans* isomers. The latter isomer is more abundant in water (by 2 to 1 at 35°) and slightly less so in acetone, whereas the *cis* isomer is preponderant in methyl sulfoxide or pyridine (by 1.2 or 1.1 to 1). In all spectra of the *cis* isomer, the observed spacings are virtually the same, which indicates that there is

a negligible proportion of the diaxial form **9** in the organic media as well as in water, By contrast, *cis*-2,6-dimethoxy-1,4-dioxane exists in the diaxial conformation to the extent of 57% in water (although of only 12% in pyridine)[14]. Nevertheless, both for the dihydroxy and dimethoxy compounds, water is at least as conducive, or more so, than are the other solvents to an axial orientation of *O*-substituents. As has already been pointed out[14], this is in the direction opposite to that observed with sugars[15–17] and methyl glycosides, which show a decrease in the magnitude of the anomeric effect in water as compared with organic media[14,15,17]. Solvent influences of these kinds were not apparent with the trisubstituted 1,4-dioxane **1**. In that instance, however, several factors combine within the molecule to heavily favor the structure shown: as seen above, an *a,e* orientation of the hydroxyl groups in 1,3-relationship is highly stable, and the axial methoxyl group should be favored by virtue of the anomeric effect. Moreover, in the arrangement shown, there are no apparent destabilizing interactions; even though the 1,4-dioxane ring can easily sustain an equatorial hydroxyl or methoxyl group, reorientation of either of the axial substituents of **1** would introduce a gauche interaction.

Equilibration of the syrupy product of periodate oxidation, as represented by these various spectra, takes place more slowly in the organic solvents than in D_2O. This is understandable if a large proportion of the material is in a polymeric form initially, as suggested above, and is hydrolysed. Even in a dry solvent, some water will be furnished when **6**, present in a significant proportion at the outset (Fig. 1B), cyclizes to form **7** and **8**. Sometimes, large differences in the rate of equilibration in a given solvent were noticed, especially with pyridine; it is possible that, in some of these experiments, contamination by moisture caused the increased rates. Although the overall attainment of equilibrium in D_2O requires several hours, the interconversion of **6**, **7**, and **8** is rapid. This is shown by the addition of acetone to the aqueous solution: resulting changes in the proportions of the three species [represented at a maximum in acetone itself (Fig. 1E), in which equilibration is slow] took place within a few minutes. Noteworthy also is the manner in which the composition changed with changes in the solvent composition. Thus, the percentage of the acyclic

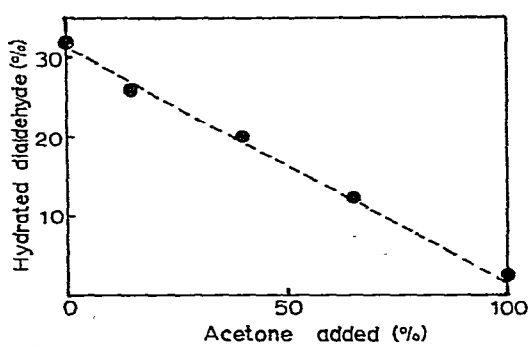

Fig. 2. Percent of hydrated dialdehyde **6** in mixtures of deuterium oxide and acetone-d_6.

form **6** decreased *linearly* (Fig. 2). Hence, although the number of water molecules greatly exceeded that of the hydrated dialdehyde (~300:1 in the solution used), the aqueous system appears to have been so delicately balanced that even a small increment of acetone led to the expulsion of a molecule of water from **6** into the water-rich medium*. As mentioned above, dehydration of **6** and cyclization to **7** and **8** is not promoted by a rise in temperature, but, rather, the proportion of **6** increases; this effect, however, is likely related to differences in entropy.

EXPERIMENTAL

General. — P.m.r. spectra were recorded with a Varian HA-100 spectrometer, using tetramethylsilane as an external lock-signal; spectra at 220 MHz were recorded at the Canadian 220-MHz Center, Sheridan Park, Ontario. Carbon-13 n.m.r. spectra were recorded at 25.15 MHz and a probe temperature of 55 ±5°, using methyl iodide-^{13}C as the reference lock-signal.

1,5-Anhydroxylitol. — The procedure of Fletcher[19] was used. 1,2,3,4-Tetra-*O*-acetyl-α-D-xylopyranose (3.2 g) was converted by treatment in the cold with hydrogen bromide in acetic acid into tetra-*O*-acetyl-α-D-xylopyranosyl bromide. The latter compound in ether (120 ml) was added to a solution of lithium aluminum hydride (3.2 g) in ether (120 ml). Work-up afforded the title compound (1.0 g); recrystallized from ethanol–hexane, it had m.p. 115–117°.

*1,5-Anhydro-*L*-arabinitol.* — As with the D-*xylo* compound, reduction of 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl bromide (0.85 g) in ether with lithium aluminum hydride (0.8 g) afforded the title compound (0.33 g); recrystallized from ethanol–ethyl acetate, it had m.p. 94–96°.

1,4-Anhydroerythritol. — Prepared by treating erythritol with 50% sulfuric acid[20], the syrup was purified by distillation and characterized further[21] by p.m.r. spectroscopy.

Periodic acid oxidation of the anhydrides. — In a typical reaction, a solution containing 1,5-anhydro-L-arabinitol (0.1 g) and periodic acid (0.13 g) in water (5 ml) was stored in the dark at room temperature for 18 h. An excess of Dowex-1(HCO_3^-) resin was introduced, and the neutralized solution was concentrated, yielding a colorless syrup (70 mg). N.m.r. spectra of this product in a variety of solvents are described above.

Bis(2-benzoyloxyethyl) ether. — The product of periodate oxidation was reduced with aqueous sodium borohydride, which was followed by treatment with benzoyl chloride in pyridine. This afforded the title compound, m.p. and mixture m.p. 155–157°.

*One might anticipate instinctively that, under these conditions, there would be a smaller, initial decrease in the percentage of **6**, rather than the linear drop observed. However, another factor to be considered is the possibility that, even without the elimination of water, such equilibria may be solvent sensitive. Thus, 6-hydroxy-2-hexanone exists[18] as such in water, but in *p*-dioxane cyclizes to 2-methyltetrahydropyran-2-ol to the extent of 40%.

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