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INTRAMOLECULAR ACETAL FORMATION BY PRIMARY *versus* SECONDARY HYDROXYL GROUPS*

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ABSTRACT

On acid-catalyzed equilibration in aqueous solution, three aldoheptoses, D-*glycero*-L-*manno*-, D-*glycero*-L-*allo*-, and D-*glycero*-L-*altro*-heptose, give 15, 54, and 98%, respectively, of the 1,6-anhydropyranose, a much higher proportion than is formed from the homomorphous aldohexoses. This is another example of the greater tendency of secondary, compared to primary, hydroxyl groups to participate in the formation of cyclic acetals.

INTRODUCTION

In discussions and calculations on the relative stabilities of the different forms of sugars[1], it has always been assumed that homomorphous sugars have the same free-energy. For example, it was assumed that an aldohexopyranose and the homomorphous aldopentopyranose, in the same conformation, differ in free energy by only the small *gauche* interaction, in the former, between the hydroxymethyl group and the neighboring hydroxyl group; that is, the pentopyranose should be slightly the more stable. It is now shown that this assumption is not correct. Secondary hydroxyl groups have a greater tendency to form intramolecular acetals than primary ones, and, in consequence, aldohexopyranoses are more stable than aldopentopyranoses.

This behavior of hydroxyl groups was first suggested by Hayward and Angyal[2]. They pointed out that, in aqueous solution, the mixture of forms of an aldopentose contains more furanoses and more aldehyde in equilibrium than the homomorphous aldohexoses which have the same conformation of their pyranose forms. As the free energy of the acyclic and the furanose forms would not be affected by the hydroxymethyl group present in the hexose forms, it follows that the pyranose forms of the aldopentoses must be less stable than those of the aldohexoses. In the former, a primary hydroxyl group is involved in the formation of the pyranose ring; in the latter, a secondary one. It was therefore postulated that primary hydroxyl groups have less tendency to form intramolecular acetals than secondary ones.

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Many examples have been found that support this postulate. It has already been pointed out[2] that dihydrostreptose, namely, 5-deoxy-3-*C*-(hydroxymethyl)-L-lyxose, forms glycosides by ring closure through the secondary OH-4, rather than the primary OH-3[1] group[3]. Solutions of D-erythrose and D-threose, sugars that can only form a ring through primary hydroxyl groups, contain considerable proportions of the aldehyde and the aldehydrol forms in equilibrium[4]. 5-Hydroxypentanal (in solution) contains 6% of free aldehyde in equilibrium[5], whereas the aldehyde form was not detected in the equilibrium solution of 5,6-dihydroxyhexanal, which cyclizes through the secondary 5-hydroxyl group[6].

The Hann–Hudson rules[7] for the formation of acetals from alditols and aldehydes tacitly include our proposal, as they state that the di-secondary (βC) acetals are formed in preference to the secondary–primary (β) acetals*. Aldehydes form six-membered acetals in preference to five-membered ones[7]; glycerol is, however, an exception, about equal amounts of the 1,2- and 1,3-acetals being in equilibrium[10]. The proposed explanation, based on the formation of hydrogen bonds, is not convincing; the more likely explanation is that the six-membered acetal is less favored because it involves two primary hydroxyl groups**.

RESULTS AND DISCUSSION

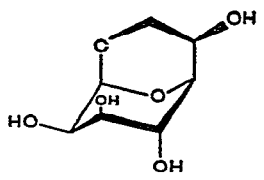
We have recently encountered a particularly striking case of the aforementioned behavior. Angyal and Dawes, in their study of the equilibria involving 1,6-anhydro-aldohexoses, cursorily investigated several aldoheptoses[12]. They found that, when heated with aqueous acids, D-*glycero*-L-*manno*-heptose gives an anhydride in ~15% yield; the anhydride was not isolated, but was assumed to be the 1,7-anhydro-pyranose **1**. As D-mannose is in equilibrium with only 0.8% of its 1,6-anhydride*** (**2**), it was argued that the homomorphous 1,6-anhydride (**3**) of the heptose would not be formed in larger proportion. Recently, however, Chaby and Szabó have studied[13] this anhydride; they did not isolate it, either, but from its mass spectrum concluded that it was the 1,6-anhydride **3**. Surprised, we prepared and isolated the anhydride and its tetraacetate. A study of their ^{1}H-n.m.r. spectra left little doubt that the anhydro compound is, indeed, 1,6-anhydro-D-*glycero*-β-L-*manno*-heptopyranose (**3**). The

*In attempting to explain the preference for secondary hydroxyl groups in the formation of acetals from alditols, Barker and co-workers[8] made the then-accepted assumption that all alditols are predominantly in the planar, zigzag conformation. They argued that the two secondary hydroxyl groups involved in the formation of the βC ring are already in the required position before the reaction, whereas the primary hydroxyl group has to be brought into the proximity of the other hydroxyl group by a rotation, against its repulsion. As we now know that those alditols which give βC acetals are not predominantly in the planar, zigzag conformation[9], this argument can no longer be regarded as valid.

**In a recent review[11] on the selective reactivities of hydroxyl groups, it was claimed that primary hydroxyl groups undergo acetalation in preference to secondary ones. The examples cited, which included only the formation of acetals by reaction of single hydroxyl groups in carbohydrates, were all reactions under kinetic control, in contrast to our discussion of equilibria.

***The formula shows the L isomer.

acetate gave a spectrum in which every signal could be assigned; the spectrum of the anhydride itself could be interpreted by comparing it with the spectrum[14] of 1,6-anhydro-β-D-mannopyranose (2). A comparison of the two spectra showed that the signals of H-2, H-3, H-4, H-7, and H-7′ were at lower field for the acetate than for the free sugar, whereas those of H-1, H-5, and H-6 were in approximately the same position for both compounds. Therefore, acetylation occurred on O-2, O-3, O-4, and O-7, and the compound must be the 1,6-anhydropyranose.



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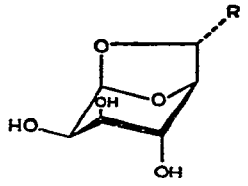


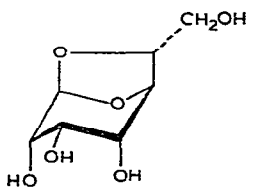
2 R = H
3 R = CH_2OH

The greater stability (15% at equilibrium) of the 1,6-anhydroheptose (3), compared with the 1,6-anhydrohexose (2) (0.8%), seems to be due to ring-formation through a secondary hydroxyl group in the former. It may therefore be predicted that other aldoheptoses will also have a higher proportion of 1,6-anhydropyranose in equilibrium than the homomorphous aldohexoses, provided that the additional hydroxymethyl group is *exo* in the anhydride and therefore does not introduce any additional steric interaction. This prediction was tested on two examples, namely, D-*glycero*-L-*allo*- and D-*glycero*-L-*altro*-heptose.

D-Allose is in equilibrium with 14% of the 1,6-anhydropyranose[12]. Equilibration of D-*glycero*-L-*allo*-heptose led to one anhydride (54%) with only traces of three other compounds. The mass spectrum of the tetraacetate of this anhydride suggests[13] that it is also the 1,6-anhydropyranose (4): the peak at *m/e* 213 is larger than the one at 215, and that at 153 is much larger than the one at 170. Again, comparison of the n.m.r. spectra of the anhydride and its tetraacetate showed that acetylation occurred on O-2, O-3, O-4, and O-7; the compound is, therefore, the 1,6-anhydropyranose.

Several features of the n.m.r. spectra of these two tetraacetates indicate that the compounds are 1,6-anhydropyranoses: (*i*) $J_{5,6}$ is small (<1 Hz), whereas, for the six-membered ring of a 1,7-anhydropyranose, it would be ~3 Hz; (*ii*) the values for $J_{6,7}$ and $J_{6,7'}$ (7.2 and 5.5 Hz) are typical of terminal CH_2OAc groups (*e.g.*, 7.2 and 4.6 Hz for galactitol hexaacetate[15]), whereas, for the six-membered ring of a 1,7-anhydropyranose, values of 10 and 3 Hz would be expected; (*iii*) the signals of the methylene group appear close to δ 4.0 (compared with δ 4.27 and 3.84 in the spectrum of galactitol hexaacetate), whereas, for the six-membered ring of a 1,7-anhydropyranose they should be found near δ 3.5 (compare, for example, with the δ values of 3.67 and 3.37 for the triacetate of 1,6-anhydro-β-D-allofuranose[16]); and (*iv*) the

signal of H-6 is near δ 4.5; if C-6 had an acetoxyl group attached to it, the signal would be close to δ 5.0.



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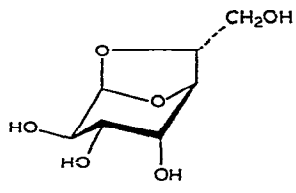

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Interestingly, the 1,7-anhydropyranose of D-*glycero*-L-*allo*-heptose would have no angle strain and no unfavorable steric interactions, and yet it is not formed to any considerable extent; in it, the ring would, of course, have closed through the primary hydroxyl group.

D-Altrose is in equilibrium with 65% of the 1,6-anhydropyranose[12]; almost complete conversion of D-*glycero*-L-*altro*-heptose into the 1,6-anhydropyranose would, therefore, be expected. In fact, after equilibration, 98% of the sugar was found as an anhydride which was again shown, by the mass spectrum and the characteristic features of the n.m.r. spectrum of its tetraacetate, to be the 1,6-anhydropyranose (**5**).

From these examples, it appears that acetal formation by a secondary hydroxyl group is favored over that by a primary hydroxyl group by ~6.5 kJ/mol (~1.5 kcal/mol).

EXPERIMENTAL

General. — Solvents were evaporated under diminished pressure in a rotary evaporator. G.l.c. analyses were conducted with a custom-made instrument, using nitrogen as the carrier gas and a hydrogen flame-ionization detector, in a column (120 × 0.3 cm) of 3% of SP-2401 on Chromosorb W at 232°. It was assumed that all of the compounds gave equal response. The compounds were analyzed as their acetates; acetylation was performed by heating on a steam-bath for 1 h with 1:1 (v/v) acetic anhydride–pyridine. To check the homogeneity of syrupy products, their acetates were also analyzed on a column of 1.5% of QF-1 on Chromosorb W.

N.m.r. spectra were recorded with a Japan Electron Optics JNM-4H-100S spectrometer; chemical shifts were measured from sodium 4,4-dimethyl-4-silapentane-1-sulfonate or Me_4Si as the internal standard. Mass spectra were recorded with an AEI MS-12 spectrometer by electron impact at 70 eV from a direct-insertion probe at 25°, at a source temperature of 230°.

1,6-Anhydro-D-glycero-β-L-manno-*heptopyranose* (**3**). — D-*glycero*-L-*manno*-Heptose[17] (2.0 g) was heated on a steam-bath with M sulfuric acid (40 mL) for 4 days. The solution was made neutral with barium carbonate, the suspension filtered, the filtrate briefly stirred with Amberlite CG-120 (H^+) resin, its pH adjusted to ~7 with

sodium hydroxide solution, and the solution evaporated. The residue was dissolved in 3:7 methanol–water (2 mL), and chromatographed on a column (35 × 1.5 cm) of Dowex AG-50W X2 (Ca^{2+}) resin (200–400 mesh) with 3:7 methanol–water as the eluant. The first fraction (76–117 mL) contained D-*glycero*-L-*manno*-heptose (1.5 g), which crystallized on evaporation of the solvent. The second fraction (194–220 mL) contained the anhydride (152 mg), pure by g.l.c. of its acetate, which slowly crystallized; recrystallization from methanol gave compound **3**, m.p. 166–168°, $[\alpha]_D^{22}$ +105° (*c* 1, water); n.m.r. data (D_2O): δ 3.54 (d, 2 H, H-7,7′, spacing 5.5 Hz), 3.75 (dq, H-3, $J_{2,3}$ 4.7, $J_{1,3}$, $J_{3,5}$, and $J_{3,4}$ ~1.5 Hz), 3.92 (m, 2 H, H-2,4), 4.33 (unresolved q, H-5, $W_{h/2}$ 4.5 Hz), 4.45 (t, H-6, J ~5.5 Hz), and 5.41 (s, H-1).

Anal. Calc. for $C_7H_{12}O_6$: C, 43.7; H, 6.25. Found: C, 43.6; H, 6.5.

The tetraacetate was prepared by treatment of **3** with acetic anhydride and pyridine for 3 h; it failed to crystallize, but was homogeneous by g.l.c. N.m.r. data ($CDCl_3$): δ 2.03 (s, Ac), 2.08 (s, Ac), 2.14 (s, 2 Ac), 3.98 (dd, H-7, $J_{6,7}$ 7.2, $J_{7,7'}$ −11.5 Hz), 4.11 (dd, H-7′, $J_{6,7'}$ 5.5 Hz), 4.42 (broad s, H-5), 4.58 (t, H-6), 4.86 (unresolved t, H-4, $J_{4,5}$ small), 5.00 (dd, H-2, $J_{1,2}$ 1.7, $J_{2,3}$ 5.7 Hz), 5.28 (dq, H-3, $J_{1,3}$, $J_{3,5}$, and $J_{3,4}$ ~1.5, $J_{3,4}$ 1.5 Hz), and 5.47 (broad s, H-1).

For comparison, the n.m.r. spectrum of the triacetate of 1,6-anhydro-β-D-mannopyranose in $CDCl_3$ was recorded: δ 2.05 (s, Ac), 2.12 (s, Ac), 2.14 (s, Ac), 3.85 (dd, H-6_{exo}, $J_{5,6exo}$ 5.8, J_{gem} −7.8 Hz), 4.24 (d, H-6_{endo}, $J_{5,6endo}$ <0.5 Hz), 4.62 (d, H-5, $J_{4,5}$ <1 Hz), 4.81 (unresolved t, H-4), 4.99 (dd, H-2, $J_{1,2}$ 1.8, $J_{2,3}$ 5.5 Hz), 5.25 (dq, H-3, $J_{1,3}$, $J_{3,5}$, and $J_{3,4}$ ~1.5 Hz), and 5.42 (broad s, H-1).

1,6-Anhydro-D-glycero-β-L-allo-*heptopyranose* (**4**). — D-*glycero*-L-*allo*-Heptose[18] (0.6 g) was heated on a steam-bath with M sulfuric acid (25 mL) for 4 days, and the mixture processed as before. G.l.c., after acetylation, showed that equilibrium had been reached and that five compounds were present: an unknown (R_t 6.8 min, 2%), the 1,6-anhydropyranose (7.2 min, 54%), an unknown (10.0 min, 1%), and the anomers of the heptose (14.0 and 21 min, 43%). The mixture, in water, was chromatographed on a jacketed column (35 × 1.5 cm) of Dowex 50W X2 (Ca^{2+}) resin kept at 60°. (The higher temperature increases the rate of mutarotation, and thereby prevents "tailing" of the heptose.) The first fraction (54–81 mL) contained the heptose (270 mg). The second fraction (121–144 mL) contained the anhydride (220 mg), which did not crystallize, $[\alpha]_D^{22}$ +66° (*c* 1, water); n.m.r. data (D_2O): δ 3.54 (d, 2 H, H-7,7′, spacing 5.4 Hz), 3.72–3.92 (m, H-2,3,4), 4.04 (t, H-6), 4.45 (unresolved q, H-5, $W_{h/2}$ 4 Hz), 5.52 (d, H-1, $J_{1,2}$ 1.6 Hz); the mass spectrum was practically identical with that published[13] for the *manno* isomer.

An aliquot (75 mg) was acetylated, and the product crystallized from benzene–petroleum ether (b.p. 60–80°), to give 2,3,4,7-tetra-*O*-acetyl-1,6-anhydro-D-*glycero*-β-L-*allo*-heptopyranose (100 mg), m.p. 97–98°, $[\alpha]_D^{22}$ +36° (*c* 2.5, chloroform); n.m.r. data ($CDCl_3$): δ 1.99, 2.09, 2.17, 2.18 (s, 4 Ac), 3.99 (dd, H-7, $J_{6,7}$ 6.6, $J_{7,7'}$ −11.2 Hz), 4.16 (dd, H-7′, $J_{6,7'}$ ~5.2 Hz), 4.27 (t, H-6), 4.50 (d, H-5, $J_{4,5}$ 1.9 Hz, $J_{5,6}$ small), 5.09 (ddd?, H-4), 5.23 (m, 2 H, H-2,3), and 5.55 (d, H-1, $J_{1,2}$ 2.5 Hz).

Anal. Calc. for $C_{15}H_{20}O_{10}$: C, 50.0; H, 5.6 Found: C, 50.3; H, 5.5.

1,6-Anhydro-D-glycero-*β*-L-altro-*heptopyranose* (**5**). — D-*glycero*-L-*altro*-Heptose was prepared according to Young and Adams[18]. It had been described as a syrup, but our sample crystallized after a few months. After recrystallization from water–ethanol, it had m.p. 132–134°, $[\alpha]_D^{22}$ −31.6 (1 min) → −29.4° (3 h) (*c* 1.35, water) (lit.[18] $[\alpha]_D$ −22°).

Anal. Calc. for $C_7H_{14}O_7$: C, 40.0; H, 6.7. Found: C, 40.0; H, 6.9.

The heptose (200 mg) was heated on a steam-bath with M sulfuric acid (10 mL) for 2 days. Processing as before gave a syrup (150 mg); g.l.c., after acetylation, showed four peaks: that of the 1,6-anhydride (R_t 6.4 min, 98%) and three peaks of the heptose (14, 17, and 19 min, 2%). The syrup crystallized on standing; recrystallization from methanol gave anhydride **5** (77 mg), m.p. 152–153°, $[\alpha]_D^{22}$ +185° (*c* 1.2, water). The mass spectrum was practically identical with that published[13] for the *manno* isomer; in particular, *m/e* 213 > that at 215, and 153 > that at 170.

Anal. Calc. for $C_7H_{12}O_6$: C, 43.7; H, 6.3 Found: C, 43.5; H, 6.2.

The tetraacetate was a syrup; n.m.r. data ($CDCl_3$): δ 2.00 (s, Ac), 2.09 (s, 2 Ac), 2.17 (s, Ac), 3.98 (dd, H-7, $J_{6,7}$ 7.0, $J_{7,7'}$ −11.5 Hz), 4.08 (dd, H-7′, $J_{6,7'}$ 5.5 Hz), 4.29 (t, H-6), 4.47 (d, H-5, $J_{4,5}$ 2.3, $J_{5,6}$ <0.5 Hz), 5.00 (dd, H-2, $J_{1,2}$ 1.6, $J_{2,3}$ 9.2 Hz), 5.19 (dd, H-3, $J_{3,4}$ 4.2 Hz), 5.34 (dd, H-4), and 5.56 (d, H-1).

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