# PYRANOSE–FURANOSE AND ANOMERIC EQUILIBRIA

## INFLUENCE OF SOLVENT AND OF PARTIAL METHYLATION[1]

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ABSTRACT

Sugars possessing the *arabino* (2,3,4-*trans*,*cis*) configuration exist as furanoses to a greater extent in dimethyl sulfoxide than in water. Their 2,3-di-*O*-methyl derivatives show an even stronger preference for a five membered ring structure in both solvents. This is most marked for 2,3-di-*O*-methyl-D-arabinose and 2,3-di-*O*-methyl-D-altrose, which are 65% and 80% furanose, respectively, in dimethyl sulfoxide. Compounds in the *xylo* (2,3,4-*trans*,*trans*) or *lyxo* (2,3,4-*cis*,*trans*) series show little tendency to be furanoses in either solvent. However, α-pyranoses in the *lyxo* series are relatively more stable in dimethyl sulfoxide than in water, whereas the anomeric composition for members of the *xylo* series is the same in both solvents. Some of these variations in the equilibria are attributed to the preferential stabilization of pyranose forms in water. D-Lyxose and D-ribose show nuclear magnetic resonance spectral differences in the two solvents that appear to be due to conformational, as well as tautomeric, equilibrium changes.

An equatorial anomeric hydroxyl proton of a given pair in dimethyl sulfoxide shows a larger spacing (6.5–8.0 c.p.s.) than an axial anomeric hydroxyl proton (4–5 c.p.s.). The signal for the latter proton occurs at higher field than an equatorial OH-1, except when OH-2 is axial.

In a recent study of hydroxyl proton magnetic resonance spectra it was found that certain sugars tend to exist as furanoses to a greater extent in dimethyl sulfoxide than in water (1). D-Arabinose shows this difference very markedly. At equilibrium, virtually no furanose is detected in the aqueous solution, whereas in dimethyl sulfoxide its proportion is one-third of the total (Table I). Galactose behaves similarly, although the final percentage of furanose is not as high. D-Altrose and D-fructose, both of which are configurationally related to these sugars, exist as furanoses to a very considerable extent in water. However, the tautomeric composition of the former (2) is altered significantly in dimethyl sulfoxide, in which it shows an even stronger preference for the five membered ring structure (Table I). The presence of mixed furanose and pyranose forms of D-fructose in water is shown by the fact that, when an aqueous solution of the sugar is concentrated, the resulting syrupy material shows several strong singlets ascribable to OH-2 when freshly dissolved in dimethyl sulfoxide. As equilibration proceeds in this solvent, the main change observed is a decrease in the relative intensity of the signal attributable to OH-2 of the β-pyranose form.

One possible explanation (1) of these compositional differences in the two solvents is that water may preferentially stabilize the pyranoses through hydrogen bonding. This is based on evidence (3) that, when water solvates a sugar molecule possessing a pyranose chair form, the structure of water itself suffers very little disorientation, and intermolecular association can take place readily. Although dimethyl sulfoxide also is strongly hydrogen bonding, there is no apparent relationship of this kind between its linear structure (4) and one specific type of cyclic sugar conformation.

To examine the possibility that water may stabilize pyranoses preferentially, the equilibrium compositions of some 2,3-di-*O*-methyl derivatives of sugars in water and dimethyl sulfoxide were measured. According to Kabayama and Patterson (3), the most

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TABLE I

Percentage of furanose in solution at equilibrium*

| | In deuterium oxide† | In dimethyl sulfoxide‡ |
|---|---|---|
| D-Arabinose | Trace | 33 |
| 2,3-Di-*O*-methyl-D-arabinose | 17 | 65 |
| D-Galactose | Trace | ca. 15§ |
| 2,3-Di-*O*-methyl-D-galactose | 10 | 38 |
| D-Altrose | 34‖ | 44¶ |
| 2,3-Di-*O*-methyl-D-altrose | >45 | ca. 80 |

*The measurements were made over prolonged periods (several weeks) until no further change was evident.

†Based on the intensity of the signal ascribed to H-1 of furanose components ($\alpha$ plus $\beta$).

‡Based on the intensity of the signal ascribed to OH-1 of furanose components ($\alpha$ plus $\beta$).

§The overlap of the doublet ascribed to furanose OH-1 with that of $\alpha$-pyranose permits only a rough estimate.

‖Based on the combined intensities of the two weakest of four H-1 signals in deuterium oxide (2).

¶Four low-field (OH-1) doublets, all of substantial intensity but of similar chemical shift, are clearly detected when an equilibrated aqueous solution is concentrated and the syrup examined in dimethyl sulfoxide. Since these signals are closely grouped, deuterium oxide was added to the solution and the percentage of furanose estimated from the appropriate H-1 signals (preceding footnote).

effective arrangement for hydrogen bonding in aqueous solutions is that involving the oxygen of water and the hydrogen of a pyranose hydroxyl group, particularly when the latter group is equatorially oriented. Since the ether derivatives contain fewer hydroxyl groups that can bond in this way, solvent stabilization of them should be minimized accordingly. The resulting data are not inconsistent with this rationalization. Thus, 2,3-di-*O*-methyl-D-arabinose (I) shows a considerably higher content of furanose in solution than does D-arabinose itself. In deuterium oxide, I produces at least three H-1 signals, whereas only two significant ones are found for arabinose (1, 2). Although unequivocal assignments have not been made, the intensity of the weakest signal shows that a minimum of 17% of furanose is present in the solution of I. A similar value (20%) is given by the OH-1 signals observed immediately after the mixture is transferred from water to dimethyl sulfoxide (compare Fig. 1A below with Fig. 5B in ref. 2). In this instance, the assignment of a furanose OH-1 signal is more straightforward since there is a corresponding upfield multiplet signal caused by a primary carbinol group (i.e. OH-5) (1, 5), the identity of which is confirmed by the use of 2,3-di-*O*-methyl-D-arabinose-5,5′-$d_2$ (II), which gives a singlet signal for OH-5 (Fig. 1C).

As with D-arabinose itself (1), the equilibrium composition of I or II changes in dimethyl sulfoxide strongly in favor of a furanose component. Figures 1C and 1D illustrate this change for I and the 5,5′-dideuterated compound (II), respectively, and the equilibrium compositions of the dimethyl ether and D-arabinose are compared in Table I. Corresponding data for 2,3-di-*O*-methyl-D-galactose included in the table show that this configurationally related sugar also tends to exist as a furanose more readily than does D-galactose itself both in water and in dimethyl sulfoxide.

An additional point about the equilibrium composition of 2,3-di-*O*-methyl-D-arabinose may be noted. This compound is an oil and, based on its nuclear magnetic resonance (n.m.r.) spectrum when freshly dissolved in dimethyl sulfoxide, has approximately the same composition as found (Fig. 1C) after it has been transferred from an aqueous solution to dimethyl sulfoxide and then equilibrated. Similarly, the H-1 signal attributed above to a furanose in deuterium oxide solution is much stronger when the spectrum is recorded

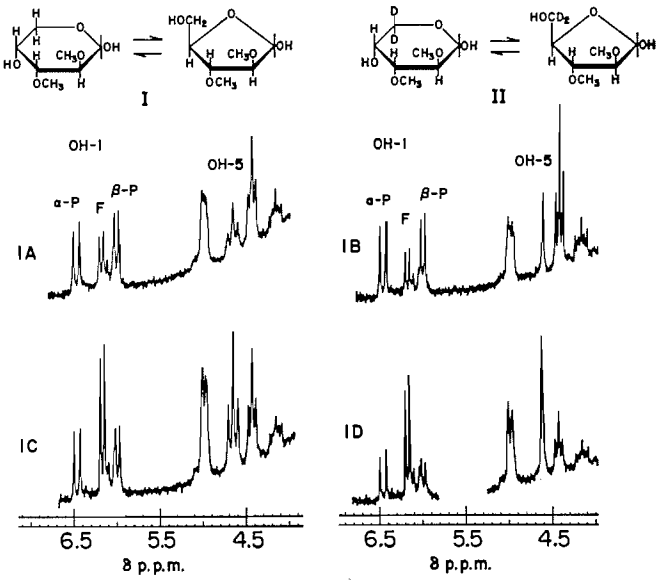


FIG. 1. Partial n.m.r. spectra at 100 Mc.p.s. of 2,3-di-*O*-methyl-D-arabinose (I) and 2,3-di-*O*-methyl-D-arabinose-5,5′-$d_2$ (II) in dimethyl sulfoxide. A and B are from the spectra of syrupy I and II directly after transfer from an aqueous solution; C and D are from the spectra recorded 2 weeks later. $\alpha$-P and $\beta$-P = $\alpha$- and $\beta$-pyranose; F = furanose.

immediately after the oil has been dissolved.[3] Hence, these observations also show that 2,3-di-*O*-methyl-D-arabinofuranose (most probably the $\alpha$-anomer) is more stable than either pyranose anomer of I when water is absent.

Since only half of the hydroxyl hydrogens of I are masked, it is not unreasonable that its equilibrium composition in water does not attain the same value as does arabinose itself in dimethyl sulfoxide, i.e. that methylation has only a partial effect in reducing the stability that could be attributed to solvation by water. However, the methyl groups also may exert a different kind of influence. Bishop and Cooper (7) have shown that some partially methylated sugars yield higher proportions of methyl furanosides than do the parent sugars under equilibrating conditions. Particularly pertinent to the present study is their finding that 2,3-di-*O*-methyl-L-arabinose yields 75% of the $\alpha,\beta$-furanosides whereas L-arabinose yields only 28%, values close to those for the free sugar equilibria in dimethyl sulfoxide. These authors suggest (7) that methylation promotes relatively stronger repulsive interactions in the pyranosides than in the furanosides by increasing the effective size of the substituents on C-2 and C-3. This idea also helps to explain the current results, although it does not account for the low proportions of furanose found in aqueous solutions. However, changes in the solvation pattern could be a complementary factor. The hydroxyl group of a sugar can form a hydrogen bond with water or dimethyl sulfoxide molecules through either its oxygen or its hydrogen atom, whereas the methoxyl group can form a hydrogen bond through only its oxygen atom. Hence, solvation should

[3]*At 1 min the estimated concentration of furanose is 34%; in 30–40 min the intensity of the signal drops to half this value (i.e. its equilibrium level), although not at a strictly exponential rate. This change provides a measure of the rate of interconversion of furanose into pyranose in water, a type of reaction that rarely has been observed in the absence of a mutarotation catalyst. The mutarotation of* D-*fructofuranose liberated by invertase is the one well-known example of this kind (6).*

increase the effective size of the methoxyl group more than that of the hydroxyl group, thereby destabilizing pyranose forms even more strongly. Similarly, dimethyl sulfoxide can form a hydrogen bond with the hydroxyl group, whereas in solvating the methoxyl group it probably interacts through its sulfur atom with the alkoxyl oxygen atom (8).

Sugars having the *xylo* or *lyxo* configuration appear to exist almost exclusively as pyranoses both in water (2, 9) and in dimethyl sulfoxide (1); accordingly, each exhibits only two anomeric proton or hydroxyl proton signals (see below, however, for an additional comment on D-lyxose). This overwhelmingly greater preference for the pyranose form is also apparent with 2,3-di-*O*-methyl-D-xylose, 2,3-di-*O*-methyl-D-glucose, and 2,3-di-*O*-methyl-D-mannose, each of which shows only two OH-1 signals[4] when equilibrated in dimethyl sulfoxide.

The relatively high stability of the altrofuranose structure is even more marked with 2,3-di-*O*-methyl-D-altrose (III), which is almost entirely in the furanose form in dimethyl sulfoxide (Table I). As seen in Fig. 2, the general characteristics of its n.m.r. spectrum show that one form greatly predominates in the solution. Although several of the signals are closely grouped together, spin decoupling permitted the chemical shifts of H-4 and H-5 to be estimated. The 6-*O*-trityl derivative of III gives a spectrum similar to that shown in Fig. 2, and permitted the H-5 signal to be located even more readily. With both compounds, irradiation at the respective frequencies of H-4 and H-5, with frequency-swept double resonance, showed that the secondary hydroxyl group proton (at 5.1 p.p.m. in Fig. 2) is coupled with H-5 but not with H-4. Hence, the 5-position of III is not engaged in ring formation, and accordingly the compound can be assigned a furanose structure. The identity of a minor component, detected from Fig. 2, is not known.

One form of 2,3-di-*O*-methyl-D-altrose is also dominant in deuterium oxide, although substantial proportions of two other components are present as well; the relative intensities

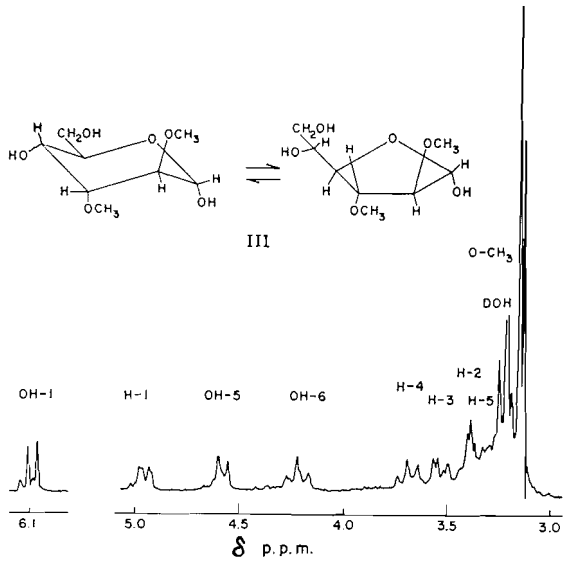


FIG. 2. The n.m.r. spectrum at 100 Mc.p.s. of 2,3-di-*O*-methyl-D-altrose in dimethyl sulfoxide-$d_6$.

[4]*The data for these signals are presented in Table IV.*

of the three anomeric proton signals detected are 1.0:2.5:2.0. The major component is likely the $\alpha$-furanose (IV) since it shows a spacing of less than 0.5 c.p.s., which is characteristic of many 1,2-*trans*-furanoses and 1,2-*trans*-furanosides. Possibly one of the other species detected is the $\beta$-furanose, and the total percentage of furanose may be higher than indicated in Table I. This is suggested by the fact that the compound consumes periodate at a rate close to that of known aldohexofuranoses and aldohexofuranosides (Table II). Although cleavage of the C-5,C-6 bond in a compound of this type could be facilitated by rapid displacement of the pyranose–furanose equilibrium, the comparatively slower rate of 2,3-di-*O*-methyl-D-galactose and the relative inertness of 2,3-di-*O*-methyl-D-glucose and 2,3-di-*O*-methyl-D-mannose are in accord with the above information about the furanose concentration of their aqueous solutions. Thus the rate for dimethyl galactose is $\frac{1}{5}$th of that of the known galactofuranoside, whereas the rate for dimethyl glucose is $\frac{1}{36}$th of that of the glucofuranose derivative (Table II). These data also show the marked contrast between the two derivatives of D-mannose substituted at positions 2 and 3, emphasizing the striking influence of the fused five-membered ring in stabilizing the D-mannofuranose structures (1, 10).

TABLE II

Periodate oxidation rates*

| Compound | $t_{\frac{1}{2}}$ |
|---|---|
| 1,2-*O*-Isopropylidene-D-glucofuranose | 40 min |
| Methyl $\beta$-D-galactofuranoside | 100 min |
| D-Mannofuranose 2,3-carbonate | 35 min |
| 2,3-Di-*O*-methyl-D-altrose | 55 min |
| 2,3-Di-*O*-methyl-D-galactose | 8 h |
| 2,3-Di-*O*-methyl-D-glucose | 24 h |
| 2,3-Di-*O*-methyl-D-mannose | 24 h |

*Measured spectroscopically at 223 m$\mu$ for highly dilute solutions (see Experimental).
These reactions were also examined directly in the n.m.r. sample tube by noting the rate of liberation of formaldehyde (10). However, at this relatively high concentration, oxidation was frequently too rapid for satisfactory measurement.

The wide differences observed between sugars having the *arabino* configuration on the one hand, and those having the *xylo* or *lyxo* configuration on the other, can be rationalized in a general way on conformational grounds (7, 11–13). Furanose forms of *arabino*-type compounds would be expected to be the more stable since their two-, three-, and four-ring substituents have a *trans,trans* arrangement, whereas one or two vicinal *cis* interactions are found in compounds of the latter two types. In the pyranose series, the relative order of stabilities is probably reversed. This additivity of effects appears to be particularly evident with D-altrose. In either pyranose chair conformation the *altro* configuration should result in substantial instability (11), whereas non-bonded interactions in the furanose forms should be comparatively slight, especially in the all-*trans* $\alpha$-anomer (IV). According to the current findings, the relative stability of furanose forms of compounds having the *arabino* configuration is enhanced by methylation and also by changing the solvent from water to dimethyl sulfoxide.

Neither of these treatments has a pronounced influence on the energy barrier separating the pyranose and furanose forms in the *xylo* and *lyxo* series. However, the effect of dimethyl sulfoxide on the two classes of compounds is quite different from that of water. In the former solvent there is a marked increase in the ratio of $\alpha$-pyranose to $\beta$-pyranose for

sugars and derivatives having the *lyxo* configuration,[5] whereas those of the *xylo* series attain nearly the same equilibrium composition in both solvents (Table III).

The overall data thus show that a change in solvent from water to dimethyl sulfoxide affects sugar equilibria in two ways. It promotes a displacement in favor of the furanose forms for compounds that would be expected to have relatively stable five membered ring structures (e.g. arabinose and galactose). With certain other sugars (e.g. mannose and lyxose) that would suffer especially unfavorable vicinal interactions as furanoses, there is a shift towards a higher proportion of $\alpha$-pyranose (axial OH-1).[6] Xylose and glucose, long

TABLE III

Equilibrium anomeric composition of aldopyranoses

| | % $\beta$-anomer | |
|---|---|---|
| | In water* | In dimethyl sulfoxide† |
| D-Glucose | 60 (64) | 62 |
| 4,6-*O*-Ethylidene-D-glucose | 60 | 63 |
| 3-*O*-Methyl-D-glucose | 58 | 57 |
| 6-Deoxy-6-fluoro-D-glucose (15) | 60 | 59 |
| D-Xylose | 62 (65) | 61 |
| D-Mannose | 36 (31) | 14 |
| 4,6-*O*-Ethylidene-D-mannose | 30 | 10 |
| D-Lyxose | 27 (24) | 12 |
| L-Rhamnose | 33 | 13 |

*Based on the relative intensity of the OH-1 signals shown by the compound in dimethyl sulfoxide. These solutions were prepared by rapidly concentrating *in vacuo* an equilibrated aqueous solution of the compound, after which the superficially dry syrup that remained was dissolved immediately in dimethyl sulfoxide. The figures in parentheses in this column are the averages of several literature values determined for aqueous solutions of these sugars by a variety of methods, including n.m.r. spectroscopy (see refs. 12 and 13).

The anomeric designation was deduced by comparison with the spectrum recorded shortly after a known crystalline anomer of the sugar was dissolved in dimethyl sulfoxide (see refs. 1 and 16).

†After the solution described above (preceding footnote) was stored for 8 weeks at room temperature. Some of the solutions were heated at 100 °C for 1–2 h, without any noticeable effect on the anomeric composition. The changes observed in the composition of the *lyxo* compounds were essentially complete within 1 week.

regarded as the most conformationally stable of the pyranoses (11), are not influenced by the solvent change. It was surmised initially that water might selectively stabilize pyranose forms of some of the sugars by hydrogen bonding, and thereby mask the relatively high stability of their furanose forms. More effective hydrogen bonding with water is also regarded as a factor that should stabilize $\beta$-pyranoses (equatorial OH-1) more than the $\alpha$-anomers (3, 12). In attempting to relate the observed changes in equilibrium in the two solvents with such hydrogen-bonding possibilities and with structural features that might be common to, for example, arabinose and mannose, one or two possibilities suggest themselves.

If, as has been suggested (3), axial groups of pyranose chair forms are not effectively solvated by water, then groups such as OH-2 of mannopyranose and OH-4 of arabinopyranose may alternatively form an intramolecular hydrogen bond with the ring oxygen

[5]*In contrast to these observations, it has been suggested recently (14) that* $\beta$-D-*mannose is stabilized by complexing with dimethyl sulfoxide. The authors have since found that this suggestion was based on incorrect information (B. Casu, private communication).*

[6]*Somewhat analogous to the effect observed with the arabino-type compounds, the ratio of* $\alpha$*-anomer to* $\beta$*-anomer also increases, even with water as the solvent, when* D-*mannose is partially methylated. Thus, deuterium oxide solutions of 2,3-di- and 2,3,4,6-tetra-O-methyl-*D-*mannose contain only 20% and 14%, respectively, of the* $\beta$*-anomer, in contrast to the value of over 30% for* D-*mannose itself (Table III). These figures are based on the relative intensity of two low-field resonance signals in each spectrum that correspond closely, both in chemical shift and spacing, to the H-1 signals of* D-*mannose.*

atoms, for which they appear to be suitably oriented. In dimethyl sulfoxide, the hydrogen-bonding pattern should be different; based on the chemical shifts of hydroxyl protons, both axial and equatorial groups are strongly bonded by this solvent (1, 5, 16, 17). Hence, if the OH-2 group of mannose (or OH-4 of arabinose) were now to be reoriented away from the molecule by association with the solvent, the oxygen orbitals should become directed inwards (3). Molecular models suggest that this arrangement would increase repulsive interactions between these orbitals and the erected para orbital of the ring oxygen (see ref. 3) (and in β-mannose, also with the O-1 orbitals). The less-favorable interaction patterns introduced by these changes presumably are relieved by a shift towards a furanose form, in one instance, or in favor of the α-pyranose form, in another. None of these considerations apply to xylose or glucose, and their equilibrium compositions accordingly are about the same in water and dimethyl sulfoxide.[7]

Some other, relatively minor differences are observed when the n.m.r. spectral properties of certain sugars in water and dimethyl sulfoxide are compared. Thus, although D-lyxose appears to exist exclusively in pyranose forms in water (2, 9), an equilibrated solution of it in dimethyl sulfoxide possibly contains a small percentage of furanose forms. This is suggested by the presence of a minor low-field signal and a shoulder on the α-H-1 signal (Fig. 3A). More striking, however, is the 3.2 c.p.s. spacing of the α-pyranose signal as compared with the 4.2 c.p.s. spacing in water. In contrast, the H-1 spacings for most of the other sugars examined are influenced little by the solvent change (Table IV). If it is accepted that the intermediate size of the 4.2 c.p.s. value reflects a chair–chair interconversion for α-D-lyxopyranose (2, 9), then the position of this equilibrium in dimethyl sulfoxide appears to be shifted strongly in favor of the C1 conformation. Although the 3.3 c.p.s. spacing is much larger than that of the configurationally related α-D-mannose, it differs little from the H-1 spacings for various other α-pyranoses in dimethyl sulfoxide (Table IV). In addition, the OH-1 spacing and chemical shift are close to those of axially oriented OH-1 groups of several other sugars, including α-D-mannose (Table IV). Therefore, the properties of D-lyxose in dimethyl sulfoxide suggest that the compound exists almost entirely as the α-pyranose and in the C1 conformation in this solvent.

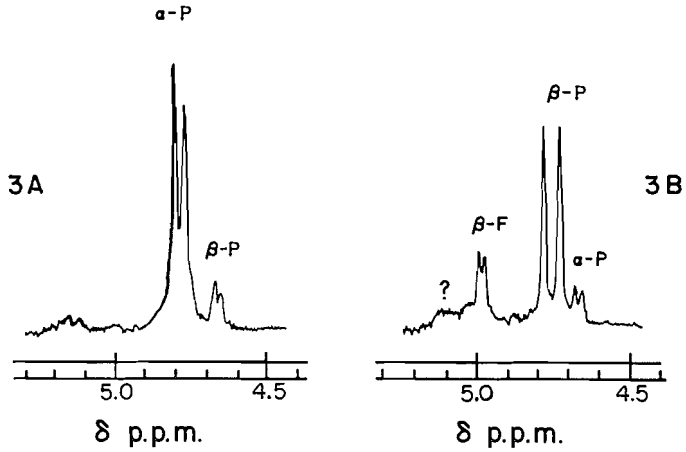


FIG. 3. Partial n.m.r. spectra at 100 Mc.p.s. of D-lyxose (A) and D-ribose (B) equilibrated in dimethyl sulfoxide-$d_6$ containing a small amount of deuterium oxide. α-P and β-P = α- and β-pyranose; β-F = β-furanose.

[7]*However, in less-polar solvents the composition of glucose shifts in favor of the α-anomer, which is thought to be due to an enhancement of the anomeric effect in such media (13). Since dimethyl sulfoxide possesses a relatively high dielectric constant, the current findings are not at variance with this view.*

TABLE IV

Nuclear magnetic resonance parameters for the anomeric protons (H-1) and hydroxyl protons (OH-1) of some aldopyranoses in dimethyl sulfoxide

| | Spacing (c.p.s.) | | | | | | |
|---|---|---|---|---|---|---|---|
| | H-1* | | OH-1 | | Chemical shift ($\delta$, p.p.m.) | | |
| | $\alpha$ | $\beta$ | $\alpha$ | $\beta$ | $\alpha$ | $\beta$ | $\delta_\beta - \delta_\alpha$ |
| D-Xylose | 3.2 (3.1) | 7.2 (7.4) | 4.5 | 6.6 | 6.00 | 6.40 | 0.40 |
| D-Lyxose | 3.2 (4.2) | 1.7 (1.4) | 4.9 | 7.9 | 6.04 | 5.92 | −0.12 |
| D-Ribose | 2.2 (2.1) | 5.3 (6.4) | 8.0 | 5.5 | 5.92 | 6.18 | 0.26 |
| D-Arabinose | 2.5 (2.8) | 6.8† (7.1) | 4.4 ($\beta$) | 6.6 ($\alpha$) | 5.88 ($\beta$) | 6.28 ($\alpha$) | 0.40 |
| D-Glucose | 3.3 (3.5) | 7.3 (7.5) | 4.5 | 6.6 | 6.06 | 6.41 | 0.35 |
| D-Galactose | 2.5 (2.8) | 7.2† (7.1) | 4.4 | 6.4 | 5.94 | 6.32 | 0.38 |
| D-Mannose | 1.5 (1.7) | 0.9 (1.0) | 4.2 | 8.0 | 6.10 | 6.00 | −0.10 |
| D-Allose | — | 7.8 (8.2) | 7.4, 5.4‡ | 6.6 | 5.88, 6.08‡ | 6.22 | 0.34, 0.14 |
| D-Altrose | ca. 1.1 (1.3) | ca. 3.0 (3.0) | — | 7.6 | | 5.92 | |
| Miscellaneous derivatives | | | | | | | |
| 2,3-Di-*O*-methyl-D-xylose | | | 4.5 | 6.4 | 6.15 | 6.60 | 0.45 |
| 2,3-Di-*O*-methyl-D-arabinose | | | 4.5 ($\beta$)§ | 6.8 ($\alpha$)§ | 5.98 ($\beta$)§ | 6.43 ($\alpha$)§ | 0.45 |
| 2,3-Di-*O*-methyl-D-galactose | | | 4.5 | 6.6 | 6.03 | 6.50 | 0.47 |
| 2,3-Di-*O*-methyl-D-glucose | | | 4.5 | 6.6 | 6.20 | 6.60 | 0.40 |
| 2,3-Di-*O*-methyl-D-mannose | | | 4.0 | 8.0 | 6.30 | 6.28 | −0.02 |
| L-Rhamnose | | | 4.1 | 8.2 | 6.02 | 5.93 | −0.11 |
| L-Fucose | | | 4.3 | 6.4 | 5.86 | 6.24 | 0.38 |
| 3-*O*-Methyl-D-glucose | | | 4.4 | 6.3 | 6.13 | 6.47 | 0.34 |
| 3,4-*O*-Isopropylidene-2-*O*-methyl-D-arabinose | | | 4.4 ($\beta$)§ | 6.4 ($\alpha$)§ | 6.32 ($\beta$)§ | 6.68 ($\beta$)§ | 0.36 |
| 4,6-*O*-Ethylidene-D-galactose | | | 4.3 | 6.8 | 6.05 | 6.38 | 0.33 |
| 4,6-*O*-Ethylidene-D-glucose | | | 4.7 | 6.6 | 6.31 | 6.63 | 0.32 |
| 4,6-*O*-Ethylidene-D-mannose | | | 4.3 | 8.4 | 6.33 | 6.15 | −0.18 |

*The values in parentheses are spacings for the corresponding signals in deuterium oxide; these agree closely with the values already reported by Lemieux and Stevens (2).
†Outer spacings; secondary splitting is evident.
‡Minor signals, probably caused by $\alpha$-pyranose and $\beta$-furanose.
§Anomeric designations based on analogy with D-arabinose itself.

The n.m.r. spectrum of D-ribose in dimethyl sulfoxide differs in several respects from that in deuterium oxide. A weak low-field multiplet ascribed by Lemieux and Stevens (2) to H-1 of either the $\alpha$-furanose or *aldehydo* form is replaced in the spectrum of the dimethyl sulfoxide solution by a broad, ill-defined signal comprising about 18% of the overall integral of the absorption signals in this region (Fig. 3B). The percentage contribution of the $\alpha$-pyranose signal drops from 20% (2) to 10%, whereas the relative intensities of the $\beta$-furanose (21%) and $\beta$-pyranose (51%) H-1 signals are altered little. Perhaps most notable are the characteristics of the $\beta$-pyranose. There is a decrease in the H-1 spacing from 6.4 c.p.s. in deuterium oxide (2) to 5.3 c.p.s. in dimethyl sulfoxide, and the OH-1 spacing is considerably smaller than those for equatorial anomeric hydroxyl groups of other sugars (Table IV, and see the next paragraph). Hence, it appears to be unlikely that $\beta$-D-ribopyranose exists entirely in the C1 conformation in dimethyl sulfoxide, in contrast to its behavior in water (2, 9). Both the H-1 and OH-1 signals for $\alpha$-D-ribopyranose are consistent with the 1C conformation attributed to this isomer in deuterium oxide (2, 9), although, as shown above by the low percentage detected, its structure is also relatively unstable in dimethyl sulfoxide. Therefore, the overall data suggest that D-ribose equilibrates in dimethyl sulfoxide to a number of forms, each of which incorporates relatively strong destabilizing interactions.

The data in Table IV permit the generalization, which has been proposed also by Casu *et al.* (17), that anomeric pyranose pairs show characteristically different OH-1 spacings. Thus, equatorial group proton signals have relatively large spacings of 6.5–8 c.p.s., whereas the axial group protons show spacings of 4.5–5 c.p.s. Although this is analogous to the fact that the axial OH signal for *cis*-4-hydroxy-*t*-butylcyclohexane has a smaller spacing than that for the equatorial *trans*-isomer (5), secondary axial and equatorial hydroxyl groups of sugars and derivatives are not as readily differentiated (ref. 17 and unpublished observations). However, the size of the hydroxyl proton spacings appears to be indicative of the orientation of the hydroxyl group of 1,4-dioxane type hemialdals (18).

Chemical shift values for anomeric hydroxyl protons also show some consistent trends. When there is an equatorial 2-*O*-substituent, the equatorial OH-1 signal occurs at lower field than that of the axial OH-1 by about 0.4 p.p.m., whereas their relative positions are reversed (by about 0.1 p.p.m.) when the substituent is axial. (Several derivatives of D-mannose, in addition to those listed, containing an *O*-acetyl, *O*-methyl, or *O*-benzyl group at C-2 give results closely similar to that for D-mannose itself.) Since 2-deoxy-D-xylohexose shows $\delta_e - \delta_a$ of 0.4 p.p.m. (17), it may be inferred that an axial oxygen at C-2 promotes increased shielding of an equatorial 1-hydroxyl proton, perhaps by weakening its ability to form a bond with dimethyl sulfoxide.

## EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded on a Varian HA-100 high-resolution spectrometer with tetramethylsilane contained in a coaxial capillary as the internal control reference signal. Spin-decoupling operations were carried out with the frequency-sweep mode facility of this instrument.

Except for 2,3-di-*O*-methyl-D-xylose (kindly provided by Dr. E. E. Percival), none of the di-*O*-methyl aldoses used in this study are crystalline. However, each of the syrupy compounds was shown to be pure, as judged by paper chromatography with four different solvent systems. Where possible, the sugar was obtained by acid hydrolysis or acetolysis of a crystalline glycoside.

*Methyl 4,6-O-Ethylidene-2,3-di-O-methyl* $\beta$-D-*Mannopyranoside*

4,6-*O*-Ethylidene-D-mannose (300 mg) (a gift from Dr. D. H. Ball) was dissolved in warm methanol (1.0 ml), and methyl iodide (10 ml) was added, followed by anhydrous calcium sulfate (2 g) and silver oxide (5 g). The suspension was shaken for 24 h, diluted with chloroform, and filtered; then the filtrate was concentrated. Methyl iodide (10 ml), anhydrous calcium sulfate (2 g), and silver oxide (4 g) were added to the

residue and the mixture was heated under reflux for 48 h. Chloroform-extractable material was recovered, and the second methylation procedure repeated. The chloroform-soluble product (0.37 g) crystallized and, after recrystallization from petroleum ether, melted at 70–71 °C; $[\alpha]$ −95° (*c*, 1.2 in chloroform).

Anal. Calcd. for $C_{11}H_{20}O_6$: C, 53.21; H, 8.06. Found: C, 52.9; H, 8.1.

*2,3-Di-O-methyl-*D*-mannose (19), 2,3-Di-O-methyl-*D*-glucose (20), and 2,3-Di-O-methyl-*D*-galactose (21)*

These were prepared by acid hydrolysis of the appropriate crystalline 4,6-*O*-ethylidene or 4,6-*O*-benzylidene methyl glycoside. For example, methyl 4,6-*O*-ethylidene-2,3-di-*O*-methyl β-D-glucoside (22) (m.p. 107–108°C) (150 mg) was hydrolyzed with 1 *N* sulfuric acid (10 ml) on the steam bath for 7 h. The hydrolysate was neutralized with barium carbonate, and filtered; then the solution was treated with Amberlite IR-120 ($H^+$) and charcoal, and concentrated *in vacuo* at 50 °C.

*2,3-Di-O-methyl-*D*-arabinose (23) and 2,3-Di-O-methyl-*D*-arabinose-5,5′-$d_2$*

These were prepared by hydrolysis, for 2 h with hot 0.5 *N* sulfuric acid, of methyl 2,3-di-*O*-methyl-α,β-D-arabinofuranoside and the 5,5′-dideuterated compound, respectively, which were synthesized according to the procedure described recently by Heyns and Muller (24).

*2,3-Di-O-methyl-*D*-altrose*

4,6-*O*-Benzylidene-2,3-di-*O*-methyl α-D-altropyranoside (25) (m.p. 85–86 °C) (160 mg) was dissolved in a 200:1 mixture of acetic anhydride and concentrated sulfuric acid (2 ml), and stored at 3 °C for 72 h (26). After an additional 48 h at room temperature, the solution was added to crushed ice, and carefully neutralized with sodium bicarbonate; then the aqueous suspension was extracted several times with chloroform. The combined extracts were dried and concentrated to yield a syrup (212 mg), which was dissolved in cold sodium methoxide (0.1 *N*, 2 ml). After 18 h at 3 °C the deacetylation mixture was neutralized with carbon dioxide, water was added, and the solution was treated with mixed-bed ion-exchange resins and concentrated. The chromatographically pure syrup (100 mg) had $[\alpha]$ +31° (*c*, 1.4 in water). The n.m.r. spectrum in dimethyl sulfoxide-$d_6$ (Fig. 2) showed that the product contained three hydroxyl groups: anomeric, secondary, and primary.

Attempts to prepare an anilide and a diphenylhydrazone failed to yield solid derivatives.

The di-*O*-methyl derivative (30 mg) was treated with triphenylchloromethane (70 mg) in dry pyridine (2 ml) for 24 h. Ice water was added, the tacky precipitate was recovered with thorough washing and dissolved in ethanol, and triphenylcarbinol was removed by repeated crystallization. The syrupy residue (52 mg) was shown by thin-layer chromatography (benzene–methanol (9:1)) to consist of one component contaminated with a trace of triphenylcarbinol. The n.m.r. spectrum of this compound, recorded in dimethyl sulfoxide, showed the presence of approximately 15 phenyl protons per 2 hydroxyl protons, consistent with the formulation of this product as 2,3-di-*O*-methyl-6-*O*-trityl-D-altrose.

*Periodate Oxidations*

An aqueous solution (2 ml) containing about 0.2 μmole of the sugar derivative was diluted with aqueous sodium metaperiodate (2 ml, containing 0.24 μmole of oxidant). Blank periodate and iodate solutions were also prepared by diluting the standard periodate solution (2 ml aliquots) with equal volumes of water or ethylene glycol solutions, according to the modification of Aspinall and Ferrier (27). Each reaction mixture was stored at 22 °C, and its optical density at 223 mμ was measured at chosen intervals.

Some typical periodate uptake data (mole/mole), from which the $t_{\frac{1}{2}}$ values listed in Table II are taken, are as follows.

| | Time (min) | | | | | | |
|---|---|---|---|---|---|---|---|
| Compound | 10 | 30 | 60 | 80 | 120 | 240 | 1440 |
| 1,2-*O*-Isopropylidene-D-glucofuranose | 0.18 | 0.41 | 0.62 | 0.72 | | | |
| D-Mannose 2,3-carbonate | 0.22 | 0.46 | 0.67 | 0.77 | | | |
| Methyl α-D-galacto-furanoside | 0.10 | 0.23 | 0.36 | 0.44 | 0.56 | | |
| 2,3-Di-*O*-methyl-D-altrose | 0.14 | 0.37 | 0.52 | 0.62 | 0.75 | | |
| 2,3-Di-*O*-methyl-D-galactose | | | | | 0.12 | 0.37 | 0.91 |
| 2,3-Di-*O*-methyl-D-glucose | | | | | | 0.11 | 0.49 |
| 2,3-Di-*O*-methyl-D-mannose | | | | | | 0.14 | 0.51 |

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