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HEXOPYRANOSE SUGARS CONFORMATION REVISED

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Abstract—Literature data for the conformations of ido- and altropyranose derivatives have been reexamined in the light of the newer values recently reported (Eliel *et al. J. Am. Chem. Soc.* **104**, 3635 (1982) for the conformational free energy of methyl and hydroxymethyl substituent at position 2 in tetrahydropyran. The conclusion is that these values readily explain why the D-$^4C_1$ (D-$^1C_4$) chain form is more prevalent than predicted beforehand. Cases of poor agreement between the vicinal proton–proton coupling constants and the dihedral angles in their chair form may be interpreted by mixing with the S_2^0 skew conformation, rather than the D-$^1C_4$ (L-$^4C_1$) chair form.

Two chair conformations have been considered so far for the pyranose sugars, called D-$^4C_1$ (or L-$^1C_4$) and D-$^1C_4$ (or L-$^4C_1$) (conformations *a* and *b* and their mirror images). The approximate free-energy content of each one has been estimated for the sixteen α- and β-D-aldohexopyranoses by summation of quantitative free-energy terms for conformational interaction-energies of various groups, also taking into account the value of the anomeric effect for the C–1 substituent.[1] These calculations predict an overwhelming proportion of the D-$^4C_1$ conformer for the twelve configurations of the D-series other than D-*ido* and D-*altro*. This is borne out by experience, and for convenience, we shall call this conformation the usual one in this paper. However the predictions were not always successful. Thus in the case of acetylated derivatives of α-D-ido-pyranose, various estimates[1,2] predicted a conformational mixture, **1a**, **1b** in solution while only the usual conformation **1a** could be observed, in spite of its four axial substituents.[3] The necessity to look for other, unknown effects was stressed in a Review article.[4] Generally speaking, the usual chair form appeared more prevalent than expected among D-*ido* and D-*altro* derivatives.

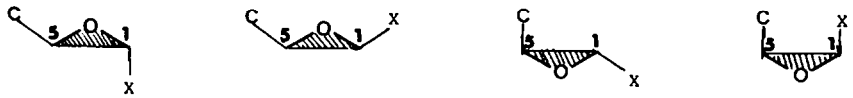
In these calculations,[1] the value adopted for the conformational free energy, $-\Delta G°$ of the side-chain in hexopyranoses was 1.8 kcal/mol, not very different from that of a Me in a cyclohexane ring. However, in a recent paper, Eliel *et al.*[5] gave methods for calculating the conformational free-energies of Me, CH_2OH and Et substituents at position 2 in a tetrahydropyran ring, which were found to be 2.86, 2.89, and 2.62 kcal/mol respectively, at $-100°$. The authors pointed out the interest of these figures for hexopyranose chemistry. In the present paper, we shall examine the *ido*- and *altro*-pyranose anomalies in the light of these new findings.

DISCUSSION

This increase in conformational free-energy was explained by its discoverers as the consequence of enhanced *syn*-diaxial repulsions between substituents at position 2 and 6 of a tetrahydropyran ring because of the short C–O bond. This is a classical steric hindrance consideration, which would be described in molecular orbitals terminology as a destabilizing interaction between filled orbitals. On the other hand, it has been known for some time that certain anomeric substituents have a preference for the equatorial position which appears greater than expected on steric grounds (see, for instance,[6] as an early paper on the subject). This was called the reverse anomeric effect, a name which suggests the operation in reverse of the mechanism of the anomeric effect which is a stabilizing interaction between filled and empty orbitals.[7] To avoid mechanistic implications, which would be out of the scope of this paper, the correction introduced by the Eliel group will be named the *proximity correction*. The four possible conformations near the ring oxygen of a pyranose sugar are depicted in Fig. 1. As well known, conformation I is the most stable one, but because of the proximity correction, conformation III is 1.1 kcal/mol more destabilized than formerly believed. Truly it has been observed once in the solid state, but in the extreme case of methyl 2,4-bis(N-acetyl-N-benzoylamino)-3, 6-di-O-benzoyl-2,4-dideoxy-α-D-idopyranoside, with two substituents of enormous bulk.[8] Now, if the repulsion between the C–5 substituent and the anomeric hydrogen is already prohibitive, it seems that conformation IV should be totally ruled out, despite its anomeric stabiliztion, because of the even greater bulk of X relative to hydrogen. Besides, the demonstrated[7] transfer of electrons from oxygen to the axial anomeric substituent which increases its bulk, and the shortening of the O–C(1) bond, both act in the direction of an increase of diaxial repulsion.

The most stable local conformation I is present in the usual chair form. Thus, because of the proximity correction, the D-$^4C_1$ conformations of the twelve sugars of the first group are even more stable than formerly calculated. Furthermore, we expect the same chair forms to be more prevalent (if not exclusive) in conformational equilibria involving D-altrose and D-idose derivatives. This is an attractive explanation to the anomalies mentioned in the introduction.

But the local conformation I is also present in the S_2^0 skew conformat *c*. Such is the solid-state conformation[9] of methyl 4,6-O-(S)-benzylidene-2-chloro-2-deoxy-α-D-idopyranoside **31** (depicted in



I II III IV

Fig. 1. The four possible disposition of the C–5 and anomeric substituents of a D-pyranose sugar.

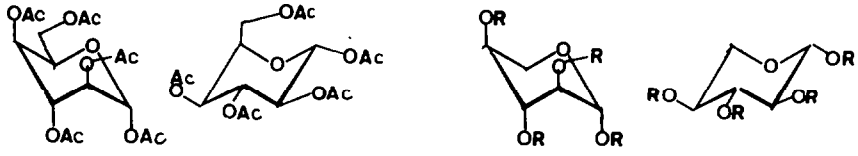
the usual chair form, which is a conformation present in solution). The three substituents on C–2, C–3 and C–4 lie in the optimal, almost equatorial orientation. To this we may add that the shifting downward of C–2, which changes the usual to the S_2^0 conformation appears to bring the antibonding anomeric orbital more coplanar, and nearer to the ring oxygen *p* type lone pair orbital, thus allowing for a stronger anomeric stabilization. Furthermore, the flexibility of the skew form, which allows it to respond easily to the effect of solvents by minor changes in conformation could be an alternative explanation of the variability of ^{1}H NMR parameters with solvents which has been often reported in the *ido* series (see, *inter alia*[10]). Calculation of the dihedral angles in **31** from 1–H to 4–H with the use of the reported atomic coordinates gives the figures 123°, 178°, 132° and 44°. These in turn correspond to the following proton–proton vicinal coupling constants (without correction for electronegativity): 2.5; 9; 3.5; 4.0 Hz. Now the benzylidene acetal ring may lock one particular skew conformation. For the "ideal" skew form,[11] the corresponding set of values would be 6.5; 8.5; 6.5; 6.0 Hz and these parameters would not allow an easy diagnosis between the S_2^0 and D-$^1C_4$ conformation.[12] Reported data will be now reexamined.

(a) *Acylated α-D-idopyranoses.* We shall discuss in this section and the following one esters with at least three acyl substituents.

In view of the near equality of conformational free-energies for Me and CH_2OH, we feel justified to adopt the same value, 2.9 kcal/mol for CH_2OAc. Its variation with temperature, and its dependence upon any solvent of low polarity will be neglected. Our method involves the summation of only two terms, one of them being this corrected free-energy value. The other one is the experimentally measured free-energy difference in a conformational equilibrium, a figure endowed with a rigorous physical meaning, and estimated with a known margin of error. Let us first consider the conformational equilibrium of per-O-acetyl-β-L-xylopyranose **2** (actually reported on the β-D-sugar)[13]:

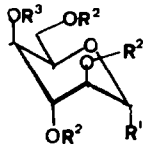
2a ⇄ **2b** $\quad \Delta G° = -0.58 \pm 0.30$ kcal/mol

a, D-$^4C_1$ b D-$^1C_4$ c D-S_2^0



1a 1b

2a R = Ac 2b R = Ac
3a R = Bz 3b R = Bz



4 R^1 = OAc R^2 = Ac R^3 = H
5 R^1 = I R^2 = R^3 = Ac
6 R^1 = O-C_6H_4-NHAc, R^2 = R^3 = Ac
7 R^1 = O-C_6H_4-NO_2, R^2 = R^3 = Ac

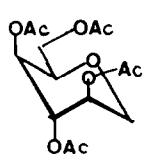
Substitution of the pro-S 5–H in **2** by CH_2OAc gives the per-O-acetyl-α-D-idopyranose configuration **1**. Let A be the conformational free energy of CH_2OAc, the free-energy difference for the equilibrium **1a**, **1b** is now $A - 0.58 \pm 0.30$ kcal/mol. Calculation of log k at 25° shows that the proportion of **1b** should lie between 7 and 22% for $A = 1.8$ kcal/mol, and between 1 and 3% for $A = 2.9$ kcal/mole. Experimentally, conformation **1b** was not detected in the mixture.[3] Then, it is not surprising that the usual conformation should be found in acetylated α-D-idopyranosides when the anomeric substituent has an anomeric effect equal to, or stronger than that of O-acetyl. Such is the case with the tetracetate **4** ($J_{1,2}$ 2.0–3.2 Hz, depending on the solvent),[10] the iodide **5** ($J_{1,2}$ 0.9 Hz)[14], and the tetra-O-acetyl aryl pyranosides **6** and **7** with *p*-acetamido and *p*-nitrophenyl aglycones ($J_{1,2}$ 0 Hz in both cases).[15] Starting from the conformational equilibrium (known in the D series)[13]:

$$\mathbf{3a} \rightleftarrows \mathbf{3b} \qquad \Delta G = 0.01 \pm 0.21 \text{ kcal/mol},$$

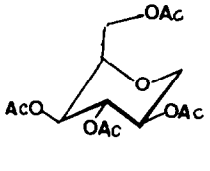
the same reasoning as above predicts the per-O-benzoyl-α-D-idopyranose will adopt exclusively the usual chair conformation, as all its analogues with an equally or more powerful axial anomeric substituent.

These examples, **1** and **3–6**, might suggest that the exclusive adoption of the usual chair form needs simultaneous stabilization by the anomeric effect and proximity correction. Clearly this is not the case: 1,5-anhydro-tetra-O-acetyl-D-iditol **8**,[16] which has no anomeric substituent, also adopts exclusively the usual chair form, as evidenced by the very small couplings of 2–H to both 1–H's, observed on the 240 MHz spectrum of a sample dissolved in $CDCl_3$: δ 3.87 (dd, 1H, $|J_{1,1'}|$ 13.1 Hz, $J_{1,2}$ 2.1 Hz, 1–H axial), 4.08 (dd, 1H, $J_{1,2}$ 1.7 Hz, 1–H equatorial).[17] This anhydro sugar should be compared to tetra-O-acetyl-α-D-xylopyranoside **9a** (drawn for convenience in this unusual way). Conformation **9a**, the only observable one, was estimated to be more stable than **9b** by at least 2.4 kcal/mol.[13] (The actual figure may be much higher as all substituents in **9a** lie in the most favourable position). Now the anhydro-iditol **8** derives on paper from **9** by the replacement of the acetoxy group, with an anomeric effect, by the CH_2OAc group. This involves a proximity correction: the result is a dramatic shift of the conformation, from triequatorial in the first tetra-O-acetate (**9a**) to tri-axial (**8a**) in the second one.

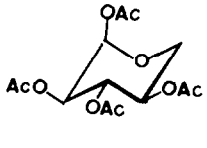
The next obvious step is to examine tri-O-acetyl-1,5-anhydroxylitol **10**, with no substituents on the carbons vicinal to the ring oxygen. The 60 MHz ^1H NMR spectrum in $CDCl_3$ confirmed the depicted, expected tri-equatorial conformation [δ 3.25 (2H, dd, $J_{1l'} = J_{5'5} = 11$, $J_{1,2} = J_{4,5} = 8$ Hz, axial protons 1–H and 5–H), 3.98 (2H, dd, $J_{1',2} = J_{4,5'} = 4.5$ Hz, equatorial 1'–H and 5'–H protons), 4.88 (2H, ddd, 2–H, 4–H), 5-11 (1H, pseudo triplet, $J_{2,3} = J_{3,4} = 7.5$ Hz, 3H)].[16,17] Starting from tri-O-acetyl-1,5-anhydroxylitol **10**, introduction of a bromine atom on C–1 or



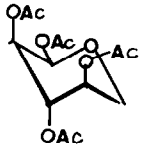
8a



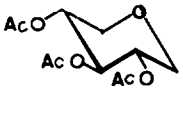
8b



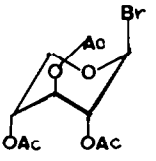
9a



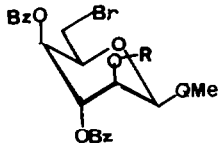
9b



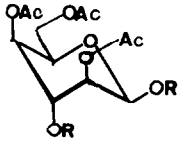
10



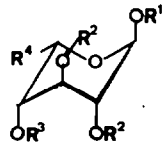
11



12 R = CHO
13 R = Bz



14 R = Me
15 R = Ac



16 $R^1 = R^2 = CH_2Ph$ $R^3 = H$ $R^4 = Me$
17 $R^1 = R^2 = CH_2Ph$ $R^3 = H$ $R^4 = CO_2Me$
18 $R^1 = Me$ $R^2 = R^3 = H$ $R^4 = CO_2^-$
19 $R^1 = Ac$ $R^2 = R^3 = CH_2Ph$ $R^4 = CH_2OCH_2Ph$

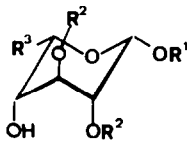
C-5 *trans* to the vicinal acetoxy group gives the configuration of tri-O-acetyl-β-xylopyranosyl bromide. Because of the anomeric effect of bromine, this compound exists only in the tetra-axial conformation **11** (or its mirror image).[18] Again starting from **10**, the introduction of CH_2OAc *cis* to the vicinal acetoxy groups gives the configuration of 1,5-anhydro-iditol, **8a** (or its mirror image). We see that the tendency of CH_2OAc to lie in the equatorial position, when reinforced by the proximity correction is in fact comparable to the powerful anomeric effect of bromine, in forcing the three ring acetoxy group to lie in the axial position.

(b) *Acylated β-D-idopyranosides.* Despite the loss of anomeric stabilization, we expect them to adopt the usual chair form, to avoid the prohibitive repulsion inherent to conformation IV (Fig. 1). The values for vicinal proton–proton coupling constants show that this is the case for methyl 3,4-di-O-benzoyl-6-bromo-6-deoxy-2-O-formyl-β-D-idopyranoside **12**, and methyl 2,3,4-tri-O-benzoyl-6-bromo-6-deoxy-β-D-idopyranoside **13** in $CDCl_3$,[19] and methyl 2,4,6-tri-O-acetyl-3-O-methyl-β-D-idopyranoside **14** in $CDCl_3$.[10] Penta-O-acetyl-β-D-idopyranose **15** in C_6D_6 shows rather high coupling constants, $J_{2,3} = J_{3,4} = 5$ Hz for *trans* diequatorial protons,[10] but we would rather explain it by a conformational equilibrium involving a non chair conformation rather than a D-$^1C_4$ chair form.

(c) *Glycosides, ethers, acetals and uronic acids derivatives with the ido configuration.* The above data show that the usual chair form is exclusive, or in any case, highly prevalent in acylated derivatives. This has several times been related to a specific property of acyl groups. While the proximity correction seems to be the most important cause, it is reasonable to consider that the bulk of the O atoms next to the ring which is a manifestation of the repulsion of electrons in filled orbitals will be decreased by electronegative substituents as acyl and increased by electron-donating alkyl groups. Evidence for a conformation other than the usual has been found among ethers. However, ^1H NMR spectroscopy indicated the seemingly exclusive presence of the usual conformation in the following pyranose derivatives: benzyl 2,3-di-O-benzyl-6-deoxy-α (**16**) and β (**20**)-L-idopyranoside, methyl 4,6-di-O-acetyl-2,3-di-O-methyl-α (**24**) and β (**26**)-D-idopyranoside,[10] methyl 4,6-O-(S)-benzylidene-α-D-idopyranoside (**27**) and its di-O-acetate (**30**),[21] methyl 4,6-O-(S)-benzylidene-3-O-methyl (**32**)-, 2,3-di-O-methyl (**33**)-β-D-idopyranoside, and the 2-O-acetate **34**,[21] 1-O-acetyl-2,3,4,6-tetra-O-benzyl-α-L-idopyranoside (**19**),[22] and the (*R*) isomer[23] of acetal **27** in $CDCl_3$, methyl (benzyl-2,3-di-O-benzyl-α (**17**) and β (**21**)-L-idopyranoside) uronate in C_6D_6,[24,25] and sodium (methyl-α-L-idopyranoside) uronate (**18**),[26] methyl 3-O-methyl (**38**) and 2,3-di-O-methyl (**39**)-α-D-idopyranoside[23] in water. There was spectroscopic evidence for intramolecular H-bonding in some of the above compounds with free 4-OH. However the argument that this was the cause of the adoption of the usual chair form in non polar solvents does not seem generally valid, for the partially methylated α-D-idopyranosides **37** and **38** show the usual conformation in water solution. The argument seems also contradictory to the opinion that the permethylated α-D-idopyranoside **23** adopts this same usual conformation in water because of chelating water bridges. However, some of the above pyranosides, when examined in other solvents, exhibited important spectral changes indicative of conformational variations. A skew form was considered as an alternative to the non usual chair form when this was deemed impossible.[23] Thus, in the case of the (*S*)-benzylidene acetals **27** to **31** the D-$^1C_4$ chair form would involve prohibitive interactions with the phenyl group. The trend of ^3J values[21] in this case are clearly compatible with those recalculated from the parameters reported for the solid-state structure **31**, assuming more or less mixing with the usual chair form.

But non-acetalized idopyranosides may also show coupling constants imcompatible with the exclusive presence of the usual conformation. We shall first examine the α-D-pyranose itself, **35** and its methyl α-D-glycoside **36** for which a semi-quantitative treatment is possible. From the $J_{1,2}$ value of α-D-*ido*pyranose in water, i.e. 5.6 Hz, the sugar was considered to be a mixture of the two chair forms with 66% of the non usual one,[1] a figure which appeared to agree very well with the result of the semi-quantitative estimation.[1] But the introduction of the proximity correction, 1.1 kcal/mol in the estimation of the free-energy difference between the two chair forms, and the further small correction for the anomeric effect of OH, finally reduces to 17% the expected proportion of the non usual chair form. Now, this figure does not seem compatible with experiment, despite the uncertainties inherent to these calculations. For methyl α-D-idopyranoside, the slight increase in anomeric stabilization, estimated as 0.3 kcal/mol, should lessen again the proportion of the non usual chair form, now calculated as 11%, a figure clearly incompatible with the reported 7.2 Hz $J_{2,3}$ value in water. This seems to give the answer to the question,[23] whether skew forms could be observed in derivatives other than benzylidene acetals. The trend of ^3J value measured[21] with compound **25**, which corresponds to dihedral angles similar to those of crystalline **31** may be a characteristic of the skew form of benzylidene acetals. Other ones are possible, as pointed above, and this flexible conformation should be quite compatible with $J_{1,2}$ and $J_{3,4}$ values near 6 Hz. For this reason, we consider legitimate to interpret as the indication of an equilibria between the usual chair form and the S_5^3 skew form the coupling constants observed on some spectra of **4**, **23**, **24**, **25**,[10] **19**,[26] **35**, **36** and **37**.[23]

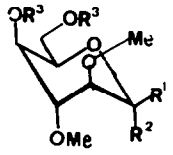
(d) α-D-*Altropyranose* **40**. The calculation indicated that the usual chair form was stabilized by 0.20 kcal/mol.[1] As a consequence of this narrow margin, one would predict near equal proportions of the two chair forms, a prediction which is impossible to conciliate with the experimental[27] $J_{1,2}$ value, of 3 Hz. When one takes the proximity correction into account, the usual chair form is found to be 1.3 kcal/mol more stable than the alternative one. The equilibrium concentration of this should be no more than 10%, and drop to 7% if we adopt a corrected value for the anomeric effect. Nevertheless, in the *altro* series, a slight deformation towards the S_2^0 conformation, or an equilibrium between the usual chair and S_2^0 conformation may eventually be observed. Methyl 2-deoxy-2-iodo-3,4-O-isopropyl-



20 R^1= CH_2Ph = R^2 R^3= Me

21 R^1= R^2= CH_2Ph R^3= CO_2Me

22 R^1= Me R^2= H R^3= CO_2^-

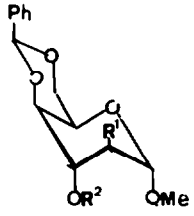


23 R^1= H R^2= OMe R^3= Me

24 R^1= H R^2= OMe R^3= Ac

25 R^1= OMe R^2= H R^3= Me

26 R^1= OMe R^2= H R^3= Ac



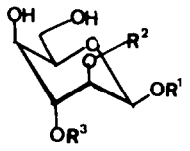
27 R^1= OH R^2= H

28 R^1= OMe R^2= Me

29 R^1= OMe R^2= H

30 R^1= OAc R^2= Ac

31 R^1= Cl R^2= H



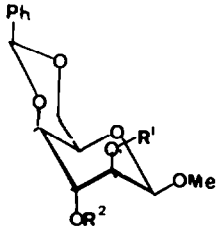
35 R^1= R^2= R^3= H

36 R^1= Me R^2= R^3= H

37 R^1= R^2= Me R^3= H

38 R^1= R^3= Me R^2= H

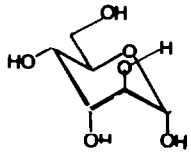
39 R^1= R^2= R^3= Me



32 R^1= H, R^2= Me

33 R^1= R^2= Me

34 R^1= Ac R^2= Me



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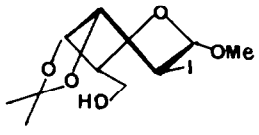

41

idene-α-D-altropyranoside (**41**),[28] which is locked in the S_2^0 conformation, shows the following vicinal coupling constants from $J_{1,2}$ to $J_{3,4}$: 6.0, 8.8, 6.6, 8.5 Hz. Any trend towards such value in altropyranoside derivatives may be an indication of a certain amount of skew form in the conformational equilibrium.

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