^1H N.M.R. Spectra and Conformations of Three Heptitols in Deuterium Oxide

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Shifts and coupling constants, obtained by computer simulation of the ^1H n.m.r. spectra of three heptitols in deuterium oxide, have been used to derive conformational data which support earlier conformational studies on these heptitols, thereby completing the study of all 4-, 5-, 6-, and 7-carbon alditols.

Acyclic polyols have preferred solution conformations which minimise parallel 1,3-interactions.[1] The tetritols (erythritol and threitol) have rather flexible chains because several of the conformers lack serious 1,3-interactions. For the pentitols and hexitols the chain is a planar zig-zag except where this would yield a 1,3-oxygen–oxygen (O‖O) interaction. Such an interaction can be relieved by a rotation of the chain to give a less strained[2] H‖C (*i.e.*, C|C *gauche*) interaction.[3] In allitol both of the O‖O interactions present in the planar chain conformer can also be relieved by a rotation of the chain to give a C‖O interaction. The heptitols present a great variety of conformations, ranging from the D-*glycero*-D-*galacto*-isomer, with a relative strain-free planar chain, to those isomers with no conformation free of serious 1,3-interactions.[4–7] Of the ten heptitols, conformational analysis based on ^1H n.m.r. spectra is reported for seven and partial data are presented on an eighth isomer.[4,7] This work gives complete data for the eighth isomer and the two remaining heptitols. The conformations of these three isomers are especially interesting since they are each sterically congested. Two of them, *meso-glycero-ido-** and *meso-glycero-allo*-heptitol, would have three O‖O interactions in their planar conformations, making them very unstable. The third, *meso-glycero-altro*-heptitol, has only one O‖O interaction in its planar form but it has no possible conformation free of 1,3-interactions; hence it could be the only alditol predominantly in a planar form having an O‖O interaction.

Results and Discussion

Spectral Data.—The Table lists the proton chemical shifts and proton–proton coupling constants of the heptitols studied.

Table. Proton chemical shifts[a] (ppm) and proton–proton coupling constants/Hz for the heptitols in D_2O.

	(1)	(2)	(3)[b]
H-1	3.78	3.88	3.765
H-1′	3.70	3.73	3.74
H-2	3.90	3.97	4.07
H-3	3.82	3.94	3.87
H-4	3.865	3.97	3.92
$J_{1,1'}$	−11.5	−11.85	−11.25
$J_{1,2}$	4.25	3.1	5.2
$J_{1',2}$	6.8	6.85	7.25
$J_{2,3}$	4.25	6.0	2.05
$J_{3,4}$	4.55	5.9	6.75

[a] Compounds referenced to external sodium 3-(trimethylsilyl)propionate (TSP). The HDO peak at δ 4.835 was used to ensure internal consistency of the spectra. Primary geminal protons are distinguished by means of a prime for the proton having the larger coupling constant to the adjacent proton. [b] Lit.,[7] 3.61, 3.61, 3.93, ~3.73, 3.77, −11.0, 5.0, 6.8, 1.8, and 7.

Conformational Data.—The three most likely conformers of *meso-glycero-ido*-heptitol (**1**) are assumed to be (*a*) $_2G^-$, $_4G^-$,* *i.e.*, O(2)–O(5) planar, (*b*) $_3G^+$, *i.e.*, O(3)–C(7) planar, and (*c*) $_2G^-$, $_5G^+$, *i.e.*, O(2)–O(6) planar. The main 1,3-interactions in (*a*), (*b*), and (*c*) are two H‖C; an H‖C and an O‖O; and two H‖C and an O‖O. Calculated ^3J values of H–C–C–H fragments were obtained using an empirical Karplus-type equation which allows[8] for the orientation and electronegativity of substituents about the coupling protons. The observed ^3J value for the H(2)–H(3) bond was equated to the sum of the products of the calculated[3] ^3J value for this coupling in each conformer and its amount (x). Equating the H(3)–H(4) coupling correspondingly, and assuming $\Sigma x = 100$, gives (*a*), 58; (*b*), 30; and (*c*) 12%. We consider the trend as important, rather than the absolute values. The observed sequence is (*a*) > (*b*) > (*c*), as predicted. ^{13}C N.m.r. spectroscopy indicated conformer (*a*) as the main one.[6]

Conformers (*a*) and (*b*) each exist as a (±) pair and they are, therefore, favoured relative to the achiral conformer (*c*) because the free energy of each is lowered by an entropy of mixing term.[9]

Galactitol and mannitol have essentially planar chains, and their hydroxymethyl group ratios [O_e (oxygen extending the chain), O_g (oxygens *gauche*), O_t (oxygen *trans*) 53, 16, 31 and 54, 46, 0] can be taken as indicative of *threo*- and *erythro*-configurations.[3] The values are considered as semi-quantitative. When values from other alditols are compared with them, they seem to give an internally consistent picture. In galactitol a hydroxymethyl group is adjacent to a *threo*-configuration [Figure (*a*)]. Rotation about C(2)–C(3) to give O-2 extending the main chain [Figure (*b*)] puts the hydroxymethyl group in a 'pseudo *erythro*'-environment,† with C-4 acting as a substituent and O-3 considered as a carbon. To a first approximation we assume that the hydroxymethyl group is in a similar environment to the hydroxymethyl group in mannitol.

The hydroxymethyl conformation ratio (53, 30, 16) for (**1**) compares well with that calculated (53, 28, 18) for a 59:41

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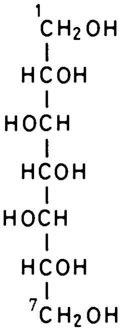
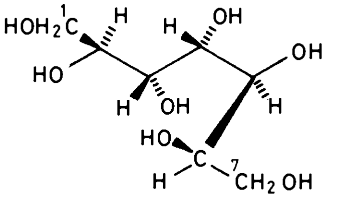
* All the *meso* compounds have been numbered in such a way that the highest numbered asymmetric carbon atom has the D configuration. For nomenclature, see ref. 10.

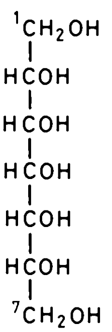
† In an earlier paper,[3] the concept of the 'pseudo *erythro*'-configuration was used (sometimes together with a true *arabino*-configuration) but was simply, though incorrectly, referred to as *arabino*-.



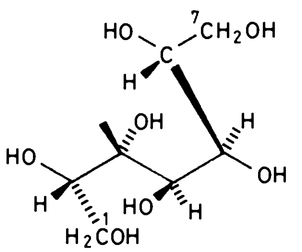
(1)



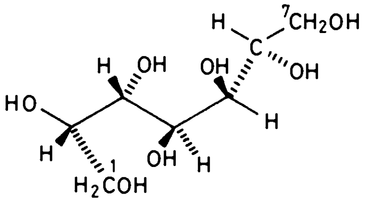
(1a)



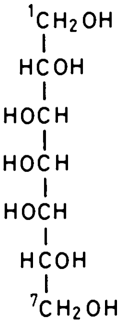
(2)



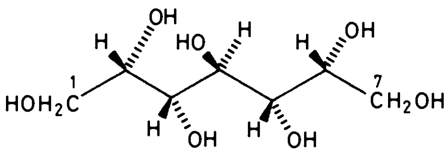
(2a)



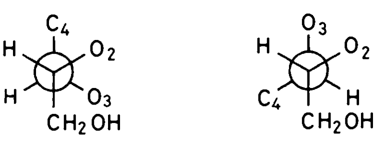
(2b)



(3)



(3)



(a) (b)

Figure. (*a*) (and enantiomer) O_2,O_3 *threo-*; (*b*) (and enantiomer) O_2,C_4 pseudo *erythro-*.

threo-: pseudo *erythro-*ratio based on conformers (*a*), (*b*), and (*c*) weighted as calculated above.

The separation (Δ, ppm) of the shifts of the protons of the hydroxymethyl group is another useful probe for the chain conformation near the group.[3] A *threo-*type arrangement has Δ *ca.* 0.0025 whereas the *erythro-*type is *ca.* 0.2. In (**1**) Δ = 0.0725, agreeing well with 0.0825 calculated for a 59:41 *threo-*: pseudo *erythro-* arrangement, based on conformers (*a*), (*b*), and (*c*). In the two main conformers ($_3G^-$; $_2G^-$, $_4G^-$) of L-iditol, the protons on C-ω and C-ω-1 share some similar environments to the corresponding protons of the main (*a*) conformer of (**1**), and their shifts are similar (δ values differ by a constant 0.06–0.07 ppm), and H-4 of conformer (**1a**) experiences similar interactions as does H-4 in the preferred ($_5G^+$) conformer of D-*glycero*-D-*manno*-heptitol, and their shifts (3.865 and 3.89) are similar.

For *meso-glycero-allo*-heptitol (**2**) the main predicted[7] conformers are (*a*) $_2G^-$, $_4G^+$, *i.e.*, O(2)–O(5) planar, and (*b*) $_2G^-$, $_4G^-$, *i.e.*, O(2)–H(5) planar. Assuming the hydroxymethyl groups are as their preferred (O_e) rotamer, then both contain the same number and type of interactions, including a $C\|O$ interaction. The predicted[3] ^3J values for the H(2)–H(3) and H(3)–H(4) couplings are both 5.9 Hz (obs. 6.0 and 5.9), consistent with the heptitol being almost completely in one, or more likely both of these forms. The $_2G^-$, $_5G^+$ conformer,[6] *i.e.*, O(2)–C(6) planar, has predicted values for these two couplings of 2.3 and 9.7 Hz, and is clearly not a favoured one. The first two conformers are also both stabilised by an entropy of mixing term.

The hydroxymethyl group distribution of (**2**) is 60, 38, 1.5, again comparing well with that calculated (60, 39, 1) assuming only conformers (*a*) and/or (*b*), (and their enantiomers), and that one hydroxymethyl group is as is in mannitol and the other as for C-6 of altritol. The separation (Δ) in (**2**) is 0.1475, giving fair agreement with that calculated (0.165) for either (*a*) or (*b*) and again taking one end as in mannitol and the other as for C-6 in altritol. The protons on C-ω and C-ω-1 in conformer (*a*) or (*b*) share some similar environments to the corresponding protons in the main ($_2G^-$, $_4G^+$; $_3G^-$; $_3G^+$) conformers of allitol, and their shifts are similar (δ values differ by a constant 0.045–0.06 ppm).

No conformation of *meso-glycero-altro*-heptitol (**3**) is free of serious 1,3-interactions.[5–7] The planar chain form seems to be the least congested form, but the predicted ^3J values for the H(2)–H(3) and H(3)–H(4) couplings are 0.5 and 9.7 Hz, which are in poor agreement with those (2.05 and 6.75) observed. Perhaps the $_3G^-$ and/or $_2G^-$, $_3G^-$ conformers and their enantiomers are also present in small amounts. If the H(3)–H(4) dihedral angle is changed from 180° to 170°, to relieve some of the $O(3)\|O(5)$ interaction in the planar chain form, this only reduces the coupling from 9.7 to 9.4 Hz.[8] The hydroxymethyl ratio (53, 19, 28) for (**3**) is essentially *threo-* like, supporting a planar chain for the C(1)–C(4) and C(4)–C(7) regions of the molecule. There is a slight pseudo *erythro-*type contribution (a raised O_g and a lowered O_t value) which could be consistent with the poor agreement of the ^3J values. For (**3**), Δ = 0.0238. Assuming one end of the molecule is *threo-*type, then the other has Δ 0.045. This value shows there is some non-planar chain conformer present, supporting the ^3J and the hydroxymethyl group rotamer evidence. The protons on C-1 and C-2 of altritol are in the same environment as those on C-ω and C-ω-1 of the planar chain form of (**3**), and the shifts of the corresponding protons are in fair agreement (δ values differ by 0.08–0.13), but the shift (3.87) of the C-3 and C-5 protons of (**3**) should be shielded[11] relative to the shift (3.66) of the C-3 proton of altritol, because they have an $H\|H$ interaction in place of an $H\|C$ interaction. This evidence again points to some perturbation from the planar chain form for (**3**). The only difference between the interactions of the H-4 proton of (**3**) and the H-4 proton of the D-*glycero*-D-*galacto*-isomer is that the former has a shielding *gauche*-hydrogen–oxygen ($H|O$) interaction instead of a deshielding[11] antiparallel oxygen interaction. It is unclear why the shift (3.92) of H-4 of (**3**) is not, therefore, shielded relative to that (3.92) of the latter.

The ^1H n.m.r. spectra of these three heptitols, therefore, confirm earlier conformational studies[7] but the nature of the minor conformers of (**3**) remains uncertain.

The results from this work complete the analysis of the 21 alditols comprising the series from the tetritols to the heptitols, and it is opportune to form an overview of the situation.

(1) Group repulsions[2] derived for substituents on six-membered rings fall in the order C‖O, O‖O, H‖C, H‖O, and O|O. The same sequence holds for the alditols except that the values are less because it is easier for a chain to flex and relieve the strain than it is for a six-membered ring to do so.

(2) Since the O|O interaction is small—in acyclic systems molecular mechanics actually show it as an attractive force[12]—the preferred chain conformations of the alditols can be deduced by considering only the 1,3-parallel interactions. The chain—or parts of it—tends to be planar except when this yields an O‖O interaction. Where possible the chain generally twists to replace an O‖O by a H‖C interaction though in cases of more than one O‖O interaction, the chain may alternatively create a C‖O interaction.

(3) Chain preference generally falls in the order: planar, single twist, double twist, as the chain attempts to reduce unfavourable interactions.[5] Doubly-twisted chains derived by rotation about adjacent C–C bonds occur but are always unfavourable and more so than when the twists occur in well separated parts of the chain.

(4) For steric reasons, chain twisting generally results in an oxygen (rather than a hydrogen) extending the chain at the bond that twists. Likewise, the preferred rotamer of the hydroxymethyl group in aqueous solution is that with the oxygen extending the chain.

Experimental

The spectra of heptitols (**1**) and (**3**) were recorded and computed as previously cited.[3] The spectrum of isomer (**2**) was recorded on a Bruker 600 MHz spectrometer, and was computed using the Bruker program PANIC.

Acknowledgements

The 400 MHz ^{1}H n.m.r. spectra were obtained from the University of London Intercollegiate Research Service (ULIRS) WH-400 n.m.r. spectrometer at Queen Mary College. The 600 MHz spectrum was obtained by courtesy of Dr. E. Curzon of Bruker, Coventry.

Experimental

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Received 28*th July* 1988; *Paper* 8/03095B