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Preliminary communication

Conformation of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal in the crystalline state and in solution*

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In a program on conformational analysis of acyclic sugar chains and pyranoid sugar systems[1], we have sought to compare, for certain key derivatives, conformations in solution (as revealed by magnetic resonance techniques) with conformations of the same molecules in the solid state (as determined by crystallography). Eschewing attempts to assign precise proton–proton dihedral angles from p.m.r. coupling-data, we have based the conformational assignments in these studies on the qualitative assumption that large couplings (>8 Hz) indicate antiparallel protons, and small ones (<4 Hz) indicate protons in gauche disposition; limiting values have been taken from suitable reference compounds that are conformationally stable[2]. The soundness of this conservative approach was affirmed in a recent, comparative study[3] on tri-*O*-acetyl-β-D-arabinopyranosyl bromide, where the qualitative p.m.r. interpretations were in excellent agreement with crystallographic data, but proton–proton dihedral angles "calculated" from the Karplus relationship showed poor quantitative correlation with the actual angles in the crystal.

This report provides a similar, direct correlation for an acyclic sugar derivative, 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal (**1**). The configuration at C-2 of this compound[4], a useful intermediate for synthesis of deoxynucleosides[5], was unknown until the appearance of a recent[6] chemical correlation, which is confirmed by the present crystallographic analysis. The n.m.r. spin-coupling data for **1** in 19:1 acetone-d_6–deuterium oxide, and for its tetraacetate **2** in chloroform-*d* (see Table I) show that, for both compounds, H-1 and H-2 are gauche-disposed, as are H-3 and H-4; in contrast, H-2 and H-3 are antiparallel, as are H-4 and H-5. Also in gauche disposition are H-5 and the more deshielded of the diastereotopic protons on C-6 in **2**; the intermediate value (5.3 Hz) of the coupling

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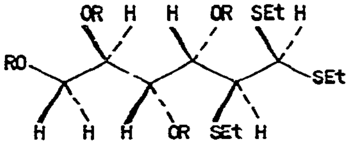
TABLE I

P.M.R. AND CRYSTALLOGRAPHIC DATA FOR 1 AND ITS TETRAACETATE (2)

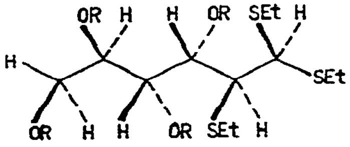
Vicinal protons	*P.m.r. data (solution)*[a] *First-order couplings (Hz)*		*Couplings calculated for* **1** *by Karplus equation from X-ray data*		*Dihedral angles (crystal) for* **1**	
	2	**1**	*I*[b]	*II*[c]	*Molecule A (degrees)*	*Molecule B (degrees)*
1,2	3.6	2.1	3.1	5.4	+64	+58
2,3	9.5	10.5	7.9	9.5	−171	−165
3,4	1.9	<1	2.2	3.2	−56	−58
4,5	7.6	6.6	8.2	9.2	−172	+172
5,6[d]	3.2	[e]	1.2	2.5	−61	−70
5,6′	5.3	[e]	2.1	3.3	+63	+53

[a] 220 MHz. [b] Uncorrected for electronegativity, cf. ref. 13. [c] Corrected for electronegativity, cf. refs. 14 and 15. [d] The proton on C-6 resonating at higher field is designated by a prime. [e] Unavailable, because of incomplete signal-separation. For other vicinal protons, $\Delta\delta > 25$ Hz.

with the other C-6 proton indicates that two rotameric states along C-5—C-6 are substantially populated. These data accord with the conformational formulations **1a** and **2a**, in equilibrium with the forms **1b** and **2b** derived by rotation along C-5—C-6. These conformational assignments are in keeping with the principles[1,2,7] developed for acyclic sugar derivatives in solution (and confirmed for alditols in the crystalline state[8]), namely, that the planar, extended, zigzag conformation is favored unless a parallel 1,3-interaction between two chain substituents would be generated, in which case the molecule adopts an alternative conformation to alleviate this interaction. For **1** and **2**, such a potential 1,3-interaction (between O-3 and a sulfur atom on C-1 in the fully staggered conformation having H-1 and H-2 antiparallel) is relieved by rotation about C-1—C-2; this rotation brings H-1 and H-2 into gauche disposition and causes S-2 to bisect the $C\overset{<}{\underset{S}{}}$ angle at C-1, despite the consequence that the sulfur atoms are thereby brought into interaction within their nominal Van der Waals radii. Nevertheless, the crystallographic data for **1** in the solid state are in full accord with this conformational assignment for **1** in solution, and reveal two slightly different conformations in the crystal. These have the chain carbon-atoms essentially in a plane, and approximate to the conformation **1b**; hydrogen bonding may account for the exclusive gauche orientation of O-6 in the crystal.



1a R=H
2a R=Ac



1b R=H
2b R=A

The crystals are monoclinic, space group $P2_1$, with cell dimensions $a = 15.73$, $b = 7.214$, $c = 16.88$ Å, and $\beta = 113°\ 23'$; there are two molecules of **1** (A and B) in the asymmetric unit. The intensities of 3,000 independent reflections were measured with a Hilger and Watts automatic four-circle diffractometer (courtesy of Professor G.A. Sim at Glasgow University) to $\sin \theta/\lambda = 0.53$. A graphite monochromator was used to select MoKα radiation, and 2,585 reflections were recorded above the background. Among $h0l$ reflections, only $h + l$ even were present in a list of E greater than 1.5.

The structure was solved by using a modification of the symbolic addition procedure[9], based on the introduction of the phase function[10]. The phase function with seven symbols gave four well-resolved maxima. The corresponding solutions were refined by the tangent formula[11], and the structure appeared on one of the four E-maps. On a difference-Fourier map, 37 of the 52 hydrogen atoms were located. The structure was refined by a full-matrix, least-squares method using anisotropic, thermal parameters for all atoms except hydrogen. The final R index was 0.06.

Distances and angles correspond to commonly observed values[8], except for the atoms of the ethyl groups, which are strongly affected by thermal agitation. The two molecules of the asymmetric unit are related by a pseudo-center of symmetry located at $a/4$ and $c/4$, as is the intermolecular, hydrogen-bonding network; differences in the arrangements of the ethyl groups are responsible for the deviations from symmetry.

True to the foregoing prediction, the sulfur atom bound to C-2 lies approximately along the bisector of the dihedral angle between the two ethylthio groups on C-1; consequently, the distances between the sulfur atoms are extremely short (see Table II) compared with the sum of the Van der Waals radii (3.7 Å). As anticipated, the carbon chain adopts the extended, planar, zigzag conformation (see Table III); there are short contacts (no intervening hydrogen atom) between oxygen atoms in each molecule (see Table II). Full details of the crystallographic work will be published separately[12].

TABLE II

SHORT INTRAMOLECULAR CONTACTS (Å)

Atoms	*Molecule A*	*Molecule B*
$S\text{-}1_r\text{–}S\text{-}1_s$	3.062	3.063
$S\text{-}1_r\text{–}S\text{-}2$	3.508	3.330
$S\text{-}1_s\text{–}S\text{-}2$	3.338	3.446
O-3–O-4	2.867	2.768
O-5–O-6	2.794	2.915

TABLE III

DEVIATIONS[a] FROM THE PLANAR, ZIGZAG ARRANGEMENT OF THE CARBON CHAIN

Carbon atom	*Distances from best plane, Å*	
	Molecule A[b]	*Molecule B*[c]
1	−0.010	0.025
2	0.036	−0.025
3	−0.059	−0.031
4	0.006	0.035
5	0.070	0.002
6	−0.044	−0.005

[a] Minimized by least-squares refinement; the plane is defined by $Ax + By + Cz = D$. [b] $A = 0.4205$, $B = 0.5506$, $C = 0.7211$, $D = 6.6656$. [c] $A = 0.2129$, $B = 0.6643$, $C = -0.7165$, $D = 7.4970$.

The dihedral angles relating substituents along the carbon chain, as determined from the crystallographic data, are given in Fig.1. Insertion of the proton–proton dihedral angles into the Karplus equation [13–15] gives "calculated", vicinal coupling-constants that show (see Table I) reasonable qualitative correlation with actual experimental values that is sufficient to affirm the validity of the qualitative approach in predicting molecular geometry from coupling data. As in the correlation with a cyclic-sugar example[3], the present data clearly demonstrate that attempts to assign precise dihedral angles from coupling data are unjustifiable and may be misleading.

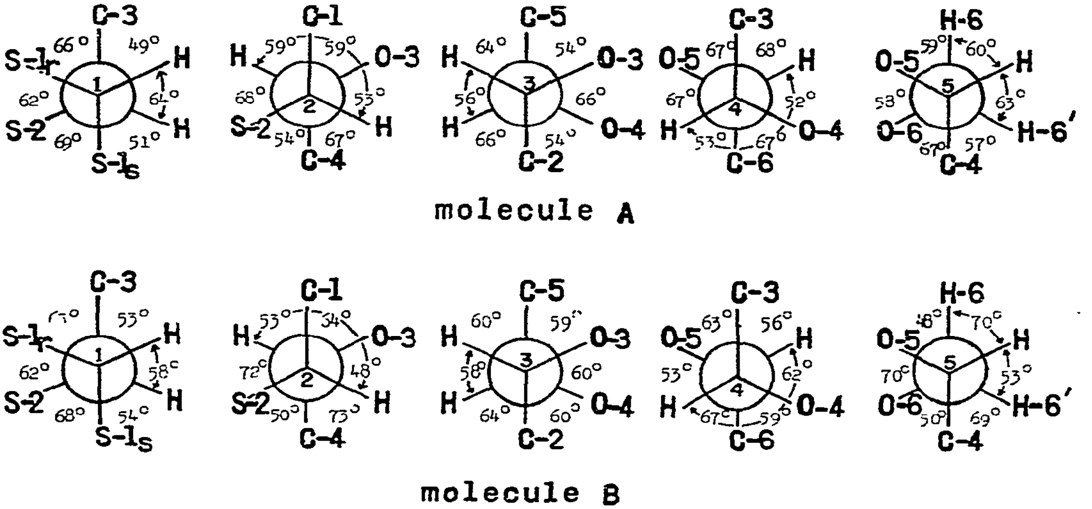


Fig.1. Newman projections illustrating dihedral angles measured in the solid state for substituents attached to the carbon chain of 1.

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