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Note

Conformations of ethyl 2-*S*-ethyl-1,2-dithio-α-D-mannofuranoside in solution and in the solid state*

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The title glycoside (**1**) was first prepared[1] by nitrous acid deamination of 2-amino-2-deoxy-D-glucose diethyl dithioacetal at a pH near neutrality; its structure was firmly established by chemical interconversions[2] and by X-ray crystal-structure analysis[3,4]. The compound may also be prepared[5,6] in good net yield in a sequence from D-glucose by way of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal[6,7], and it is a useful starting-material for the synthesis of 2′-deoxynucleosides[7,8]. It was of interest to compare the conformation of **1** in the crystal with that of **1**, and such derivatives as its triacetate **2**, in solution, as revealed by ^{1}H-n.m.r. spectroscopy.

It is well recognized that molecules not constrained into rigid conformations may adopt in solution, or the liquid state, a conformation, or mixture of equilibrating conformations, that differs from that in the crystal, especially when such forces as intramolecular hydrogen-bonding help to dictate the most stable structure in the solid state. Nevertheless, the literature is sparse as regards efforts to correlate the underlying factors responsible for such differences, and much early work attributing precise molecular geometry from ^{1}H-n.m.r. parameters is unreliable, or incorrect, because of unjustified reliance on the quantitative validity of the Karplus equation[9]. A more conservative, qualitative approach for the interpretation of ^{1}H-n.m.r. data has demonstrated[10] a close relationship between the solution and crystalline-state conformations of tri-*O*-acetyl-β-D-arabinopyranosyl bromide, a 6-membered-ring sugar derivative in which no hydrogen-bonding interactions are implicated.

In an acyclic-sugar example, it has been shown[11] for 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal that the molecule adopts in solution a planar, zigzag conformation essentially the same as that found in the crystal, except for a C-5–C-6 rotation in the crystal fixing O-6 in *gauche* disposition with the chain and thereby permitting stabilization through a 6-OH···O-5 intramolecular hydrogen-bond. For a more complex example, involving an acyclic sugar derivative (tetra-*O*-acetyl-D-

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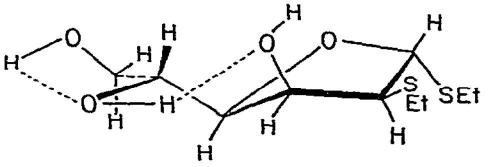
lyxose diisobutyl dithioacetal) conformationally unstable because of parallel 1,3-interactions of substituents, it has been demonstrated[12] by variable-temperature, ^{1}H-n.m.r. spectroscopy that the conformation in solution changes from an equilibrating mixture at room temperature toward a single conformer, at low temperature, that corresponds with the conformation anticipated for the solid state of compounds of similar geometry.



1-E_4 (crystal)

The present example (**1**) is a furanoid-ring derivative whose X-ray crystallographic analysis[4] showed that it adopts the E_4(D) conformation depicted, with 6-OH···O-5 and 5-OH···O-3 hydrogen bonds serving to anchor the C-4 side-chain into a fixed orientation. In solution, in deuterium oxide and in pyridine-d_5, the compound gives well resolved, high-field ^{1}H-n.m.r. spectra, and the close similarity of the vicinal spin-coupling values (see Table I) indicate little difference in the favored conformation in the two solvents; similar indications are evident from the (less well-resolved) spectrum recorded for solutions in dimethyl sulfoxide-d_6. Likewise, the triacetate (**2**) of **1** in pyridine-d_5 shows (see Table I) vicinal proton–proton couplings in close accord with those recorded for the triol **1**.

The dihedral angles of vicinal protons in crystalline[4] **1** are recorded in Table II. Insertion of these angles into an optimized version[13] of the Karplus equation that takes into account electronegativity factors of substituents along each carbon–carbon bond leads to "calculated" vicinal proton–proton couplings for **1** (and, likewise, for the conformationally similar triacetate **2**) that are manifestly (see Table II) in very significant variance with the experimental values. Use of a further refinement[14] of the Karplus equation does not lead to a significant improvement of the correlation between the "calculated" and the experimental values. This deviation may be attributed either to (*a*) a fundamental unreliability of the $J_{H,H'}$–$\phi_{H,H'}$ relationship, even as modified to take electronegativity factors into account, and avoiding its application to strained ring-systems, or (*b*) a significant difference in conformation between the molecule in the solid state and in solution.

Possibility (*a*) can certainly not be excluded entirely, but the relationship[13] used has been shown to be reasonably reliable, at least when applied to systems free from ring strain and without excessive precision in specifying dihedral angles. Table II records such angles (rounded to the nearest 5°) as calculated from the observed spin-couplings for **1** and **2**. Assuming the validity of this treatment, it may then be concluded that factor (*b*) is operative, and that there is a significant difference in the conformation of **1** in solution from that found in the solid state. The estimated

TABLE I

^{1}H-N.M.R.-SPECTRAL DATA FOR ETHYL 2-*S*-ETHYL-1,2-DITHIO-α-D-MANNOFURANOSIDE (**1**) AND ITS TRIACETATE **2**

Com-	Solvent	Chemical shifts (δ)							First-order couplings (Hz)						
pound		H-1	H-2	H-3	H-4	H-5	H-6a	H-6b[a]	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
1[b]	D_2O[c]	5.13d	3.42dd	4.38dd	4.04dd	3.91dq	3.80q	3.62q	9	4.5	2.4	8.5	3	6	12
	C_5D_5N[d]	5.70d	3.55dd	4.91dd	4.60dd	4.83dq	4.43q	4.24q	8	4.4	2.4	8.3	3.2	6.3	11.5
	Me_2SO-d_6[d]	5.06d	3.15dd	4.13m[e]	← 3.70m[e] →		3.54m[e]	3.30m	8.5	4.5	2[e]	—	—	6	11
	Me_2SO-d_6–D_2O[d]	5.05d	3.16dd	4.14dd	← 3.72m[e] →		3.56q	3.42q	8.2	4.5	2	—	2.5	6	11.5
2[f]	C_5D_5N[d]	5.17d	3.22dd	5.54dd	4.34dd	5.22dq	4.50q	4.12q	8.3	4.8	2.8	9.3	2.3	5.8	12.2

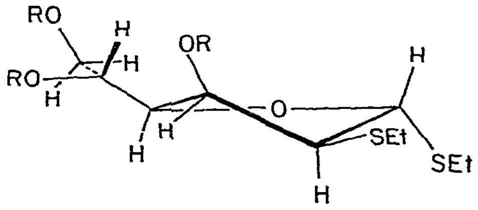
[a] The proton at C-6 resonating at highest field is designated H-6b. [b] Spectra recorded at 250 MHz with a Cameca apparatus. [c] At 30°, with sodium 2,2,3,3-tetradeuterio-4,4-dimethyl-4-silapentanoate as the reference standard and lock. [d] Tetramethylsilane used as the reference standard and lock. [e] Second-order effects evident. [f] Recorded at 220 MHz with a Varian HR-220 spectrometer.

TABLE II

PROTON–PROTON DIHEDRAL ANGLES[a] IN CRYSTALLINE ETHYL 2-*S*-ETHYL-1,2-DITHIO-α-D-MANNOFURANOSIDE (1), AND COMPARISON WITH ^{1}H-N.M.R. SPIN-COUPLING DATA OBSERVED FOR 1 AND ITS TRIACETATE 2 IN SOLUTION

Vicinal protons	*Dihedral angles for* 1 *from crystal data*[a] *(degrees)*	*Vicinal proton–proton couplings (Hz)*				*Estimated*[b] *dihedral angles from n.m.r. data (degrees)*	
		Estimated from crystal data[b]		*Observed in solution*[c]			
		Triol 1	*Triacetate*[d] 2	*Triol* 1	*Triacetate*[e] 2	1	2
1,2	120	5.03	5.03	9	8.3	150	140
2,3	30	7.69	7.30	4.5	4.8	50	50
3,4	41	5.95	5.64	2	2.8	75	65
4,5	170	10.7	10.1	8.5	9.3	150	160
5,6a	77	2.04	1.84	3	2.3	65	70
5,6b	180	11.5	10.6	6	5.8	120	130

[a]Crystallographic data from ref. 4. [b]By use of the equation[13] $J_{H,H'} = (7.8 - 1.0 \cos \phi + 5.6 \cos 2 \phi)(1 - 0.1\Delta X)$, where ΔX is an electronegativity term $= \Sigma_1^4 (X_n - X_H)$ for the system R^1R^2CH-CHR^3R^4, using the values for X of H = 2.1, C = 2.5, -O- = 3.3, OAc = 3.7, and -S- = 2.6. [c]From Table I, solution in D_2O. [d]Using the same interproton, dihedral angles as observed[4] in crystalline 1. [e]In C_5D_5N.



$^3T_2$ (solution)

1 R = H

2 R = Ac

dihedral angles for 1 in solution (see Table II) differ little from those estimated for the triacetate 2, and show appreciable, albeit not major, differences from the corresponding angles in the crystal. The solution data for 1 and 2 are consistent with the $^3T_2$(D) conformation of the furanoid ring as depicted, notably by enlargement of the angles between H-1, H-2, and H-3 with respect to those adopted in crystalline 1. The observed couplings undoubtedly constitute weighted averages from various furanoid conformers in pseudorotational equilibrium. Likewise, the "low" $J_{5,6b}$ values observed reflect time-averaging of C-5–C-6 rotamers in solution, with a substantial population of rotamers other than the one depicted. Both factors may be attributed to the absence of the conformation-locking pattern of hydrogen bonds that fixes the conformation of 1 in the crystal.

For other furanoid derivatives, Paulsen *et al.*[15] have also demonstrated significant differences between the geometry in the crystal and estimates made from n.m.r. data. The general question warrants a detailed, correlative study employing a broad range of examples.

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