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CONFORMATIONS IN SOLUTION OF THE STEREOISOMERIC, PER-ACETYLATED ALDOHEXOSE DIMETHYL ACETALS AND DIETHYL DITHIOACETALS*†

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ABSTRACT

The conformations in solution of acyclic carbohydrate derivatives having four contiguous asymmetric centers in all eight diastereoisomeric forms have been studied by ^{1}H-n.m.r. spectroscopy. The 250-MHz, ^{1}H-n.m.r. spectra for solutions in chloroform-*d* of eight penta-*O*-acetylaldohexose dimethyl acetals, and the corresponding diethyl dithioacetals, furnished a complete set of chemical shifts and proton–proton spin-couplings that are interpreted in terms of conformational compositions at room temperature. The *galacto* and *manno* derivatives adopt planar, extended conformations, whereas the other six stereoisomers all adopt one or more non-extended ("sickle") conformations. The results are interpreted on the basis of the avoidance of parallel 1,3-interactions of substituents. The conformational assignments are correlated with observations made previously for aldopentose analogs. An assessment is made of the extent to which valid conformational predictions may be advanced for four-center, and longer, asymmetrically substituted chains, based on observations made for shorter-chain analogs.

INTRODUCTION

This series of investigations[1–3] has been concerned with the conformational behavior of polysubstituted carbon chains as a function of systematic variation of substituent geometry through a complete range of stereoisomers. Acyclic-sugar derivatives have constituted the source compounds having hydroxyl (or substituted hydroxyl) groups along the carbon chain; ^{1}H-n.m.r. spectroscopy has provided the tool for probing conformations in solution, and the results have been correlated[4]

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with solid-state conformations established by crystallography. Most of the investigations have employed 5-carbon (aldopentose) sugar derivatives, in their four different diastereoisomeric forms, and the substitution-mode at C-1 has encompassed compounds having both sp^2 and sp^3 hybridization at this position. Compounds having acetal and thioacetal groups at C-1 have received especial emphasis, as their ^{1}H-n.m.r. spectra have proved particularly amenable to analysis and conformational interpretation. Generalizations have been advanced and tabulated[3] coordinating both *O*-substituted (generally *O*-acetylated) and unsubstituted derivatives, and it is now well recognized[4] from this work that the avoidance of parallel 1,3-interactions between substituents is a major factor in establishing the favored conformation.

Spectral resolution adequate for reliable interpretations has been achieved for most of the substituted C_5 compounds by use of spectrometers operating at 100 MHz, but high-field, superconducting spectrometers have proved essential for probing conformational variations as a function of temperature[5], and for most investigations with free-hydroxyl compounds[1-3]. Similar high-resolution capability is also mandated for work with longer-chain homologs, at least if complete spectral analysis of an entire series of stereoisomers is contemplated.

Comparative conformational analyses of the stereoisomeric, peracetylated aldopentose diethyl dithioacetals[6] and dimethyl acetals[7] have already been reported. This investigation now extends the analysis to the homologs having four asymmetric centers, namely, the eight diastereoisomeric aldohexoses, as their peracetylated dimethyl acetals (**1–8**) and diethyl dithioacetals (**9–16**). It is shown that application of the concept of homomorphology permits the conformational dispositions of these derivatives to be correlated with conformations already established[6,7] for the aldopentose analogs.

DISCUSSION

Compounds prepared. — The aldohexoses were converted conventionally into their dithioacetals[8], and these products were subsequently acetylated. The well known dithioacetals of D-galactose[9], D-glucose[9], D-mannose[9], and their respective pentaacetates[10-12] had physical constants in good agreement with literature values. For other derivatives (*a*) that have not yet been described, (*b*) for which the mode of preparation differed from that in the literature, or (*c*) for which the literature[13] records no m.p., $[\alpha]_D$, or analytical data, the appropriate details are given in the Experimental section. The acetylated dithioacetals were subsequently converted, by the action of methanolic mercuric chloride in the presence of cadmium carbonate, into the corresponding, acetylated aldohexose dimethyl acetals. The appropriate derivatives of D-galactose[14] and D-glucose[15] had physical data in accord with literature values; those for the remaining stereoisomers are recorded in the Experimental section, together with information on the corresponding, free aldohexose dimethyl acetals (obtained by Zemplén deacetylation[16] of the pentaacetates). The latter

TABLE I

^{1}H-N.M.R. SPECTRAL DATA AT 250 MHz FOR ALDOHEXOSE DIMETHYL ACETAL PENTAACETATES IN CHLOROFORM-*d*

Aldose	*First-order coupling-constants, Hz*[a]							*Chemical shifts*[a], *δ (and multiplicities)*								
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	*H-1 (d)*	*H-2 (dd)*	*H-3 (dd)*	*H-4 (dd)*	*H-5 (m)*	*H-6 (q)*	*H-6' (q)*	*OMe (s)*	*OAc (s)*
D-Allose	6.7	4.2	5.5	3.6	3.0	7.6	12.3	4.52	5.24	5.40	5.45	5.35	4.44	4.15	3.66, 3.36	2.119, 2.103, 2.085, 2.077, 2.049
D-Altrose	6.8	2.5	8.3	3.4	3.3	7.5	12.2	4.29	5.21	5.46	5.27	5.16	4.36	4.20	3.36, 3.31	2.171, 2.084, 2.071(2), 2.055
D-Galactose	6.8	2.0	10.0	1.8[b]	4.6	7.4	11.8	4.23	5.15	5.52	5.24	5.22	4.30	3.82	3.35, 3.31	2.108(2), 2.100, 2.096, 2.016
D-Glucose	5.4	5.3	5.0	6.2	4.1	6.0	11.7	4.36	5.18[c]	5.51[c]	5.40	5.09	4.30	4.11	3.40, 3.36	2.136, 2.104, 2.076, 2.072, 2.044
L-Gulose	7.1	4.1	6.0	4.8	4.7	6.3	11.9	4.55	5.01	5.42	5.50	5.41	4.30	3.96	3.46, 3.30	2.14, 2.10, 2.07, 2.06, 2.05
L-Idose	6.0	3.9	6.5	4.4	4.5	6.2	11.8	4.34	5.16	5.44	5.30	5.38	4.26	4.03	3.38, 3.33	2.142, 2.113, 2.100, 2.095, 2.056
D-Mannose	5.7	7.6	2.3[d]	8.5	2.8	5.5	12.5	4.45	5.14	5.47	5.45	5.11	4.23	4.06	3.40, 3.37	2.093, 2.074(2), 2.070, 2.048
D-Talose	7.1	2.9	8.4	2.5	4.4	7.5	11.8	4.43	5.14	5.34	5.46	5.37	4.33	3.95	3.44, 3.32	2.16, 2.11, 2.09, 2.07, 2.05

[a]The proton designated H-6' resonates at higher field than that designated H-6. [b]Subject to second-order effects, because of the proximity of the H-4 and H-5 signals. [c]Apparent triplet, because $J_{1,2} \sim J_{2,3} \sim J_{3,4}$. [d]Subject to second-order effects, because of proximity of H-3 and H-4 signals.

TABLE II

^{1}H-N.M.R. SPECTRAL DATA AT 250 MHz FOR ALDOHEXOSE DIETHYL DITHIOACETAL PENTAACETATES IN CHLOROFORM-*d*

Aldose	*First-order coupling-constants, Hz*[a]							*Chemical shifts*[a], *δ (and multiplicities)*									
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	*H-1 (d)*	*H-2 (dd)*	*H-3 (dd)*	*H-4 (dd)*	*H-5 (m)*	*H-6 (q)*	*H-6′ (q)*	SCH_2 *(q)*	CH_3 *(t)*	*OAc (s)*
D-Allose	6.5	6.2	3.8	5.3	2.8	7.0	12.2	4.01	5.38[b]	5.68	5.50	5.30	4.44	4.13	2.70, 2.66	1.26, 1.24	2.149, 2.101, 2.091, 2.088, 2.055
D-Altrose	7.9	3.0	7.3	3.9	3.2	7.2	12.2	3.90	5.28	5.71	5.30	5.17	4.36	4.25	2.70, 2.66	1.26, 1.24	2.160, 2.107, 2.078, 2.068, 2.064
D-Galactose	8.1	1.8	9.5	2.1	4.9	7.0	11.8	3.83	5.17	5.78	5.25	5.20	4.29	3.84	2.68, 2.62	1.26, 1.23	2.135, 2.116, 2.113, 2.109, 2.025
D-Glucose	4.4	7.5	2.9	8.0	3.0	4.6	12.6	4.08	5.29	5.77	5.44	5.07	4.25	4.14	2.76, 2.58	1.34, 1.24	2.151, 2.095, 2.084, 2.065, 2.048
L-Gulose	6.4	6.1	2.0	7.7	3.5	5.8	12.4	3.96	5.31[b]	5.68	5.54	5.19	4.39	4.05	2.70, 2.66	1.28, 1.24	2.144, 2.096, 2.085, 2.078, 2.064
L-Idose	5.4	5.6	4.7	6.0	3.9	5.6	12.3	4.00	5.30[b]	5.70	5.39	5.27	4.35	4.04	2.70, 2.60	1.28, 1.22	2.128, 2.122, 2.102, 2.100, 2.072
D-Mannose	5.4	7.2	1.7	9.0	2.6	5.0	12.5	3.91	5.29	5.75	5.50	5.08	4.22	4.08	2.670, 2.665	1.27, 1.24	2.100, 2.091, 2.088, 2.084, 2.056
D-Talose[c]	5.6	~5.5	~5.5	~5.5	4.0	6.2	11.9	3.92	5.43	5.59	5.38	5.42	4.31	4.07	2.70, 2.66	1.26, 1.24	2.153, 2.121, 2.076, 2.071, 2.054
D-Talose[c,d]	5.0	6.2	5.0	5.0	4.5	6.5	12.0	4.04	5.40	5.54	5.35	5.42	4.21	4.05	2.67, 2.66	1.20, 1.18	2.08, 2.06, 2.00, 1.98
D-Talose[c,e]	6.0	~5.5	~5.5	~5.5	4.2	6.5	11.5	4.13		← 6.05 →			4.48	4.21	2.68, 2.60	1.12, 1.08	1.96, 1.82, 1.78

[a]The proton designated H-6′ resonates at higher field than that designated H-6. [b]Apparent triplet, because $J_{1,2} \approx J_{2,3}$ [c]Partially second-order spectrum; assignments aided by INDOR experiments. [d]In acetone-d_6. [e]In benzene-d_6.

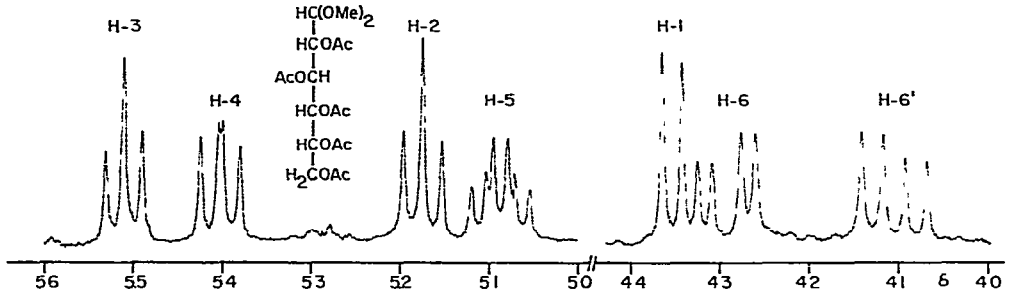


Fig. 1. The low-field portion of the 250-MHz, ^{1}H-n.m.r. spectrum of penta-*O*-acetyl-*aldehydo*-D-glucose dimethyl acetal (**4**) in chloroform-*d* at ~15°

products were needed for a comparative investigation of their behavior in chemical-ionization, mass spectrometry[17].

General features of the ^{1}H-n.m.r. spectra. — The chemical shifts and first-order coupling-constants obtained from 250-MHz spectra for solutions at ~15° in chloroform-*d* are recorded in Table I for the penta-*O*-acetylaldohexose dimethyl acetals having the D-*allo* (**1**), D-*altro* (**2**), D-*galacto* (**3**), D-*gluco* (**4**), L-*gulo* (**5**), L-*ido* (**6**), D-*manno* (**7**), and D-*talo* (**8**) configurations, respectively. Similarly, Table II records corresponding data for the penta-*O*-acetylaldohexose diethyl dithioacetals having the D-*allo* (**9**), D-*altro* (**10**), D-*galacto* (**11**), D-*gluco* (**12**), L-*gulo* (**13**), L-*ido* (**14**), D-*manno* (**15**), and D-*talo* (**16**) configurations. For compound **16**, corresponding data recorded for solutions in acetone-d_6 and benzene-d_6 are also given.

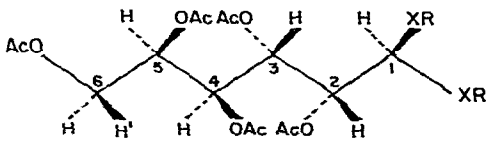
The spectra of acetals **1**–**8** were all essentially first-order, and Fig. 1 shows the low-field region of a representative example (the D-*gluco* isomer, **4**) that illustrates the separated signals of the seven protons along the chain; H-1 gives rise to a doublet, the methylene group at C-6 in conjunction with H-5 generates a classic ABX system, and the remaining signals, and the spin couplings determined from the signal spacings, are readily attributed by direct inspection. The assignments were verified in all instances by appropriate decoupling or INDOR experiments. Upfield of the region displayed in Fig. 1 are observed two 3-proton singlets for the (nonequivalent) methoxyl groups and, at considerably higher field, five individual signals for the five acetyl groups The remaining seven dimethyl acetals gave broadly similar spectra. In most instances, all of the acetate-group signals were discretely separated, and the methoxyl-group signals showed separations of ~10 Hz for **2**, **3**, **4**, **6**, and **7**; large separations (30–40 Hz) were observed for **5** and **8**, and that for **1** was of intermediate (~20 Hz) magnitude. In the low-field region of the spectra, certain of the multiplets showed partial overlap in some instances, but, for noncoupled protons, this was of no significance as regards the coupling constants determined. Two of the first-order coupling-values (see Table I) may differ slightly from the absolute values, because of the proximity of signals of coupled protons ($\delta/J \sim 3$), but the difference was not expected to be sufficient to affect the interpretations that follow.

The dithioacetals **9**–**16** gave spectra that, in the low-field region, closely re-

sembled those of the acetals, except that the H-1 signal appeared ~0.4 p.p.m. to higher field. The acetate-group resonances were again, in most instances, resolved into five separate signals, and the two ethyl groups were nonequivalent in every example. Complete separation of all low-field signals was evident for compounds **12**, **13**, **14**, and **15**, and overlap of certain noncoupled signals was observed with **9**, **10**, and **11**. For the D-*talo* derivative **16** in chloroform-*d*, the signals of H-4 and H-5 were practically superposed, so that the validity of certain first-order couplings was open to question; in benzene-d_6, the spectrum remained poorly resolved, but adequate dispersal of signals was achieved in acetone-d_6.

For the sake of uniformity in presentation, all structures in the following conformational interpretations are presented as being of the D series, even though the actual compounds used were the L enantiomorphs for the *gulo* and *ido* derivatives.

Conformational analysis. — Galactose derivatives (**3** *and* **11**). The vicinal spin-couplings observed between H-2, H-3, H-4, and H-5 for both the acetal (**3**) and dithioacetal (**11**) all lie at "extreme" limits, either of small magnitude (~2 Hz, indicating gauche-disposed protons, observed for $J_{2,3}$ and $J_{4,5}$) or large magnitude (9–10 Hz, indicating *trans*-periplanar protons, observed for $J_{3,4}$). These values, taken in conjunction with the $J_{1,2}$, $J_{5,6}$, and $J_{5,6'}$ couplings, establish that the molecules exist, essentially exclusively, in the fully extended, planar, zigzag conformation illustrated; the symbolism[3] **P** is assigned to indicate that this conformer is virtually the exclusive form present.



D-*galacto* **3-P, 11-P**

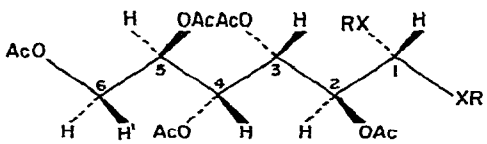
For dithioacetal **11**, the $J_{1,2}$ value is 8.1 Hz, and for acetal **3**, it is 6.5 Hz; these values are also near the "extreme" limit for *trans*-periplanar protons if electronegativity factors of the two XR groups[18] (which tend to decrease the $J_{1,2}$ values by comparison with vicinal couplings of similarly disposed protons along the chain) are taken into account. The fact that the $J_{5,6}$ (~4.7 Hz) and $J_{5,6'}$ (~7.2 Hz) values are, respectively, somewhat large for exclusively gauche-disposed protons and somewhat small for exclusively *trans*-periplanar protons suggests that there is limited occupation of other rotameric states about C-5–C-6 [presumably that[3] ($_5G^-$) derived by clockwise rotation by 120° of O-6 along the C-5–C-6 bond]; this type of chain-end flexibility is encountered in other examples in this study and in previous work in this Series, and crystallographic studies[19] have supported the idea that the terminal oxygen atom of an acyclic sugar derivative may readily adopt a disposition gauche to O-4 as well as a *trans*-periplanar arrangement.

The conformations indicated for **3** and **11** from the n.m.r. data are entirely as expected in view of the fact that, when the molecule is fully extended, there are no

parallel 1,3-interactions of substituents in any region of the molecule. An entirely analogous situation is observed[6] with the 6-deoxy analog (tetra-*O*-acetyl-L-fucose diethyl dithioacetal) of **11**, which shows corresponding couplings almost identical with those of **11**.

A carbon chain having four contiguous asymmetric centers in the *galacto* relative stereochemistry may be considered as being constituted from an *arabino* 3-center segment (C-3,4,5) in conjunction with a second *arabino* 3-center segment (C-2,3,4). Previous work has established the **P** conformation for the acetylated dithioacetals[6] and acetals[7] of arabinose. Consideration of homomorphological relationships between the aldopentose and aldohexose configurations allows conformational predictions that correlate exactly with the results of experimental observation.

Mannose derivatives (**7** *and* **15**). Data for the two derivatives correspond very closely and, for the same reasons already advanced for the *galacto* series with respect to "extreme" coupling-values, the **P** backbone conformation shown may be confidently assigned, with one small modification concerning the rotameric state about



D-*manno* **7-P, 15-P**

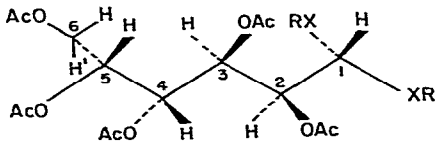
C-1–C-2. The values of $J_{1,2}$ (5.7 Hz for **7**, and 5.4 Hz for **15**) are somewhat low for exclusive population of the rotamer having H-1 and H-2 *trans*-periplanar, and indicate substantial population of a rotamer (presumably ${}_1G^+$) having these protons gauche-disposed; the latter is free from the parallel interaction between the OAc-3 group and one of the XR-1 groups present in the conformation illustrated. The molecule may, in fact, exist either as a mixture of these two C-1 rotamers, or in a favored, C-1–C-2, torsional state that deviates sufficiently from the idealized, staggered geometry to alleviate the interaction between the two substituents; the present data do not permit differentiation. Similar considerations of rotameric flexibility about C-5–C-6 apply, as already advanced for the *galacto* series.

The results presented here for the *manno* series again show excellent correlation with experimental spin-couplings ($J_{1,2}$, $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$) and conformational interpretations[6] for the 6-deoxy analog (tetra-*O*-acetyl-L-rhamnose diethyl dithioacetal) of **15**.

The *manno* sequence of asymmetric centers corresponds at C-3,4,5 to the *arabino*, and at C-2,3,4 to the *lyxo*, arrangement, and the net conformational properties observed for **7** and **15** may be interpreted on the basis of appropriately juxtaposed *arabino* and *lyxo* analogs, the corresponding acetals[6,7] of which both exist in the

P backbone conformation (with C-1–C-2 torsion in the *lyxo* derivatives to alleviate the XR-1–OAc-3 interaction).

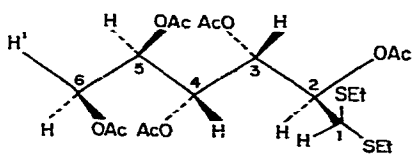
Altrose derivatives (**2** *and* **10**). The two compounds show closely similar sets of spin couplings, and the values observed are all close to extreme ones, indicating a considerable degree of conformational homogeneity. Essential coplanarity along C-1–C-4 is indicated by the data, but the small value of $J_{4,5}$ (3.4 Hz for **2**, and 3.9 Hz for **10**) provides clear evidence that H-4 and H-5 are not *trans*-periplanar as would be dictated by a **P** conformation (which would generate a parallel interaction between O-3 and O-5). The observed data are accommodated in the ${}_4G^+$ conformation illustrated, which may be regarded as virtually the exclusive form: it is free from any parallel 1,3-interactions.



D-*altro* **2** $-{}_4G^+$, **10** $-{}_4G^+$

As with the previous examples, homomorphic relationships with pentose analogs[6,7] may be correlated with the observed aldohexose conformation; the C-2,3,4 centers have the *arabino* relative stereochemistry, for which the **P** conformation is expected (and observed), whereas the *ribo* arrangement present at C-3,4,5 would lead to prediction of a sickle conformation in this segment. Although the acetylated D-ribose dimethyl acetals[7] and diethyl dithioacetals[6] favor different sickle conformers (${}_2G^-$ and ${}_3G^+$, respectively), the *altro* derivatives **2** and **10** studied here both display the same conformation, with the C-3,4,5 sequence in a conformational disposition corresponding to the ${}_3G^+$ arrangement of a D-ribose derivative.

Glucose derivatives (**4** *and* **12**). Spin-coupling data exhibit noteworthy differences between the two compounds. Those for **4** are all of "intermediate" magnitude, corresponding to mixing of conformational states, whereas those of **12** are all (except $J_{1,2}$) close to extreme values, indicative of conformational homogeneity. For **12**, the data correlate with a preponderant ${}_2G^-$ conformation of the backbone chain, as required by the large (7.5 Hz) value of $J_{2,3}$, and the small values of both $J_{5,6}$ and $J_{5,6'}$ (3 0 and 4.6 Hz, respectively) show that there is substantial population of the ${}_5G^+$ rotamer, instead of the fully extended form. The fact that C-2–O-2 bisects the



D-*gluco* **12** $-{}_2G^-,{}_5G^+$

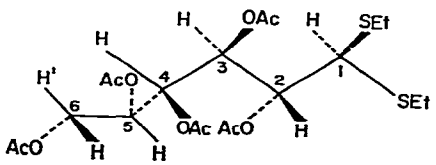
angle of the C-1–S bonds is not considered a significant constraint: comparable arrangements have been found[19] by crystallography on related compounds. A minor degree of mixing of C-1–C-2 rotameric states may exist, but it should be noted that the other two C-1–C-2 rotamers of **12** would engender a parallel interaction between C-4 and one of the sulfur atoms.

This conformational assignment accords well with predictions based on homomorphic considerations for a segment (C-3,4,5) having the *arabino* geometry (which would be expected to be fully extended) in juxtaposition with one (C-2,3,4) having the *xylo* arrangement; tetra-*O*-acetyl-D-xylose diethyl dithioacetal has been shown[6] to exist in a mixture of conformational states in which the ${}_2G^-$ sickle conformation is favored.

The dimethyl acetal **4** cannot be formulated as any single, preponderant conformer; the coupling data accord with substantial, but not exclusive, population of the extended state in the C-4,5,6 segment. The values of $J_{2,3}$ and $J_{3,4}$ (5.3 and 5.0 Hz, respectively) demonstrate that ${}_2G^-$ and ${}_3G^+$ sickle forms both contribute to the conformational equilibrium of **4**: the conformational description (**4**-${}_2G^-$ + **4**-${}_3G^+$) may thus be applied to **4**. In this regard, it may be noted that tetra-*O*-acetyl-D-xylose dimethyl acetal (corresponding to the C-2,3,4 segment of **4**) exists[7] as a conformational mixture in which the ${}_3G^+$ form is a major contributor.

The OAc-2/OAc-4 interaction that would be present in the extended form of **4** and **12** is thus mainly alleviated by C-2–C-3 rotation in the dithioacetal **12**, whereas C-3–C-4 rotation is also significant in the acetal **4**; possibly, the greater steric bulk of the $CH(SEt)_2$ group is a determinant factor in favoring one rotamer over the other.

Allose derivatives (**1** *and* **9**). The *allo* derivatives, in common with the *ido* derivatives, would have two sets of parallel interactions of acetoxyl groups (OAc-2/OAc-4 and OAC-3/OAc-5) in the fully extended conformation The coupling data show that these interactions are alleviated differently for compounds **1** and **9**, and that each compound exists as a conformational mixture in which one conformer may, nevertheless, be identified as preponderant The dithioacetal **9** favors an extended arrangement of the C-4,5,6 segment (although the value of 5.3 Hz for $J_{4,5}$ demonstrates that the *trans*-periplanar disposition of H-4 and H-5 is far from exclusive), and the small value of $J_{3,4}$ (3.8 Hz) dictates the ${}_3G^-$ sickle form as being the major conformational state of the backbone chain (the ${}_3G^+$ form would generate an inter-

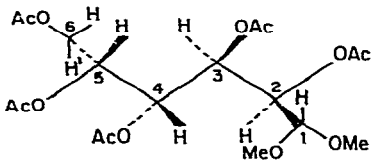


D-*allo* **9** – ${}_3G^-$, ${}_1G^+$

action between C-2 and O-5); the large magnitude of $J_{1,2}$ also requires C-1–C-2 rotation to the ${}_1G^+$ rotamer.

This conformation is to be considered in conjunction with lesser contributions from other gauche rotamers (${}_2G^-$ and ${}_4G^-$), and it is not entirely free from parallel interactions (one exists between SEt-1 and OAC-3).

For the acetal **1**, there is more conformational mixing than with **9**; the ${}_3G^-$ rotamer is considerably less significant, whereas the ${}_2G^-$ and ${}_4G^+$ rotamers are adopted simultaneously in the conformational state most heavily populated, which may thus be expressed as a double sickle arrangement (${}_2G^-$, ${}_4G^+$). There is also C-1–C-2 rotation, to bring H-1 and H-2 into *trans*-periplanar disposition.

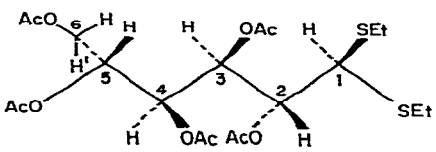


D-*allo* **1** $-{}_2G^-, {}_4G^+; {}_1G^+$

This conformation is free from parallel interactions within the chain, although one exists between C-4 and one of the methoxyl groups.

Homomorphic consideration of **1** and **9** indicates the *ribo* geometry for the C-2,3,4 and C-3,4,5 segments. Tetra-*O*-acetyl-D-ribose diethyl dithioacetal[6] favors the ${}_3G^-$, and the dimethyl acetal analog[7], the ${}_2G^-$, conformation; both of these backbone rotations are evident in the principal conformation of **1**, but are less important for **9**, where the major contributor (${}_3G^-$) may be correlated, through its C-3,4,5 segment, with the ${}_2G^-$ conformer observed with the aldopentose dimethyl acetal derivative.

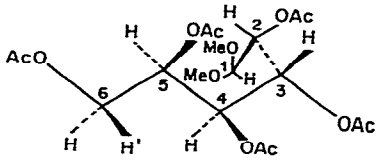
Gulose derivatives (**5** *and* **13**). Considerable homogeneity in the conformation of dithioacetal **13** is indicated from the coupling data, but there is more conformational mixing for acetal **5**. The $J_{4,5}$ value (7.7 Hz) for **13** establishes the ${}_4G^+$ form as the principal conformer, and the other couplings essentially support the extended arrangement for the remainder of the chain; the somewhat low (6 1 Hz) value of $J_{2,3}$ shows that there is a minor contribution from other C-1–C-2 rotameric states.



D-*gulo* **13** $-{}_4G^+$

The acetal **5** has a low (4.1 Hz) value of $J_{2,3}$ (suggesting the ${}_2G^-$ rotamer) and the magnitude (6.0 Hz) of $J_{3,4}$ indicates substantial contribution from the

$_3G^-$ rotamer. Each of these rotamers alone would generate a new, parallel interaction of chain substituents, but taking them together generates a doubly skewed conformation free from such interactions (an interaction exists between C-4 and one methoxyl group) that may be regarded as the major conformer of **5**.

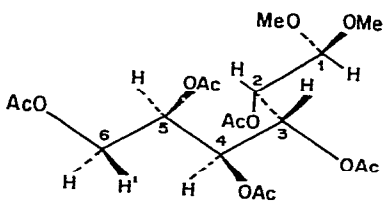


D-*gulo* **5** $-{}_2G^-;\ {}_3G^-$

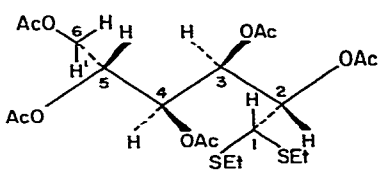
The observed behavior of **13** follows that predicted for the C-3,4,5 (*xylo*) and C-2,3,4 (*lyxo*) segments: the extended backbone chain for the latter segment is observed in both series of corresponding aldopentose derivatives, and tetra-*O*-acetyl-D-xylose dimethyl acetal exists[7] mainly in the $_3G^+$ conformation corresponding to that favored for **13** (although tetra-*O*-acetyl-D-xylose diethyl dithioacetal actually favors[6] the $_2G^-$ form, thus correlating with the C-3–C-4 rotamer of acetal **5**, rather than with the observed behavior of **13**). The factors responsible for the different behavior of **5** and **13** are not readily apparent.

Idose derivatives (**6** *and* **14**). Extensive conformational mixing is apparent for both examples, although each compound has a different major conformer, achieved by different modes of rotation to alleviate the double, parallel interactions of chain substituents present in the extended form. In acetal **6**, H-3 and H-4 are preponderantly *trans*-periplanar, whereas this arrangement is favored between H-4 and H-5 (and to a lesser extent between H-2 and H-3) in the dithioacetal **14**.

The C-3–C-4 rotation in **6** generates the $_3G^-$ form, the major contributory conformer, whereas **14** exists mainly as the double sickle $_2G^+$, $_4G^-$ form.



D-*ido* **6** $-{}_3G^-$

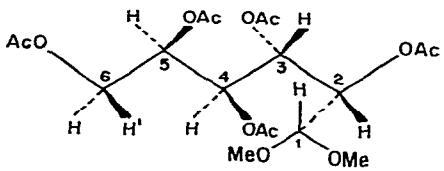


D-*ido* **14** $-{}_2G^+;\ {}_4G^-$

For the aldopentose analogs in the *xylo* series (configurational model for the C-2,3,4 and the C-3,4,5 sequences), the $_3G^+$ form is favored for the acetals[7], and the $_2G^-$ for the dithioacetals[6]. The $_3G^-$ conformation of acetal **6** is actually related directly to the pentose *dithio*acetal ($_2G^-$) rather than the acetal, and the $_4G^+$ arrange-

ment for the dithioacetal **14** corresponds to the disposition ($_3G^+$) for the pentose *acetal*

Talose derivatives (**8** *and* **16**) The acetal **8** shows extreme coupling values consistent with high conformational homogeneity, whereas the dithioacetal **16** appears to be a conformational mixture. In compound **8**, the OAc-2/OAc-4 interaction is clearly alleviated by C-2–C-3 rotation to an H-2–H-3 gauche conformer, which is essentially the exclusive form present. The $_2G^+$ form depicted would appear to be strongly favored, as it has no parallel interactions within the chain (one exists between OMe and C-4), whereas the $_2G^-$ conformer would have a C-1/O-4 parallel interaction.



D-*talo* **8** – $_2G^+$

The dithioacetal **16** was the only compound in the series whose spectrum in chloroform-*d* was not sufficiently well resolved to allow determination of reliable coupling-data, but the values obtained for a solution in acetone-d_6 are expected to be close to the absolute values. The intermediate magnitudes of $J_{3,4}$ and $J_{4,5}$ (5.0 Hz) are indicative of conformational mixing; the somewhat larger (6.2 Hz) $J_{2,3}$ coupling indicates that, in contrast to **8**, conformers having C-1–C-4 approximately coplanar, and torsion about C-3–C-4 and C-4–C-5, are important contributors. No single conformation can be clearly defined for **16**, but $_3G$ and $_4G$ conformers are presumably present in the equilibrium conformational mixture, unless a favored state is established having the torsional angles deviating from staggered geometry

The conformation observed for **8** along the C-3,4,5 (*lyxo*) segment is planar, as expected, and that along C-2,3,4 (*ribo* segment) shows C-2–C-3 rotation, also as expected by comparison with the aldopentose analog[7], but in the opposite sense from the latter, which favors the $_2G^-$ conformation. No clear relationships can be drawn with regard to the dithioacetal **16**

General correlations. — The comparative conformational interpretations presented here are based on experimental evidence for two series of acyclic, 6-carbon sugar derivatives (in solution) in which all eight possible diastereoisomers are considered. This study advances the previous[6,7] comparative analyses for the lower, 5-carbon homologs, for which the four different diastereoisomers were likewise considered from a comparative viewpoint. It is considered that such stereochemically complete investigations are more meaningful than partial investigations in which only the more readily accessible derivatives are examined. The present study is restricted to substituted sugar derivatives in a solvent of low polarity, and thus the interactive forces are essentially limited to intramolecular, van der Waals and dipole–

dipole forces; such stronger interactions as hydrogen bonding (intramolecular or molecule–solvent, or both, as encountered with the unsubstituted derivatives) and intermolecular interactions (as present in the crystalline state and in concentrated solution at low temperature) are not significantly involved in the present examples, which thus constitute a means of assessing the fine balance through the interplay of relatively weak forces in determining the most favored shapes of these molecules.

The generalizations advanced from the studies[6,7] on molecules having three contiguous, chiral centers are here shown to provide a useful base for predictions, based on considerations of homomorphic relationships, of the favored conformations of homologs containing four chiral centers. The correlations developed should prove applicable with related series of derivatives, and to compounds possessing still longer sequences of contiguous, chiral centers. Not only is it possible to make such broad general predictions[20] as "extended" or "bent" for a given structure; it may also permit reasonable prediction of which particular "bent" conformer is (or conformers are) the most favored. Such knowledge may be important in comprehending such factors as the enzyme-binding ability of chirally substituted chains, polymer structure and properties, and differential accessibility of functional groups in such chains towards chemical reagents, as in glycol-group and chain-terminus oxidation-reactions.

The extent to which such interpretations may require modification or extension to encompass unsubstituted molecules is not yet fully apparent, although the comparative studies and interpretations advanced by Jeffrey and Kim[20] from considerations of certain alditols in the solid state provide a valuable, general basis. Detailed, comparative investigations of such stereochemically complete series as the unsubstituted analogs of the compounds studied here, both in solution and in the solid state, should permit the development of broader generalizations.

EXPERIMENTAL

N.m.r. spectra. — Spectra were recorded at 250 MHz with a Cameca-250 spectrometer, at ~15°, for solutions (~5%) in chloroform-*d* containing ~10% of tetramethylsilane as the internal standard and lock Assignments were verified, as necessary, by spin decoupling or by the INDOR technique. Chemical-shift and spin-coupling data are recorded in Tables I and II. Spin-coupling values were measured directly from scans recorded at 300 Hz sweep-width and, except as indicated, exceeded the first-order approximation.

General procedure for preparation of aldohexose diethyl dithioacetals and their pentaacetates. — Except for those dithioacetals long established in the literature, and directly prepared crystalline by the classic procedure of Fischer[9], the following procedure was used. The free hexose (1 g) or derivative thereof was shaken vigorously at ~20° with conc. hydrochloric acid (2 mL) and ethanethiol (3 mL), and the reaction was monitored by t.l.c. (silica gel, 5:1 ethyl acetate–ethanol) to establish the optimal time of reaction. At this point, the mixture was diluted with methanol (~50 mL) and made neutral by stirring with an excess of lead carbonate. The solids were

filtered off, the filtrate evaporated, and the residue, generally an oil, purified on a column of silica gel eluted by the t.l.c. solvent, to afford the chromatographically pure dithioacetal, which was recrystallized from a suitable solvent.

The corresponding pentaacetates were prepared conventionally by keeping solutions of the dithioacetals in acetic anhydride–pyridine for 18 h at ~20°, pouring into water, and extracting the products with chloroform. The extracts were washed successively with aqueous sodium hydrogensulfate, sodium hydrogencarbonate, and water, dried (sodium sulfate), and evaporated, to give the pentaacetates in essentially quantitative yield.

D-*Allose diethyl dithioacetal.* — The starting material was methyl 4,6-*O*-benzylidene-α-D-allopyranoside[21]. The reaction was conducted for 2 h, and after chromatographic purification, the product was obtained as a crystalline solid; yield 50%, m.p. 92.5–94°, $[\alpha]_D^{20}$ −29.7° (*c* 0.7, methanol); lit.[22] m.p. 95–96°, $[\alpha]_D$ −30.8° in methanol, and[23] m.p. 94–95°, $[\alpha]_D^{26}$ −27.4° in methanol.

Anal. Calc. for $C_{10}H_{22}O_5S_2$: C, 41.93; H, 7.74; S, 22.39. Found: C, 41.71; H, 7.45; S, 22.35.

The *pentaacetate* was obtained as an oil: $[\alpha]_D^{20}$ +24° (*c* 0.8, chloroform).

Anal. Calc for $C_{20}H_{32}O_{10}S_2$: C, 48.37; H, 6.49; S, 12.91. Found: C, 48.49; H, 6.52; S, 12.70.

D-*Altrose diethyl dithioacetal pentaacetate.* — Prepared from the known[24] dithioacetal, this pentaacetate was crystallized from methanol–water; m.p. 90–91°, $[\alpha]_D^{20}$ +29.6° (*c* 0.5, chloroform).

Anal. Calc. for $C_{20}H_{32}O_{10}S_2$: C, 48.37; H, 6.49; S, 12.91. Found: C, 48.67; H, 6.21; S, 12.88.

L-*Gulose diethyl dithioacetal.* — Starting from L-gulose[25], and with a reaction time of 15 min, the product was obtained in 64% yield after column-chromatographic purification, and was crystallized from acetone–petroleum ether; m.p. 85.5–86°, $[\alpha]_D^{20}$ +20° (*c* 0.6, methanol).

Anal. Calc. for $C_{10}H_{22}O_5S_2$: C, 41.93; H, 7.74; S, 22.39. Found: C, 41.99; H, 7.48; S, 22.59.

The *pentaacetate* was crystallized from methanol–water; m.p. 50–52°, $[\alpha]_D^{20}$ +21.2° (*c* 0.8, chloroform).

Anal. Calc. for $C_{20}H_{32}O_{10}S_2$: C, 48.37; H, 6.49; S, 12.91. Found: C, 48.51; H, 6.29; S, 12.79.

L-*Idose diethyl dithioacetal.* — This compound, m.p. 96–97° (ethyl acetate), $[\alpha]_D^{22}$ −7.4° (*c* 1, methanol), and its pentaacetate, m.p. 55.5–57° (ether–petroleum ether), $[\alpha]_D^{22}$ −4.2° (*c* 1.2, chloroform) were prepared as recently described[26].

D-*Talose diethyl dithioacetal.* — This product was prepared from D-talose[27] according to a literature procedure[28]. The reaction was conducted for 1 h at 0°, and the product, purified by column chromatography, was obtained as a crystalline solid; yield 31%, m.p. 89–91°, $[\alpha]_D^{20}$ +24.5° (*c* 1, methanol); lit.[28] m.p. 92–93°, $[\alpha]_D$ +16° (*c* 0.19 methanol).

Anal. Calc. for $C_{10}H_{22}O_5S_2$: C, 41.93; H, 7.74; S, 22 39 Found: C, 42.10: H, 7.45; S, 22.24.

The *pentaacetate* was obtained crystalline from ether–petroleum ether: m.p. 72.5–73°, $[\alpha]_D^{20}$ +25.4° (*c* 1, chloroform).

Anal. Calc. for $C_{20}H_{32}O_{10}S_2$: C, 48.37; H, 6.49: S, 12 91 Found. C, 48.22: H, 6.35; S, 13.02.

*General procedure for preparation of penta-*O*-acetylaldohexose dimethyl acetals and their* O*-deacetylated counterparts.* — A solution of the penta-*O*-acetylaldohexose diethyl dithioacetal (10 mmol) in dry methanol (45 mL) containing cadmium carbonate (3.5 mol. equiv.) was mixed with a methanolic solution (35 mL) of mercuric chloride (6 mol. equiv.). The mixture was boiled (65°) under reflux for 24 h, and then evaporated. The residue was extracted with chloroform, processed conventionally[7] by extraction with chloroform, and the product purified by chromatography on a column of silica gel with 3:1 dichloromethane–ether as the eluant: the fastest-migrating product was the desired acetal.

O-Deacetylation of the products was achieved by the classic Zemplén procedure[16], employing methanol containing a trace of sodium methoxide. Evaporation of the methanolic solution afforded the desired product, which was either recrystallized from the solvent indicated or, for those products not obtained crystalline, passed through a column of silica gel (Merck 60, 70–230 mesh) by use of 5:1 (v/v) ethyl acetate–ethanol. In all instances, the use of a cation-exchange resin for demineralization was strictly avoided.

*Penta-*O*-acetyl-*D*-allose dimethyl acetal.* — This compound was obtained as an oil, $[\alpha]_D^{20}$ +16° (*c* 0.8, chloroform).

Anal. Calc. for $C_{18}H_{28}O_{12}$: C, 49.53; H, 6.46. Found: C, 49.33; H, 6.46.

Deacetylation afforded D-*allose dimethyl acetal* as an oil, $[\alpha]_D^{20}$ +9° (*c* 1.8, methanol).

Anal. Calc. for $C_8H_{18}O_7$: C, 42.47; H, 8.02. Found. C, 42.30, H, 8.00.

*Penta-*O*-acetyl-*D*-altrose dimethyl acetal.* — Crystallization was effected from ether–petroleum ether; m.p. 54–56°, $[\alpha]_D^{20}$ +28.5° (*c* 1, chloroform).

Anal. Calc. for $C_{18}H_{28}O_{12}$: C, 49.53: H, 6.46. Found· C, 49.54; H, 6.35.

Deacetylation gave D-*altrose dimethyl acetal* as an oil, $[\alpha]_D^{20}$ −24° (*c* 0.6, methanol).

Anal. Calc. for $C_8H_{18}O_7$: C, 42.47; H, 8.02. Found: C, 41.94, H, 8.16.

*Penta-*O*-acetyl-*L*-gulose dimethyl acetal.* — This compound was crystallized from ether–petroleum ether; m.p. 113–115°, $[\alpha]_D^{20}$ −13° (*c* 0.8, chloroform).

Anal. Calc. for $C_{18}H_{28}O_{12}$: C, 49.53; H, 6.46. Found: C, 49.65; H, 6.58.

L-*Gulose dimethyl acetal*, obtained as an oil, had $[\alpha]_D^{20}$ −5° (*c* 2, methanol)

Anal Calc. for $C_8H_{18}O_7$· C, 42.47; H, 8.02 Found: C, 41.83; H, 8.09.

*Penta-*O*-acetyl-*L*-idose dimethyl acetal.* — Crystallization from ether–petroleum ether gave this compound, having m.p. 85–86°, $[\alpha]_D^{20}$ −25.4° (*c* 1, chloroform).

Anal. Calc. for $C_{18}H_{28}O_{12}$: C, 49.53; H, 6.46 Found: C, 49.70; H, 6.39.

Crystallization of the deacetylated product from methanol–ether gave L-*idose dimethyl acetal*, m.p. 95–96°, $[\alpha]_D^{20}$ +30° (*c* 0.7, methanol).

Anal. Calc. for $C_8H_{18}O_7$: C, 42.47; H, 8.02. Found: C, 42.46; H, 8.20.

Penta-O-acetyl-D-mannose dimethyl acetal. — This compound was obtained crystalline from ether–petroleum ether: m.p. 66–68°, $[\alpha]_D^{20}$ +27.3° (*c* 1.3, chloroform).

Anal. Calc. for $C_{18}H_{28}O_{12}$: C, 49.53; H, 6.46. Found: C, 49.69; H, 6.50.

O-Deacetylation gave the known[29], crystalline D-*mannose dimethyl acetal*, m.p. 98–99°, $[\alpha]_D^{25}$ −5.9° (*c* 1.2, methanol), $[\alpha]_D^{25}$ −2.0° (*c* 1, water); lit.[29] m.p. 101°, $[\alpha]_D^{20}$ +0.6° in water.

Penta-O-acetyl-D-talose dimethyl acetal — This compound was obtained as an oil, $[\alpha]_D^{20}$ +27° (*c* 0.9, chloroform).

Anal. Calc. for $C_{18}H_{28}O_{12}$: C, 49.53; H, 6.46. Found: C, 49.46; H, 6.50.

O-Deacetylation gave D-*talose dimethyl acetal* as an oil, $[\alpha]_D^{20}$ −16° (*c* 2.5, methanol).

Anal. Calc. for $C_8H_{18}O_7$: C, 42.47; H, 8.02. Found: C, 42.22; H, 8.02.

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