Conformation of Acyclic Derivatives of Sugars. XI. Conformations of the D-Aldopentose Diethyl and Diphenyl Dithioacetals in Solution[1]

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Received November 27, 1973

The conformations of the unsubstituted aldopentose diethyl and diphenyl dithioacetals having the D-ribo [1 (Et), 2 (Ph)], D-arabino [3 (Et), 4 (Ph)], D-xylo [5 (Et), 6 (Ph)], and D-lyxo [7 (Et), 8 (Ph)] configurations have been examined in methanol-d_4 solution by pmr spectroscopy at 100 MHz. Complete sets of proton–proton spin-coupling constants were determined for **2** (in a mixed solvent), **3** (in the presence of 0–100 mequiv of $PrCl_3 \cdot 6D_2O$), **6**, **7**, and **8**; partial spin-coupling data were obtained for the remainder. Clearly preponderant conformations are indicated for **3**, **7**, and **8** (all planar zigzag), for **2** and **5** [a sickle ($_3G^+$) form derived by rotation of the carbon chain about the C-3–C-4 bond] and, to a somewhat lesser extent, for **1** [a sickle ($_2G^-$) form generated by rotation of the chain about the C-2–C-3 bond]; $J_{1,2}$ values for **4** are consistent with the extended conformation, whereas the xylo derivative **5** is manifestly in a state of conformational instability. Variations in the solvent appear to exert no major influence upon these conformations. Conclusions from previous studies on acetylated derivatives are compared in an effort to assess the relative importance of 1,2 and 1,3 interactions in determining the stability of conformers. Attempts to describe quantitatively the conformational behavior of acyclic carbohydrates in terms of simple substituent-interaction parameters are not considered justifiable.

An extended, planar zigzag arrangement of carbon atoms, corresponding to maximal staggering of large substituents along each carbon–carbon bond, is considered[2] to be the favored conformation in polymethylene chains. Extension of this conformational concept to alditols was invoked in an effort to interpret the course of reactions leading to cyclic acetals.[3] In the latter study, the influence of thermodynamic control upon the product distribution was, however, not taken into account.[4]

Pmr data have indicated[5] that various isotactic vinyl polymers, such as polypropylene, in which the extended zigzag conformation would generate nonbonded interactions between parallel substituents on β-related carbon atoms, adopt, by internal carbon–carbon bond rotation, a conformation wherein these interactions are minimized at the expense of establishing a gauche disposition of carbon substituents along a carbon–carbon bond. Similar parallel interactions, between β-related hydroxyl groups, would exist in a tetrahydroxybutyl chain having the ribo or xylo stereochemistry were it to adopt the extended, zigzag conformation.

Numerous reports[1a,6-22] appearing during the past 6 years have described the use of pmr-spectral techniques [predicated on the premise[23-25] that small (~3 Hz) vicinal proton–proton couplings indicate a gauche (~60°) and large (~8 Hz) ones an antiparallel (~180°) dihedral relationship of the respective protons] to probe the influence of stereochemical configuration on the conformational properties of various polysubstituted acyclic chains that are present in open-chain sugar derivatives (see Table I). Slight liberties of reinterpretation have been taken for the sake of uniformity of presentation in a summary.

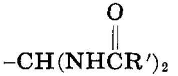
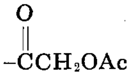
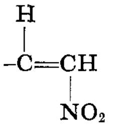
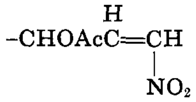
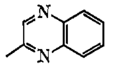
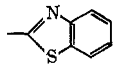
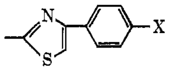
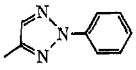
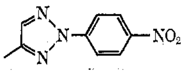
It is at once apparent from Table I that arabino, and to a somewhat lesser extent lyxo, side chains exhibit the anticipated predisposition for the planar, zigzag conformation; it is likewise manifest that the conformational behavior of both ribo and xylo systems is virtually devoid of clear patterns, save for the general tendency for them to exhibit conformational instability and to avoid planar, zigzag forms as favored conformations. However, three additional examples, 3,4-di-*O*-acetyl-1,2:5,6-bis(thioanhydro)-D-mannitol, -D-glucitol, and -L-iditol, have been examined by pmr spectroscopy and it was concluded[29] that *all three* adopt a $_3G^-$ (see footnote *a*, Table I) conformation that includes *parallel eclipsed interactions between both acetoxyl groups and the respective remote epithio rings,* so that there is considerable evidence to dictate caution in the formulation of hard and fast rules to predict conformational behavior in these acyclic molecules; it has been suggested,[27] moreover, from studies[30] of the conformationally simpler pentopyranose acetates, that specific interactions may exist between ester groups within the molecule.

Investigations on the conformations in solution of the nonacylated analogs of acylic compounds such as those listed in Table I are warranted for two reasons in particular. First of all, acylated carbohydrates are rare in biological systems, whereas nonacylated forms are ubiquitous; information on the favored shapes and conformational dynamics of simple polyhydroxyalkyl chains is of direct relevance for gaining insight into numerous biological processes. Secondly, the additional complication of possible acyl-group interaction is absent from the unsubstituted compounds, and correlation with solid-state X-ray crystallographic data is facilitated; such data are much more abundant in the literature for the unsubstituted derivatives than for the acylated analogs, which offer considerably greater procedural difficulty. Although X-ray crystallographic studies have indicated[31] that the conformations of such unsubstituted acyclic sugar derivatives as the alditols are governed by factors similar to those set out for the molecules in solution, specific examples of solid-state crystallographic data and detailed pmr data for the same molecules in solution are notably lacking. One such comparison has been described in a recent report,[1a] where it was shown that 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal adopts in the crystal an extended conformation closely analogous to that postulated from pmr data as the favored form in acetone-d_6 solution; the corresponding tetraacetate in chloroform-*d* solution likewise adopts a very similar conformation of the backbone chain, as judged from pmr-spectral data.

Fragmentary data have been reported for some unsubstituted phenylosotriazoles,[19,20] quinoxalines,[21] and benzylphenylhydrazones[22] in solution and a recent report[12] indicates that the 2-(tetrahydroxybutyl)benzothiazole isomers having the D-ribo, D-arabino, and D-xylo stereochemistry adopt a partially unstable $_2G^-$, a virtually exclusive planar zigzag, and a completely unstable conformation, respectively, in almost exact correspondence with their respective acetates.

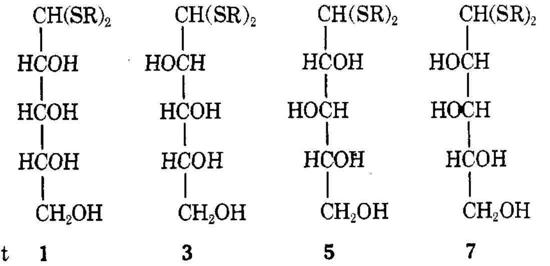
The present report describes the conformation in solu-

Table I
Favored Conformations of 1,2,3,4-Tetraacetoxybutyl Derivatives [$R(CHOAc)_3CH_2OAc$] in Solution as Determined by Pmr Spectroscopy

R	Favored conformation[a]				Ref
	D-ribo	D-arabino	D-xylo	D-lyxo	
$-CH(SPh)_2$				**P** ($_4G^-$)	4
	$_3G^+$	*P*[b]	$_3G^+$		5
$-CH(SEt)_2$	Unstable	**P**	Unstable	*P*[b]	6
$-CH(OMe)_2$	[$_2G^-$]	*P*[b]	Unstable	*P*[b]	3
 $-CH(NH\overset{O}{\overset{\Vert}{C}}R')_2$	[$_2G^-$]	**P**	$_3G^+$	**P**[b]	7
$-CH_2OAc$	Unstable	**P**	Unstable	*d*	9
 $-\overset{O}{\overset{\Vert}{C}}CH_2OAc$	$_2G^-$	**P**	$_3G^+$		14
$-CO_2CH_3$[e]	$_2G^-$	**P**	Unstable	*P*	14
$-CHO$	$_2G^-$ ($_4G^-$)	**P**	Unstable	Unstable	4
$-CSNH_2$		**P** ($_4G^-$)[f]	$_3G^+$		13
$-C{\equiv}N$	$_2G^-$ ($_4G^-$)	*P* ($_4G^-$)[g]	$_3G^+$	Unstable	11
 $-\overset{H}{\overset{\vert}{C}}{=}\underset{\underset{NO_2}{\vert}}{CH}$	$_2G^-$ ($_4G^-$)	**P** ($_4G^-$)	Unstable[h]		12
 $-CHOAc\overset{H}{C}{=}\underset{\underset{NO_2}{\vert}}{CH}$		*P*		**P**[i]	10
		*P*[j]	Unstable	*P*	17
	[$_2G^-$]	*P*	[$_3G^+$]		8
		*P*	[$_2G^-$][c]		13
		*P* ($_4G^-$)	$_2G^-$[f]	*P*	2
(5–deoxy)		Unstable[f]			2
		*P*	$_3G^+$[c,f]	*P*	2
(5–deoxy)		[$_2G^+{}_4G^+$][f]			2

[a] *P* denotes planar, zigzag preponderates; **P** denotes planar, zigzag is virtually exclusive form; [*P*] indicates slight preference for the planar, zigzag (or other) conformation, but modest conformational instability and large contribution by two or more states to the conformational equilibrium;[26] $_2G^-$ denotes[27] the sickle obtained by 120° clockwise rotation of the remote atom along the C-2–C-3 bond; $_3G^+$ denotes[27] the sickle form obtained by 120° counterclockwise rotation of the remote atom along the C-3–C-4 bond; unstable signifies that there is no single, identifiable, favored conformation and indicates a high degree of conformational instability. [b] There is some instability about the C-1–C-2 bond. [c] There is some instability about the C-4–C-5 bond. [d] Identical with D-arabino; the symmetry of this derivative precludes conclusions about D-ribo and D-xylo conformations. [e] The $-CH_2OAc$ terminus is replaced by $-C(=O)CH_2OAc$. [f] Data are reported for the enantiomorph. [g] Data for this compound are reported also in ref 13. [h] Data for this compound are reported also in ref 28. [i] Rotation occurs about the C-1–C-2 axis to remove the nonextended C-1 substituent from 1,3 interaction with O-3. [j] Data for this compound are reported also in ref 15.

tion (methanol-d_4), as determined by analysis of 100-MHz pmr coupling constants, of two configurationally complete series of acyclic D-aldopentose derivatives having tetrahedrally hybridized end groups, namely D-ribose diethyl[32] (1) and diphenyl dithioacetal[9] (2), D-arabinose diethyl[33] (3) and diphenyl dithioacetal[9] (4), D-xylose diethyl[34] (5) and diphenyl dithioacetal[9] (6), and D-lyxose diethyl[35] (7) and diphenyl dithioacetal[8] (8).



R = Et	1	3	5	7
R = Ph	2	4	6	8

Experimental Section

Compounds 1–8 had physical constants in agreement with published values. After exchange of the hydroxyl protons in D_2O, 100-MHz spectra of each compound [20 ± 2 mg in 0.3 ml of methanol-d_4 (Stohler) containing 3% Me_4Si as a lock signal and internal calibrant] were recorded on a Varian HA-100 spectrometer in the frequency-swept mode at a probe temperature of ~30°. Additions of pyridine-d_5 or of a solution (0.01 molar equiv per drop) of $PrCl_3 \cdot 6D_2O$ in methanol-d_4 were dropwise, with regular spectral scanning to monitor the effect of each addition. $PrCl_3 \cdot 6D_2O$ was prepared from the hexahydrate (Alfa-Ventron) by three repetitions of a cycle consisting of heating in two volumes of D_2O for 1 hr followed by lyophilization.

Table II
Pmr-Spectral Parameters Determined at 100 MHz for Solutions ($\sim$0.5 *M*) of Dithioacetals 1–8 in Methanol-d_4 at $\sim$30°

H_i or $J_{i,j}$	Chemical shifts of H_i, τ, and coupling constants $J_{i,j}$, Hz							
	D-ribo		D-arabino		D-xylo		D-lyxo	
	Ethyl (1)	Phenyl[a] (2)	Ethyl[b] (3)	Phenyl[c] (4)	Ethyl[d] (5)	Phenyl (6)	Ethyl (7)	Phenyl (8)
$J_{1,2}$	8.0	1.6	9	8[e]	2.2	5.5	1.9	1.3
$J_{2,3}$	3.6	7.9	2		8.5	4.2	8.5	8.6
$J_{3,4}$	3.6[e]	3.6	8		4.5[e]	4.0	1.3	2.5
$J_{4,5}$		2.6	4			1.8	6.0	6.0
$J_{4,5'}$		7.2	6.5			9.1		
$J_{5,5'}$		10.3	12			11.6		
H-1	5.96	4.48	5.88	5.10	5.72	5.23	5.72	4.96
H-2	6.22	5.51	6.12	6.02	6.04	6.05	5.98	5.89
H-3	5.94	5.40	5.95			5.84	6.21	6.09
H-4	$\sim$6.28	5.71	6.19			6.27	6.05	6.03
H-5	$\sim$6.32	5.86	6.01			6.36	6.36	6.39
H-5′	$\sim$6.40	5.91	6.33	6.62	6.32	6.41	6.36	6.39
CH_2	7.29		7.23, 7.22		7.30, 7.26		7.31, 7.28	
CH_3	8.77		8.76, 8.75		8.74, 8.73		8.78, 8.76	
Ph		2.40–2.75		2.49–2.76		2.39–2.77		2.43–2.75

[a] Spectrum determined in 1:1 methanol-d_4–pyridine-d_5. [b] J values were determined in the presence of varying amounts of Pr^{3+}; chemical shifts were estimated by extrapolation back to zero concentration of the lanthanide. [c] In methyl sulfoxide-d_6; $J_{1,2}$ was unchanged in pyridine-d_5. [d] J values were determined in the presence of 30 millimolar equiv of $PrCl_3 \cdot 6D_2O$. [e] Measured spacings from X portion of presumed second-order systems.

Nmr Spectra. The 100-MHz pmr spectra of $\sim$0.2 *M* solutions of the (hydroxyl proton-exchanged) dithioacetals 1–3 and 5–8 in methanol-d_4 at $\sim$30° confirmed that the compounds were essentially free from contaminants and from hydroxylic protons; the insolubility of compound 4 in this solvent necessitated the use of methyl sulfoxide-d_6 or of pyridine-d_5 to obtain data on 4. The diphenyl dithioacetals 2, 4, 6, and 8 showed at lowest field between τ 2.40 and 2.75 a complex, ten-proton multiplet corresponding to the protons of the arylthio groups; at high field in the spectra of the corresponding diethyl dithioacetals are two three-proton triplets of identical or nearly identical chemical shift (near τ 8.75) and two two-proton quartets exhibiting similar chemical-shift relationships near τ 7.25, which are assigned to the methyl and methylene resonances, respectively, of the ethyl groups. The spectra of 1–3 and 5–8 are otherwise largely dissimilar, having the H-1 resonance at lowest field (near τ 5.8 for 1, 3, 5, and 7 or near τ 5.0 for 2, 6, and 8), generally as a doublet, and the remaining five resonances in the region from τ $\sim$5.8 to $\sim$6.4; the details of the skeletal proton resonances are discussed individually. A singlet near τ 5.2 in all these spectra is attributed to residual hydroxylic protons present in the solvent and the sample.

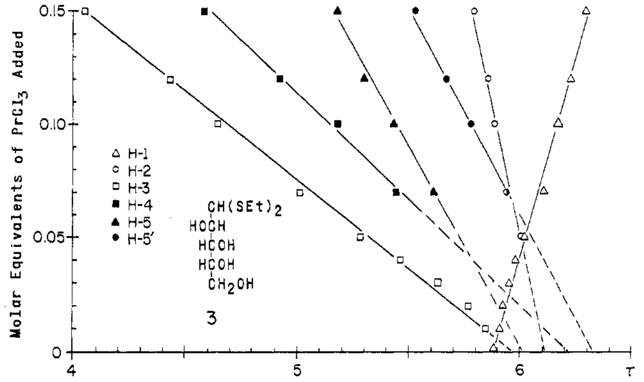


Figure 1. Plot of the chemical shifts of the proton resonances of D-arabinose diethyl dithioacetal (3) *vs.* the relative concentration of $PrCl_3 \cdot 6D_2O$ added. Values for the unperturbed chemical shifts were estimated by extrapolation back to zero concentration of Pr^{3+}.

Discussion

General Considerations Underlying the Deduction of Conformational Dispositions from Spin-Coupling Data. As in earlier studies,[4,6] it is assumed that interconversion between rotameric states is rapid, and that a pure antiparallel or a pure gauche relationship between vicinal pairs of protons gives rise to a coupling constant of $\sim$9 or $\sim$2 Hz, respectively. The latter assumption is reasonable, in that the effective electronegativity of the hydroxyl oxygen atom should be only slightly greater than that in the acetylated analog.

D-Arabinose Diethyl Dithioacetal (3). Compound 3 in methanol-d_4 gives a single, connected multiplet from τ 5.8 to 6.4 for the six skeletal-proton resonances. Incremental additions of $PrCl_3 \cdot 6D_2O$ in methanol-d_4 caused the identifiable separation of various signals in the spectrum at different lanthanide-ion concentrations (at the expense of some line broadening), and it was possible to measure the splittings of each resonance as it emerged from the envelope; at the low relative concentrations of Pr^{3+} employed, it appears that no significant alteration of conformation is caused by complexation[36] with the cation. Chemical-shift values were estimated by extrapolation of the approximately linearly dependent, paramagnetically altered field positions to zero concentration of added lanthanide, as illustrated in Figures 1 and 2. It is noteworthy that the lanthanide causes progressive downfield shifts for all protons except H-1: the signal of the latter undergoes moderate upfield shifts as the concentration of lanthanide increases.

The coupling parameters thus derived (Table II) accord with a dominant contribution to the conformational equilibrium[26] by a conformer having H-1 antiparallel to H-2, H-2 gauche to H-3, H-3 antiparallel to H-4, and an equilibrium about the C-4–C-5 bond between the forms having O-5 in the extended position (major) and in the gauche position remote from O-3 (minor), as shown by the planar zigzag representation **3a** and the derived conformation **3b**.

D-Arabinose Diphenyl Dithioacetal (4). Compound 4 is so insoluble in D_2O that hydroxyl-proton exchange could be accomplished only under extended refluxing, and it is also insoluble in methanol-d_4. The nmr spectra of solutions of 4 in pyridine-d_5 or methyl sulfoxide-d_6 exhibited gross similarity to those observed for the other seven examples in this study, displaying a well-separated H-1 doublet (from which $J_{1,2}$ was estimated) located between the aromatic resonances at low field and an effectively featureless, broadened envelope of signals from H-2 to H-5′; the addition of relatively enormous amounts of Pr^{3+} to these and similar solutions succeeded only in producing further broadening and negligible ($\sim$0.2 ppm/mol of Pr^{3+}) dislocations of the resonance positions, owing (presum-

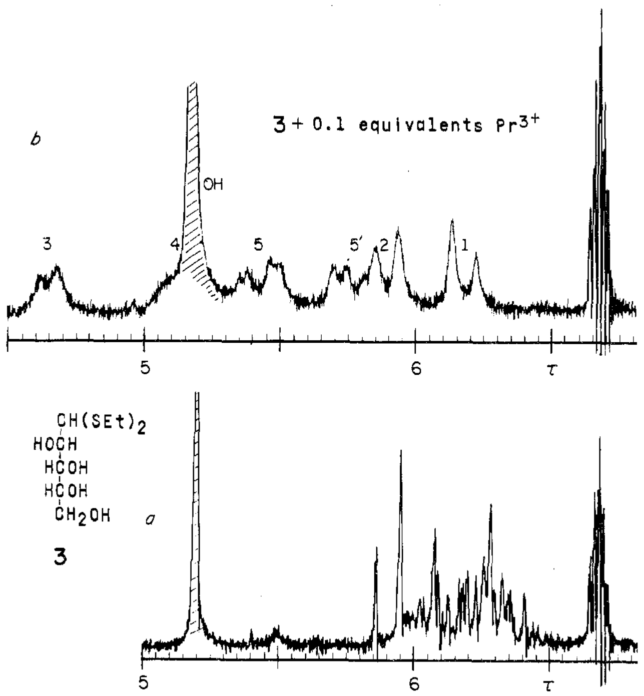


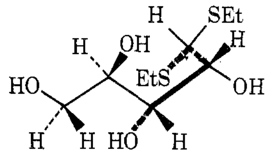
Figure 2. Pmr spectrum at 100 MHz of the chain protons of 3 in methanol-d_4 in the presence of (*a*) 0 and (*b*) 100 mequiv of $PrCl_3$; the signal to highest field is due to the solvent.

ably) to extremely efficient competition by the solvents for the cation.

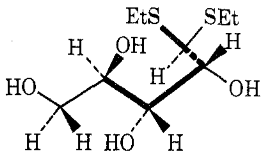
As dominance of the conformational equilibrium of 4 by the planar, zigzag form is predicted by analogy with most of the examples in Table I, the preponderant extended conformation may be assumed[19-22] with reasonable confidence, even though only the $J_{1,2}$ value is available experimentally.

D-Lyxose Diethyl (7) and Diphenyl Dithioacetals (8). Closely similar spectra and conformations are observed for both 7 and 8. The H-1 resonance is observed at low field as a doublet ($J_{1,2} > 2$ Hz), followed, in turn, by the H-2, H-4, and H-3 signals and a doublet for the fortuitously equivalent, terminal methylene protons. The values in Table II were secured by approximate second-order analysis;[37] addition of $PrCl_3 \cdot 6D_2O$ or of $EuCl_3 \cdot 6D_2O$ failed to produce any spectral simplification. The values for $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ are clearly extreme ones, so that, despite the fact that the anisochronous methylene protons at C-5 resonate at the same field position and thus obscure any information contained in $J_{4,5}$ and $J_{4,5'}$, a conformational equilibrium may be specified (for both 7 and 8) that is absolutely dominated by the planar, zigzag form.

D-Ribose Diethyl Dithioacetal (1). The spectrum of 1 in methanol-d_4 is only partly separated and attempted simplification by additions of paramagnetic ions or of second solvents generally failed; observable H-1 and H-2 signals, however, allowed the determination of $J_{1,2}$ and $J_{2,3}$, and an estimation of $J_{3,4}$ (Table II). These values accord with the ${}_2G^-$ sickle conformation **1a**, which complements the elucidation of this arrangement for eight of nine examples in Table I, although the tendency toward intermediacy in the coupling magnitudes is suggestive of some degree of conformational nonuniformity (that is, instability). This observation points up a trend in the ribo column of Table I, which reveals that trigonally (or linearly) hybridized R groups seem to favor enhanced stability in the ${}_2G^-$ conformation compared to tetrahedral termini. Examination of the ${}_2G^-$ representations **1a** and **1b** (with particular reference to the intensified bonds) reveals that these sickle forms are *not* totally free of parallel, eclipsed interactions where R is tetrahedral and disubstituted so that this trend in Table I can thus be rationalized. The slightly low $J_{1,2}$ value may also reflect some distortion of **1b** away from exact staggering about the C-1–C-2 bond in order to alleviate the parallel, C-4–S interaction.



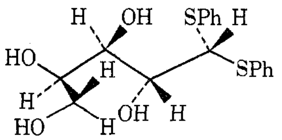
1a



1b

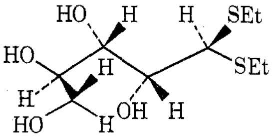
D-Ribose Diphenyl Dithioacetal (2). The spectrum of 2 in methanol-d_4 was only partially resolved and, although sequential additions of either Pr^{3+} or Eu^{3+} failed to imporve signal separation before excessive line broadening prevailed, it was found that the addition of pyridine-d_5 (up to 50% of the final solvent mixture) effected sufficient spectral dispersion to permit second-order calculation by using the LAOCN3 program. The magnitude of $J_{1,2}$ was observed to be relatively solvent independent, as are other examples of this type.

Coupling constants in Table II support a ${}_3G^+$ (sickle) conformation (**2a**) for 2 generated from the planar, zigzag form by counterclockwise rotation about the C-3–C-4 bond in order to place O-4 in the extended position formerly occupied by C-5; this conformation, which *is* free of eclipsed 1,3 interactions, has been reported for only one previous[9] example, the corresponding acetate. The possibility exists of an attractive interaction between the two aromatic groups, especially in methanol-d_4, although such an effect should serve to decrease, rather than increase, the effective size of the sulfur atoms.



2a

D-Xylose Diethyl Dithioacetal (5). The addition of 30 mequiv of $PrCl_3 \cdot 6D_2O$ to a solution of 5 in methanol-d_4 produced the most informative spectrum of this compound, allowing measurement of $J_{1,2}$ and $J_{2,3}$ and estimation of $J_{3,4}$. The values of the former two coupling constants, 2.2 and 8.5 Hz, respectively, indicate a substantial energetic preference for the ${}_3G^+$ conformer **5a**, whereas the intermediacy of the somewhat uncertain $J_{3,4}$ (4.5 Hz) offers the possibility of a moderate degree of instability about the C-3–C-4 bond. The unavailability of coupling information for H-4–H-5 interactions precludes speculation about the C-4–C-5 rotameric state.



5a

D-Xylose Diphenyl Dithioacetal (6). The spectrum of 6 in methanol-d_4, which is unique in this series of derivatives in having all of its resonances completely separated, is presented in Figure 3 to illustrate the resolution available in this solvent. In contrast to the preceding examples, the conformational behavior of 6 appears to feature extreme instability about the C-1–C-2–C-3 portion of the molecule, for which no discrete conformation can be identified as an important contributor to the rotameric equilibrium, but to exhibit almost total uniformity of confor-

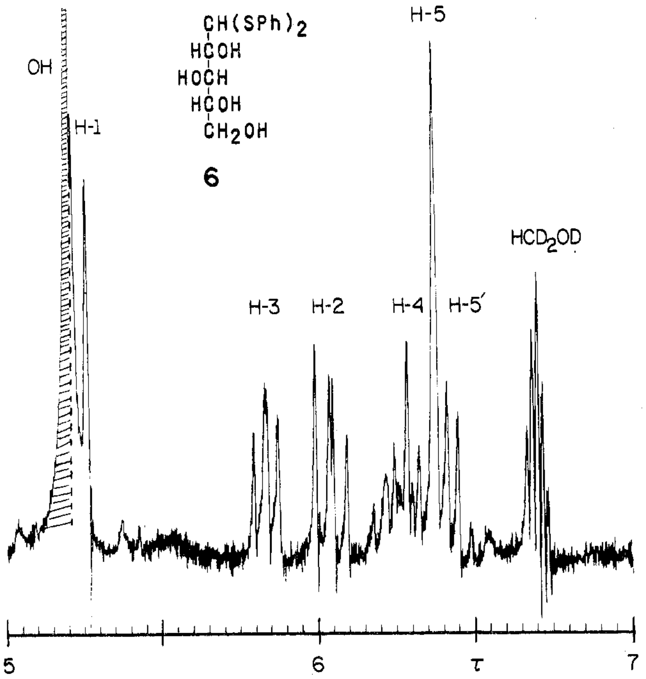


Figure 3. Pmr spectrum at 100 MHz of D-xylose diphenyl dithioacetal (6) in methanol-d_4.

mation in the C-3–C-4–C-5 segment. A decrease in effective size[38] of the arylthio sulfur atom, as anticipated (but not observed) for the xylo analogs, would act to minimize parallel, eclipsed interactions involving the sulfur atoms and O-3 or C-4 and might thus increase the relative stability of the zigzag and the $_2G^-$ conformations,[38] although no rationalization is immediately apparent for the seeming reversal of this effect in the ribo compounds **1** and **2**.

Summarizing, compounds **1–8** appear to follow the broad generalization that conformations incorporating eclipsed, 1,3 interactions between pairs of large groups tend to be relatively destabilized, so that, within the limits of their general validity, the conclusions drawn from studies of acetylated analogs can be extended with some degree of confidence to the unacylated carbohydrates. Quantitative, conformational predictions, either for acetylated or for unsubstituted acyclic carbohydrates, are currently out of the question, and, although a direct demonstration such as that presented[26c] to establish that conformations of the comparatively simpler aldopentopyranosyl derivatives are not amenable to quantitative correlation to simple, substituent-interaction parameters cannot be mustered, the prospect of such a simple correlation's evolving for the acyclic series is not optimistic.

Acknowledgments. Assistance in effecting some of the deuterium-exchange operations was tendered by Donnie Bixler and Edward W. Rhode, III.

Registry No.—**1**, 7152-47-8; **2**, 6748-71-6; **3**, 1941-50-0; **4**, 6838-07-9; **5**, 13263-74-6; **6**, 28712-17-6; **7**, 6838-08-0; **8**, 30571-60-9.

References and Notes

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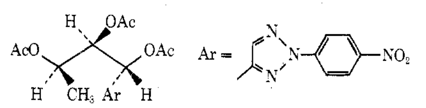
(38) The concept of effective size was invoked[6] originally to formulate the rationalization that the observed $_2G^-$ $_4G^-$ (enantiomorphic to $_2G^+$ $_4G^+$ in the D series) conformation of tri-*O*-acetyl-6-deoxy-L-*arabino*-hexulose *p*-nitrophenylosotriazole corresponds to a planar, zigzag form if the effective size of the methyl and heterocyclic sub-



stituents that represent the termini of the backbone in the Fischer projection is smaller than that of the two acetoxyl groups (O-2 and O-4 in the convention of Table I) occupying the extended positions of the reported conformation. The sensitivity of the conformation of this molecule to the presence of the physically remote nitro group highlights the weaknesses in arguments seeking to describe[17] this phenomenon quantitatively.