Solution Conformation of Sucrose from Optical Rotation

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Abstract: We have calculated the optical rotation of methyl β-D-arabinofuranoside, methyl β-D-fructofuranoside, and sucrose as a function of ring conformation and, in the case of sucrose, of linkage conformation. Comparison with experimentally observed optical rotations allows assignments of solution conformations; our results agree with some but not all of the previously reported assignments. We conclude that the furanose ring form that predominates in aqueous solution has the same phase angle of pseudorotation for all three compounds, slightly to the northeast of the canonical northern conformer; i.e., ${}^{3}_{4}$T-${}_{4}$E in methyl β-D-arabinofuranoside, ${}^{4}_{5}$T-${}_{5}$E in methyl β-D-fructofuranoside, and ^{4}E-${}^{4}_{5}$T-${}_{5}$E in the β-D-fructofuranosyl moiety of sucrose. These assignments are shown to be consistent with NMR parameters in the literature. The optical rotation of sucrose is best accounted for in terms of an equilibrium mixture of two linkage conformers, the predominant one being similar to the crystalline structure in which the O1′-O2 intramolecular hydrogen bond persists and the other representing a secondary energy minimum in which the O1′-O2 hydrogen bond is replaced with an O3′-O2 intramolecular hydrogen bond.

The sweetness of chlorodeoxy analogues of sucrose [β-D-fructofuranosyl-(2′-1)-α-D-glucopyranoside] is many times that of sucrose itself.[1] In at least one of these, TGS,[1e] the crystalline structure[1e] contains an O3′-O2 intramolecular hydrogen bond rather than the O1′-O2 hydrogen bond of crystalline sucrose. Recent NMR evidence indicates that in solutions of sucrose both intramolecularly hydrogen bonded forms exist in equilibrium with one another.[2] The possibility therefore exists that the sweetness of sucrose is less related to its crystalline structure than the alternative solution conformer, making the detailed description of the structure of sucrose in solution a matter of continuing interest.[3]

The optical activity of saccharides is determined by their chemical composition, configuration, and conformation, and a detailed calculational model has recently been developed aimed at allowing conformational assignments to be obtained from measurements of optical rotation.[4,5] The model has its origins in Kirkwood's polarizability theory of optical activity[6] and is somewhat less empirical than earlier analyses by Hudson,[7] Whiffen,[8] Brewster,[9] Lemieux,[10] Rees,[11] and others. It has previously been applied to maltose,[12] cellobiose,[12] lactose,[13] and trehalose.[14]

We have extended the method here to sucrose, beginning with an examination of the dependence of optical rotation on the furanose ring conformation in methyl β-D-fructofuranoside and its simpler analogue methyl β-D-arabinofuranoside. Furanoses have not previously been examined with this model; the optical rotation of a tetrahydrofuran derivative, however, has been successfully reproduced.[4c]

In spite of the conformational lability of furanoid rings, conformational preferences exist.[15-17] Ring conformation assignments for methyl β-D-arabinofuranoside have been proposed on the basis of kinetics[18] and NMR[17,19,20] measurements. Methyl β-D-fructofuranoside has been studied by NMR spectroscopy,[21-23] and D-fructofuranose has been the object of molecular mechanics calculations.[24,25] In the case of sucrose, interest has mainly been in establishing the interresidue linkage conformation in solution, but some attention has been paid to the ring conformation of the fructose moiety. Molecular modeling calculations,[26-28] NMR spectroscopy,[2,21,26,29] and other[30] methods have been used. The

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(16) Evidence that conformational fluctuations in furanoid rings can sometimes be quite limited comes from NMR spectroscopy. For example, in methyl β-D-arabinofuranoside $J_{H2,H3}$ = 8.0 Hz and $J_{H3,H4}$ = 7.1 Hz.[17] Any significant conformational averaging involving the C2-C3-C4 framework would reduce the observed values below these nearly maximum values.

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crystal structure of sucrose is well established.[31] Evidence both for[26,29] and against[2,30] crystal–solution structural equivalence has been described.

The chiroptical method of saccharide conformational analysis described here is intended to complement NMR methods. The interpretation of NMR data is not always simple. Karplus relationships used to interpret coupling constants contain an inherent degeneracy; e.g., dihedral angles of θ and $-\theta$ lead to the same coupling constant. When the molecule has significant flexibility, scalar NMR parameters represent a time-averaged conformation and NOE's, for example, may give a picture in which excessive weight is given to conformers in which internuclear separations are small.[32] It is not uncommon for residual ambiguities in conformational assignments based on NMR data to be removed by resort to steric arguments or calculated potential energy surfaces. Molecular modeling force fields, however, are still in the developmental stage,[33] and guidance for their refinement must come from experiment.

Our approach has been[12-14] to combine our interpretive model of optical activity with literature NMR results and molecular modeling calculations to generate descriptions of solution conformations most consistent with all three methods.

Calculational Method

The calculational method, previously described in detail,[4,12] is based on a coupled-oscillator model which requires the solution of the secular equations

$$\sum_{i=1}^{N} C_{ik}(V_{ij} - E_k\delta_{ij}) = 0 \qquad j = 1, 2, \ldots N$$

where V_{ij} is the coulombic interaction energy of transition dipole moments μ_i and μ_j representing far-UV electronic transitions localized on C–C, C–O, and C–H bonds; the model is thereby geometry dependent. The solution yields eigenvalues, E_k, specifying molecular transition energies, and eigencoefficients, C_{ik}, which describe the molecular transition moments as linear combinations of the unperturbed bond-localized transition moments. Circular dichroic rotational strengths are obtained directly, from which the optical rotation is calculated via a Kronig–Kramers transform. We report results as the molar rotation [M] at 589 nm. In the present work the same transition moment parameters, solvent correction, and scale factor were used as in the original description of the method.[4,12]

For each furanose ring 20 conformers were examined separately, 10 envelope forms (E) and 10 twisted forms (T).[25,28,34] In envelopes, one ring atom is out of the plane of the remaining four; in twists two neighboring ring atoms are on opposite sides of the plane of the remaining three. The terms β-face and α-face, as usually defined, are taken to specify the regions above and below the plane, respectively. Specific conformers are denoted with a superscript indicating an above-plane atom and a subscript indicating a below-plane atom; thus ${}_5$E denotes the envelop with C5 below the plane and ${}^0_5$T denotes the twisted form with the ring oxygen above and C5 below the plane. The anomeric carbon is C1 in aldofuranoses but C2 in 2-ketofuranoses, so that the ring conformer specified as ${}_4$E for arabinofuranoside, for example, is specified as ${}_5$E in the case of fructofuranoside. Conversion among the 20 conformers is pictured as taking place through a pseudorotational itinerary, the position of each conformer being specified by a phase angle.[34] By convention[34] North–South–East–West indicators (N, S, E, W) are used along the itinerary; here the ${}^3_2$T arabinofuranoside and the ${}^4_3$T fructofuranoside rings define the canonical North position (Tables I, II, and III).

Atomic coordinates for the furanose ring conformers were generated using the crystal structure of sucrose as a basis.[31c] Coordinates for three consecutive atoms in the ring (i, $i+1$, $i+2$) defined a plane. The $i+3$ and $i+4$ atoms were initially positioned in the plane with the crystal structure bond lengths and bond angles. For envelopes, the ($i+3$)–($i+4$) bond was rotated about the ($i+2$)–($i+3$) bond until the (i)–($i+4$) bond length differed from that in the crystal structure by less than 0.02 Å. This procedure led to a slight decrease in the ($i+3$)–($i+4$)–(i) bond angle from that observed; the difference was less than 4° in most cases and never more than 7°. For twists, the ($i+2$)–($i+3$) and ($i+4$)–(i) bonds were rotated simultaneously until the ($i+3$)–($i+4$) bond length differed from the crystal structure value by less than 0.02 Å; bond angles were compressed to about the same degree as in envelopes. The puckering parameter,[34a] τ_m, for rings generated in this manner had values in the range 43 ± 10°.

In the two furanosides the methoxy group on the anomeric carbon atom was fixed in the *gt* conformation, gauche to the ring oxygen and trans to the next nearest ring carbon; the hydroxymethyl group, C5 in arabinofuranoside and C6 in fructofuranoside, was examined in all three conformations, *gt*, *gg*, and *tg*. Fructofuranoside was examined with its anomeric carbon hydroxymethyl group either trans to the ring oxygen and gauche to C3 (*tg*) or gauche to both (*gg*). Hydroxyl hydrogen atoms do not enter into the calculation; their positions need not be specified.

Thus, three exocyclic group conformers were examined separately for each arabinofuranoside ring conformation, and six exocyclic group conformers were examined for each fructofuranoside ring conformation. The calculated optical rotation for each arabinofuranoside ring conformation was averaged over the three C5 hydroxymethyl group conformations using the statistical weights *gt*/*gg*/*tg* = 0.62/0.20/0.18 determined from NMR measurements.[35] The same statistical weights were used in the case of the C6 hydroxymethyl group conformations of fructofuranoside. The C1 hydroxymethyl group conformers in fructofuranoside were taken to be equally probable, *gg*/*tg* = 0.50/0.50.

The sucrose linkage geometry is defined by the glycosidic bond angle, taken to be 117°, and by the two dihedral angles ϕ and ψ, where $\phi = 0°$ corresponds to the C1–H1 bond *cis* to the O1–C2′ bond, $\psi = 0°$ corresponds to the O1–C1 bond cis to the C2′–C1′bond, and positive values of ϕ and ψ refer to clockwise rotation of the fructofuranose residue (primed coordinates) as viewed from the glucopyranose residue. Optical rotations were calculated for linkage geometries representing energetically favored regions of ϕ,ψ-space, as indicated in the recent flexible-residue molecular modeling calculations of Tran and Brady.[28] In each linkage geometry examined the C6 hydroxymethyl group of the glucose residue was placed in both the *gt* and *gg* conformations; the calculated

Table I. Methyl β-D-Arabinofuranoside Molar Rotation ([M], deg cm^2 dmol^{-1}) Calculated as a Function of Ring Conformation ([M]^{obs} = −202[18])

	exocyclic group conformer[a]			
ring conformer	*gt*	*gg*	*tg*	[M][b]
${}^3_2$T (N)	−229	−303	−350	−265
^{3}E	−220	−282	−327	−252
${}^3_4$T	−201	−260	−294	−230
${}_4$E	−166	−220	−238	−190
${}^0_4$T	−130	−190	−188	−152
^{0}E (E)	−103	−169	−158	−126
${}^0_1$T	−95	−164	−153	−119
${}_1$E	−120	−199	−203	−151
${}^2_1$T	−116	−199	−209	−149
^{2}E	−137	−227	−248	−175
${}^2_3$T (S)	−154	−251	−278	−195
${}_3$E	−177	−277	−312	−221
${}^3_4$T	−221	−323	−361	−266
^{4}E	−268	−378	−415	−316
${}^4_0$T	−307	−434	−467	−361
${}_0$E (W)	−295	−423	−459	−350
${}^1_0$T	−291	−408	−451	−343
^{1}E	−247	−348	−389	−293
${}^1_2$T	−247	−332	−382	−288
${}_2$E	−237	−316	−367	−276

[a] Conformation of the C5 hydroxymethyl group. [b] Averaged value using statistical weights[35] of *gt*/*gg*/*tg* = 0.62/0.20/0.18 (see text).

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Table II. Methyl β-D-Fructofuranoside Molar Rotation ([M], deg cm^2 dmol^{-1}) Calculated as a Function of Ring Conformation ([M]^{obs} = −89[37])

	exocyclic group conformer[a]						
ring conformer	*gg,gt*	*gg,gg*	*gg,tg*	*tg,gt*	*tg,gg*	*tg,tg*	[M̄][b]
$^4_3$T (N)	−183	−235	−275	−123	−207	−259	−187
^{4}E	−164	−215	−243	−131	−188	−227	−173
$^4_5$T	−150	−186	−199	−123	−162	−188	−154
$_5$E	−94	−118	−126	−61	−88	−102	−89
$^0_5$T	−82	−131	−126	−61	−117	−122	−91
^{0}E (E)	−42	−79	−59	−12	−52	−40	−38
$^0_2$T	−58	−105	−93	−31	−74	−70	−60
$_2$E	−96	−157	−175	−69	−137	−164	−110
$^3_2$T	−62	−124	−131	−150	−100	−114	−109
^{3}E	−77	−149	−165	−51	−129	−155	−96
$^3_4$T (S)	−67	−140	−168	−45	−126	−164	−91
$_4$E	−117	−203	−233	−88	−182	−222	−143
$^5_4$T	−163	−263	−300	−136	−245	−293	−196
^{5}E	−199	−281	−315	−164	−253	−298	−220
$^5_0$T	−196	−318	−344	−169	−303	−339	−236
$_0$E (W)	−221	−336	−364	−184	−311	−347	−253
$^2_0$T	−210	−313	−344	−168	−284	−322	−236
^{2}E	−172	−255	−290	−138	−231	−277	−195
$^2_3$T	−199	−277	−316	−158	−245	−294	−217
$_3$E	−184	−253	−291	−148	−225	−273	−201

[a] The first index labels the C1 hydroxymethyl conformer; the second index labels the C6 hydroxymethyl conformer. [b] Averaged value for statistical weights of *gg*/*tg* = 0.50/0.50 for the C1 hydroxymethyl group and *gt*/*gg*/*tg* = 0.62/0.20/0.18 for the C6 hydroxymethyl group.[35]

rotation was averaged over these conformations using statistical weights of *gt*/*gg* = 0.50/0.50, taken from recent NMR measurements.[36] The C1′ hydroxymethyl group of the fructose residue was placed in the *gg* and *tg* conformations (as above), and the C6′ hydroxymethyl group of the fructose residue was placed in the *gt*, *gg*, and *tg* conformations (as above). Thus, for each linkage geometry 12 combinations of exocyclic group conformations were considered, for each of the 20 fructofuranoside ring conformers.

Results

Methyl β-D-Arabinofuranoside. Table I displays the calculated results for the 20 ring conformers of methyl β-D-arabinofuranoside in each of the three C5 hydroxymethyl group conformations; weighted averages are shown in the last column.

The variation in optical rotation through the pseudorotational itinerary is large and qualitatively the same in all three hydroxymethyl group conformations; i.e., the calculated rotation is smallest in magnitude near the E region and largest near the W region. Because the calculated rotation for all three exocyclic group conformations displays similar variations, the variation in the weighted average is likewise similar and not strongly dependent on the statistical weights[35] assigned to the hydroxymethyl group conformers.

The observed optical rotation[18] is −202 deg cm^2 dmol^{-1}. NMR spectroscopy indicates limited flexibility in this compound;[16,17,19,20] the observed rotation therefore does not reflect an average over a large number of ring conformations. Only the NE($^3_4$T−$_4$E) and S($^3_3$T−$_3$E) regions of the pseudorotational itinerary are compatible with the observed optical rotation. Furthermore, the large $J_{H2,H3}$ and $J_{H3,H4}$ coupling constants[16,17,19,20] indicate trans diaxial CH groups and preclude all S hemisphere ring conformations. (In $^2_3$T, for example, the H2–C2–C3–H3 dihedral angle approaches 90° in strongly puckered rings.) Optical rotation, by this analysis, indicates a preference for the NE conformers, $^3_4$T−$_4$E.

NW conformers have optical rotations approximately 100 deg cm^2 dmol^{-1} more negative than the observed value. The uncertainty in the calculational model has previously been estimated[12] to be ±24 deg cm^2 dmol^{-1}.

Methyl β-D-Fructofuranoside. Table II shows the calculated optical rotation for all methyl β-D-fructofuranoside ring conformations, in each of the six examined combinations of exocyclic group conformations. Statistically averaged optical rotations are shown in the last column.

The variation of optical rotation through the pseudorotational itinerary is more complex than in methyl β-D-arabinofuranoside but similarly substantial. Smallest magnitudes are observed in the E region and largest in the W region, but there is only a small variation among the SE conformers.

We tested the dependence of the average calculated optical rotation (last column of Table II) on the values assigned to the statistical weights of individual conformers. Variations of 10–20% in statistical weights did not qualitatively change the variation along the pseudorotational itinerary.

The observed optical rotation of methyl β-D-fructofuranoside,[37] −89 deg cm^2 dmol^{-1}, is the same as the calculated values for NE($_5$E−$^0_5$T) and S(^{3}E−$^3_4$T) conformers, as in the case of methyl β-D-arabinofuranoside. Large $J_{H3,H4}$ and $J_{H4,H5}$ coupling constants[21-23] preclude S hemisphere ring conformers. Optical rotation by this analysis, therefore, indicates a preference for NE conformers (see Discussion). NW conformers have optical rotations approximately 100 deg cm^2 dmol^{-1} more negative than the observed value.

We take it to be of special significance that our analysis of optical rotation leads to the same ring conformation assignments (NE) in methyl β-D-arabinofuranoside and methyl β-D-fructofuranoside, even though their observed rotations differ by 113 deg cm^2 dmol^{-1}. That is, the observed increase in optical rotation resulting from the replacement of a hydrogen atom with a hydroxymethyl group is approximately reproduced by the calculational model when the ring conformation is not changed. This in turn indicates that the factors which stabilize the preferred ring conformation in methyl β-D-arabinofuranoside continue to exert a dominant influence in methyl β-D-fructofuranoside (see Discussion).

Sucrose. Table III summarizes the calculated sucrose optical rotations as a function of fructose ring conformations for representative linkage geometries. A_1 and A_2 conformations represent a major energetically favored region; B and C conformations represent two secondary regions.[28]

The optical rotation depends strongly on both the linkage conformation and the furanosyl ring conformation. Table III displays two significant trends. First, for any given linkage conformation, the most positive optical rotations arise for fructofuranosyl ring conformations in the E region, and the least positive rotations occur for W region conformers, as was observed for methyl β-D-arabinofuranoside and methyl β-D-fructofuranoside. Second, for any given ring conformation, A_1 and A_2 linkage conformations have rotations approximately 300 deg cm^2 dmol^{-1} more positive than the rotation calculated for methyl β-D-fructofuranoside in the same furanose ring conformation (Table

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Table III. Sucrose Molar Rotation ([M], deg cm^2 dmol^{-1}) Calculated as a Function of Fructose Ring Conformation and Linkage Conformation ([M]^{obs} = 228[38])

		A_1							A_2		B	C
	ϕ	−15	0	−15	0	−30	−30	−15	−50	−60	−30	10
	ψ	60	60	75	75	75	90	90	20	40	−60	150
$^4_3$T (N)		80	81	116	79	136	160	127	105	81	192	−45
^{4}E		103	87	135	91	162	182	143	163	139	233	10
$^4_5$T		173	136	166	123	197	199	161	234	206	286	7
$_5$E		239	192	239	192	275	254	214	341	317	364	54
$^0_5$T		260	218	246	300	280	272	232	352	323	382	65
^{0}E (E)		336	285	318	266	359	342	299	447	426	442	123
$^0_2$T		323	274	311	257	352	341	297	412	394	412	121
$_2$E		233	197	227	184	257	257	221	299	271	340	71
$^3_2$T		292	248	286	236	322	320	279	358	338	373	94
^{3}E		245	208	242	198	273	275	239	308	287	341	87
$^3_4$T (S)		215	181	214	174	242	248	213	277	250	313	71
$_4$E		162	132	165	127	189	202	167	211	182	265	8
$^5_4$T		78	54	86	53	105	97	96	119	87	195	−46
^{5}E		55	30	68	33	45	83	52	47	27	145	−54
$^5_0$T		7	19	19	19	37	53	34	7	−18	157	−67
$_0$E (W)		−24	−41	−10	−28	−9	31	29	−55	−70	103	−50
$^2_0$T		15	26	35	7	47	90	65	−29	−39	112	−31
^{2}E		98	74	108	72	105	124	92	72	52	188	−32
$^2_3$T		52	55	71	59	128	126	106	15	6	142	−24
$_3$E		97	73	110	74	129	131	124	61	45	177	−27

II). This approximately constant contribution from the glucose moiety is not too different from the observed rotation[38] of methyl α-D-glucopyranoside, 309 deg cm^2 dmol^{-1}, indicating that the residue contributions are approximately additive in the "extended" A_1 and A_2 conformations. B and C conformations are "folded" or "twisted"; i.e., the fructose ring is displaced in a left-handed (counterclockwise) or right-handed (clockwise) sense, respectively, relative to the "extended" A conformations. These displacements generate positive and negative contributions, respectively, to optical rotation (Table III). A mixture of A and B conformations, for example, would display more positive rotations than A conformations alone, for any ring conformation.

In order to clarify the possible relationship between ring and linkage conformations, we surveyed the allowed linkages for each furanosyl ring conformation using a simple hard-sphere calculation.[39] The results are shown in Figure 1. The first row of Figure 1 represents the NE quadrant of the pseudorotational itinerary; the second, third, and fourth rows represent the SE, SW, and NW quadrants, respectively. Figure 1 complements the comprehensive calculations by Tran and Brady[28] of an adiabatic potential energy surface for sucrose, in spite of the different representation of ϕ,ψ-preferences. Their major region of preferred ϕ,ψ-space, region A, is represented in Figure 1 with the two regions near ϕ,ψ = −15°,75° (A_1) and ϕ,ψ = −60°;30° (A_2). Region A_1 includes the observed solid-state structure[31] ϕ,ψ = −8°,74° with $^4_3$T(N). Their region B appears in Figure 1 centered near ϕ,ψ = −30°, −60°; region C is present near ϕ,ψ = 10°,150°.

Figure 1 illustrates the effect that the fructose ring conformation has on hard-sphere allowed linkage conformations. With C5′ below the ring, as in NE conformers ($^4_5$T–$_5$E), the C6′ hydroxymethyl group is quasiequatorial and directed away from the glucose ring, resulting in several allowed regions of ϕ,ψ-space. With C5′ above the ring, as in SW conformers (^{5}E–$^5_0$T), the C6′ hydroxymethyl group is quasiaxial, and only a small region of ϕ,ψ-space is allowed. Similarly, when C2′ is above the plane, as in NW conformers (^{2}E–$^2_3$T), the fructose ring is brought to close to the glucose ring and only small regions are allowed in a hard-sphere representation. In spite of the limitations of a hard-sphere model, Figure 1 suggests that NE ring conformers allow a wider range of unhindered linkage geometries than do NW ring conformers.

The experimentally observed sucrose rotation[38] of 228 deg cm^2 dmol^{-1} is compatible with a number of conformations or mixtures

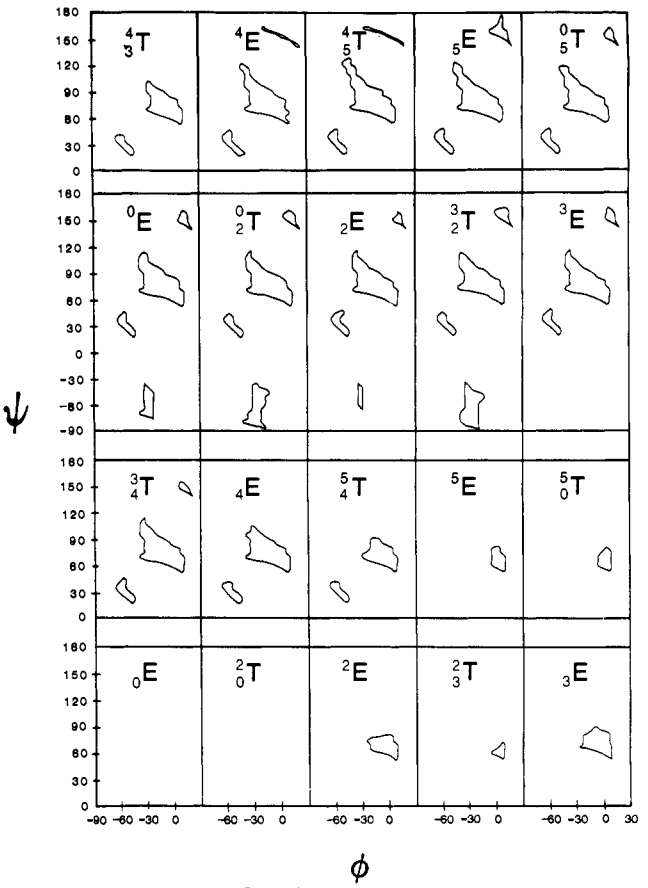

Figure 1. Hard-sphere allowed linkage conformations of sucrose for the 20 E and T fructose ring geometries.

of conformations. However, in combination with sucrose NMR data,[2,21,26,29] molecular modeling calculations,[26-28] and our results for methyl β-D-arabinofuranoside and methyl β-D-fructofuranoside, specific conclusions can be drawn (see Discussion).

Discussion

Methyl β-D-Arabinofuranoside. Ring conformation assignments for methyl β-D-arabinofuranoside based on NMR appear incongruent.[17,19,20] The observed large values of $J_{H2,H3}$ (7.5–8.0 Hz) and $J_{H3,H4}$ (7.1–7.5 Hz) clearly indicate transdiaxial CH groups,

(38) Bates, F. J. *Polarimetry, Saccharimetry and the Sugars*; NBS Circular No. 440; U.S. Government Printing Office: Washington, DC, 1942.
(39) Rees, D.; Scott, W. E. *J. Chem. Soc. B* **1971**, 469–479.

which eliminates all S hemisphere ring conformations (see above).[40] The observed value of $J_{H1,H2}$ (4.3–4.6 Hz)[17,19,20] is then compatible with either NW conformers or NE conformers. $J_{C1,H3}$ (0.0 Hz)[17,19] indicates that C1–C2 is approximately perpendicular to C3–H3, likewise eliminating conformers in the S hemisphere, but not eliminating NW or NE conformers.

The remaining measured ^3J values lead to an ambiguity. $J_{C2,H4}$ (0.0 Hz)[20] indicates that C4–H4 is approximately perpendicular to C2–C3, which is compatible with NE conformers, where the C5 hydroxymethyl group is equatorial, but only marginally compatible with NW conformers (e.g., $^1_2$T, where C2 is below the plane). On the other hand, $J_{C1,H4}$ (3.0–3.2 Hz)[17,20] indicates that C4–H4 is not approximately perpendicular to C1–O4, which is compatible with NW conformers, but only marginally compatible with NE conformers (where C4 is below the plane). Cyr and Perlin,[20] using both $J_{C2,H4}$ and $J_{C1,H4}$, proposed two alternative conformers;[40] Serianni and Barker, using $J_{C1,H4}$ alone, make an assignment to the NW quadrant.[17] Our conclusion, based on optical rotation, that NE conformers (e.g., $^3_4$T–$_4$E) are favored is therefore not inconsistent with the NMR data collected to date.

Nonbonded interactions play an important role in determining furanoid ring conformations.[15] Among the important considerations are the following: (a) bulky substituents tend to occupy equatorial rather than axial positions, (b) the anomeric effect is operative leading to an axial or quasiaxial orientation of the anomeric oxygen atom, (c) 1,2- and 1,3-cis substituents tend to be staggered rather than eclipsed, and (d) O–C–C–O groups tend to be gauche rather than trans. In many cases, these stabilizing tendencies counter one another, and no heirarchy has been established; indeed, it may not be possible to do so. There are particularly serious conflicts in the working of nonbonded interactions in the molecules of interest here.

In NW conformers, the anomeric effect provides maximal stabilization on account of the fully axial C1–O1 group; 1,2-cis substituents are staggered and C2–O2 is gauche to C3–O3. Bishop and Cooper[18] assigned methyl β-D-arabinofuranoside to $_2$E on those steric grounds. In NW conformers, however, the C5 hydroxymethyl group is axial, and the 1,3-cis interactions of O1 and C5 are not relieved.

In NE conformers, the C5 hydroxymethyl group is fully equatorial; eclipsing of 1,3-cis substituents is thereby relieved and C2–O2 is gauche to C3–O3. However, the C1 methoxy group is only quasiaxial, allowing a less than maximal anomeric effect, and eclipsing of 1,2-cis substituents is only partially relieved.

The N conformer $^3_2$T represents a compromise and is often found in the solid state of furanoid rings.[15b] The C1 methoxy group is quasiaxial and the hydroxymethyl group is quasiequatorial. In solution the combination of nonbonded interactions must lead to a delicate balance of energetic factors, and experimental means are required to establish preferences. Our analysis of optical rotation leads in the present case to the conclusion that, although several N hemisphere conformers are likely to be present in an equilibrium mixture, there is an excess of NE over NW conformers in methyl β-D-arabinofuranoside.

In tetrofuranosides the situation is quite different. In methyl β-D-threofuranoside, for example, which has been assigned $_0$E–^{1}E,[17] there is no hydroxymethyl group, and no 1,3-cis interactions; i.e., nothing counters the factors favoring NW conformers. In methyl β-D-arabinofuranoside, which differs only in the presence of the hydroxymethyl group attached to C4, it is the tendency of that group to occupy an equatorial position, and simultaneously relieve the newly introduced 1,3-cis interactions which must "compete" with the tendencies of the methoxy group to take up a fully axial position and to relieve 1,2-cis interactions. The result is a shift to NE conformers in which C4 is below the plane. The introduction of the hydroxymethyl group is accompanied by changes in $J_{H3,H4}$ from 6.1 to 7.1 Hz and $J_{H2,H3}$ from 4.6 to 8.0 Hz,[17] changes which themselves indicate some shift along the pseudorotational itinerary.

Methyl β-D-Fructofuranoside. NMR ring conformation assignments for methyl β-D-fructofuranoside have been based only on $J_{H,H}$ coupling constants. Large values of $J_{H3,H4}$ and $J_{H4,H5}$ exclude all S hemisphere conformers, i.e., 7.5 Hz for both in acetone,[21] 8.2 and 8.0 Hz, respectively, in $(CD_3)_2SO$,[23] and 8.0 Hz for both for the tetraacetate in chloroform.[22] NE conformer assignments have consistently been preferred over NW assignments; $^4_3$T–^{4}E,[23] ^{4}E[22], and ^{4}E–$^4_5$T.[21] Our assignment, based on optical rotation, is consistent with these assignments with respect to the preference for NE conformers, but our range of specific conformers is shifted further into the NE quadrant (Table II).

Methyl β-D-fructofuranoside differs from methyl β-D-arabinofuranoside only in the replacement of a hydrogen atom at the anomeric carbon with a hydroxymethyl group. In terms of the nonbonded interactions discussed above, there is no reason to expect a large change in the preferred ring conformation. In this respect, our assignment to NE conformers for both is consistent. The apparent shift further into the NE quadrant for methyl β-D-fructofuranoside may be an artefact partly arising from the more extensive statistical averaging over exocyclic group conformations required in that case. Considering the smaller uncertainty in the methyl β-D-arabinofuranoside calculations, and the intrinsic uncertainty in the method[12] (±24 deg cm^2 dmol^{-1}), we conclude that the best optical rotation based ring conformation assignment is to $^4_5$T–$_5$E (Table II).

French and Tran[25] carried out MM2 molecular mechanics calculations on the free β-D-fructofuranose. They found a strong preference for N hemisphere conformers over S hemisphere conformers. Their minimum energy conformer, however, lies in the NNW region ($_3$E–$^4_3$T), close to the canonical $^4_3$T conformer. Their NE $^4_5$T–$_5$E energy contour appears to be approximately 2.5 kcal mol^{-1} higher than the calculated minimum energy. This may simply reflect a difference in the delicate balance of energetic factors between the fructofuranoside and free fructofuranose. Since the $^4_3$T conformer is the one often found in solid-state furanoside structures,[15b] however, the shift we find into the NE quadrant may be a solvation effect.

Sucrose—Fructofuranosyl Ring Conformation. Sucrose NMR data, as in the cases of methyl β-D-arabinofuranoside and methyl β-D-fructofuranoside, indicate that S hemisphere furanose ring conformers are not present. Thus, Bock and Lemieux[26] observed $J_{H3',H4'}$ and $J_{H4',H5'}$ values of 8.8 and 8.6 Hz, respectively, in D_2O and 8.1 and 7.6 Hz in $(CD_3)_2SO$; Steefkerk et al.[21] found 8.1 Hz for both constants in acetone. The two pairs of transdiaxial CH groups effectively indicate N hemisphere conformers. Steefkerk et al.,[21] moreover, on the basis of a parametrized Karplus relationship, found better agreement for NE conformers (^{4}E–$^4_3$T) than NW. Particularly large coupling constants are expected with C4′ above the ring.

We take Steefkerk et al.'s sucrose assignment to ^{4}E–$^4_5$T and our assignment of methyl β-D-fructofuranoside to $^4_5$T–$_5$E to be sufficient grounds for assigning the sucrose fructofuranosyl ring conformation in solution to $^4_5$T, with fluctuations to either side, i.e., ^{4}E–$^4_5$T–$_5$E. That assignment provides a uniform and consistent picture of NE conformers being predominant in methyl β-D-arabinofuranoside, methyl β-D-fructofuranoside, and the β-D-fructofuranosyl moiety of sucrose. The important structural features of the conformation, as described above, are the equatorial orientation of the C6′ hydroxymethyl group and the relieved 1,3-*cis* interactions. Figure 1 indicates that NE conformers do not restrict the linkage geometry, and Table III shows that NW and N furanosyl ring conformations impart to sucrose an optical rotation much smaller than the observed value no matter what the linkage geometry is.

Solid-state furanose structures are commonly the canonical N conformer $^4_3$T. In a flexible-residue energy minimization of sucrose in vacuo, Tran and Brady[28] found N and NW conformers to be

(40) Cyr and Perlin's assignment to a SW quadrant conformer appears to have resulted from a conflation of ring structures of β-arabinofuranoside and α-galactofuranoside, as indicated in Scheme 3[20] where the C5 hydroxymethyl group in the preferred conformer of β-arabinofuranoside is shown in the equatorial position (it is axial in $^4_3$T), and in Table 4[20] where β-arabinofuranoside dihedral angles are incorrectly shown as identical to those of α-galactofuranoside. Their preferred ring conformer is thus simply misnamed; an equatorial C5 hydroxymethyl group corresponds to a NE conformer.

prevalent. On the other hand, in the crystal structure of anhydrous TGS[1e] the furanose ring occurs in the $^4_5$T conformer.[41] Molecular modeling calculations with solvent molecules included explicitly may ultimately shed light on the matter.[32b]

Sucrose—Linkage Conformation. In sucrose crystals the linkage geometry is $\phi,\psi = -8°,74°$; there are two intramolecular hydrogen bonds, O1′–O2 and O6′–O5.[31]

Bock and Lemieux,[26] using a Kitaigorodski potential energy function, found all of ϕ,ψ-space effectively excluded except for a small region near the crystal structure linkage geometry, described by $-20° \le \phi \le -10°$; $70° \le \psi \le 90°$. This result alone implied crystal–solution structural equivalence. Small temperature dependencies of NMR ^{1}H and ^{13}C chemical shifts and coupling constants in the glucose residue supported such a conclusion; significant variations in the fructose residue parameters were attributed to furanoid ring conformational fluctuations. In addition, NMR parameters in D_2O and $(CD_3)_2SO$ were similar, indicating similar structures in the two solvents, and further supporting the notion of linkage inflexibility. In solution, therefore, the O1′–O2 hydrogen bond was pictured as persisting in a relatively rigid linkage geometry. (NMR data indicated[26] that the O6′–O5 hydrogen bond is broken in solution, which itself does not necessitate any change in linkage geometry).

McCain and Markely[29] measured ^{13}C spin relaxation rates which displayed a pattern that could be explained by crystal–solution structural equivalence. Furthermore, correlation times were not temperature dependent, and the rotational spectral density amplitude factors correlated well with thermal amplitudes from neutron diffraction data[31b,c] for most carbon ring positions, as one would expect with crystal–solution structural equivalence.

Two counterproposals have been presented that the solution conformation is not that in the crystal. The origins of the proposals are quite different, but both are related to intramolecular hydrogen bonding patterns.

Mathlouthi et al.[30a,b] observed a concentration dependence of Raman frequencies assigned to the CH_2 groups of the C1′ and C6′ hydroxymethyl groups. They interpreted this result as indicating that both hydrogen bonds exist at high concentrations, but are, successively, broken upon dilution, with a single hydrogen bond existing at intermediate concentrations. Breaking of the O1′–O2 hydrogen bond, at low concentrations, was suggested to be accompanied by a change in linkage geometry. A concentration dependence in the low-angle X-ray diffraction behavior of sucrose solutions was described as consistent with that model.[30c] FTIR data on solutions, quenched melts, and freeze-dried samples and CPMAS ^{13}C NMR data on freeze-dried samples were subjected to factor analysis and the results interpreted as supporting the model.[30d]

Davies and co-workers[2] have reported NMR evidence that O1′–O2 and O3′–O2 hydrogen bonds both exist, in competitive equilibrium, in $(CD_3)_2SO$ solutions of sucrose. The O3′–O2 hydrogen bond was also found with chlorodeoxy sucrose derivatives in which chlorine replaces the hydroxyl group at C1′. In sucrose solutions they estimate the ratio of O1′–O2 to O3′–O2 hydrogen bonded conformations to be 2:1. The O3′–O2 hydrogen bond is possible only in linkage conformers of region B, implying a 2:1 ratio of A and B conformers.

The observed optical rotation of sucrose, 228 deg cm^2 dmol^{-1}, and the calculated values of Table III are consistent with this picture. For $^4_5$T fructose ring conformers, or a mixture of ^{4}E–T–$_5$E conformers, the calculated sucrose rotation is significantly less than the observed value, if the only linkage conformations present are those near the crystal structure (A_1 conformers). The corresponding "folded" B conformers have substantially more positive optical rotations, such that an equilibrium mixture of A_1 and B conformers accounts for the observed value. For example, the average rotation of all A_1 and B conformers in the three predominant ring forms (Table III), in a 2:1 ratio, is 217 deg cm^2 dmol^{-1}.

A_1 conformers, alone, display the observed sucrose rotation only for fructose rings further into the NE quadrant than we found present in methyl β-D-fructofuranoside and for fructose rings in the S hemisphere, the presence of which is incompatible with the observed NMR coupling constants. B conformers, alone, display the observed sucrose rotation for ^{4}E fructose ring forms, but do not account for the NMR evidence for O1′–O2 hydrogen bonds.[2,26] A_2 conformers, alone, display the observed sucrose rotation for $^4_5$T fructose ring conformers, but do not account for the NMR evidence for O3′–O2 hydrogen bonds.[2] C conformers, alone, are not compatible with the observed sucrose rotation.

The bulk of the evidence to date, therefore, indicates that whereas the predominant solution conformation is not much different from the crystal structure (an A_1 conformer)[26] there is a significant representation of B conformers.[2] It may be that the experimental results of Mathlouthi et al.[30] can also be reinterpreted in terms of such a description.

The following findings provide additional, corollary, support for this picture.

(a) The recent calculations of Tran and Brady[28] have shown that the low-energy region of ϕ,ψ-space is considerably enlarged in a flexible-residue model, relative to rigid-residue calculations.[26] Region B becomes a significant secondary region only moderately less accessible than the A region, and a B–A interconversion was observed in dynamic simulations, accompanied by an interconversion of O3′–O2 and O1′–O2 hydrogen bonded forms.[28]

(b) The O3′–O2 hydrogen bond is observed in the crystal structure of TGS[1e,41] in which the linkage geometry is $\phi,\psi = -21°, -46°$, i.e., it is a B linkage conformer. That hydrogen bond persists in solution.[2] These experimental results indicate that the B region is not a region of prohibitively high potential energy.

(c) NMR coupling constant data reflecting linkage geometry are equally consistent with an equilibrium mixture of A and B conformers or with A conformers alone. Values of $J_{C2'H1}$ in D_2O (3.8 Hz) and $(CD_3)_2SO$ (4.0 Hz)[2e] are consistent with an average value of ϕ of approximately −30°. A and B regions, while differing greatly in ψ, are similar with respect to ϕ (Figure 1).

Conclusions

The observed optical rotations for solutions of methyl β-D-arabinofuranoside and of methyl β-D-fructofuranoside agree with those calculated for furanose ring conformations in the NE region of the pseudorotational itinerary. The observed optical rotation of sucrose in solution agrees with that calculated for an equilibrium mixture of A_1 and B type linkage conformations having NE fructose rings, with the A_1 crystal-structure conformation predominating.

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Registry No. Methyl β-D-arabinofuranoside, 25129-51-5; methyl β-D-fructofuranoside, 13403-14-0; sucrose, 57-50-1.

(41) In ref 1e, the *b* and *c* unit cell dimensions are inadvertently interchanged on p 7, and a left-handed coordinate system is shown in Figure 3, such that conversion to a right-handed coordinate system requires taking -*z* coordinates as presented in the table of coordinates. The dihedral angles in the fructose ring calculated from those coordinates are the following: (C5′–O2′–C2′–C3′) = −10.4°, (O2′–C2′–C3′–C4′) = −11.0°, (C2′–C3′–C4′–C5′) = 26.9°, (C3′–C4′–C5′–O2′) = −33.5°, (C4′–C5′–O2′–C2′) = 27.7°. C4′ is 0.37 Å above, and C5′ is 0.20 Å below the plane defined by O2′–C2′–C3′. The linkage geometry calculated from the coordinates is ϕ(O5–C1–O1–C2′) = 94.4°, ψ(C1–O1–C2′–C1′) = −46.0°. Therefore, ϕ(H1–C1–O1–C2′)[31c] = −115.85 + 94.4° = −21.4°. The O3′–O2 distance is 2.82 Å.