Preferred Conformation of C-Glycosides. 11. C-Sucrose: New Practical Synthesis, Structural Reassignment, and Solid-State and Solution Conformation of Its Octaacetate

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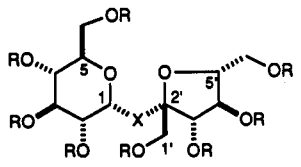
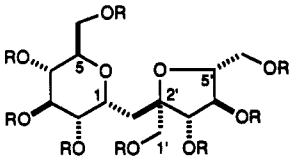
Summary: The stereochemistry of C-sucrose, previously reported from this laboratory, was revised as *epi*-C.2'-C-sucrose (5) from ^{1}H NOE measurements on octaacetates 2 and 6 and an X-ray analysis of 2. A new, stereospecific, and practical synthesis of C-sucrose (1) was developed. The solid-state conformation and solution behavior of the octaacetate 2 of C-sucrose were compared with the corresponding octaacetate 4 of parent sucrose.

The preferred solution conformation of sucrose has been a topic of debate in the recent chemical literature.[1] This compound has been described as maintaining its crystal structure in solution[1a] or as a flexible[1b] molecule with respect to degrees of freedom about the glycosidic torsional angles. We have recently examined the conformational preferences of certain C-di- and trisaccharides and showed that they are favorably compared to their oxygen counterparts.[2] With a proper degree of interpretation, we feel that the study of C-sucrose (1) can reveal hidden conformational features in sucrose (3), principally because of the reliable ^3J spin coupling information contained in carbon-linked sugars. Additionally, this information can provide new insights with respect to the rational design of nonnutritive sweetners.[3] During the course of studies[4] probing the preferred solution conformation of C-sucrose, it became apparent that our earlier disclosed synthesis[5] of C-sucrose had in fact produced the C.2' epimer of C-sucrose. In this paper, we report the results of our studies, including a new, stereospecific, and practical synthesis of C-sucrose and a single-crystal X-ray analysis of its octaacetate 2. Additionally, we compare both solution NMR and X-ray data of 2 with the corresponding octaacetate 4 of parent sucrose.





1 X = $CH_\alpha H_\beta$ R = H
2 X = $CH_\alpha H_\beta$ R = Ac
3 X = O R = H
4 X = O R = Ac

5 R = H
6 R = Ac

Our evidence for the misassigned C.2' stereocenter in the previously disclosed C-sucrose initially came from comparative 1D ^{1}H NOE difference measurements (Table I) on the octaacetates 2 and 6, compounds available from the previous synthetic route.[5] Compound 6, originally assigned as 2, showed enhancements (H.1–H.5', H.β–H.5') consistent with a cis relationship between the hydroxymethyl groups at C.2' and C.5'. Conversely, 2 exhibited enhancements (H.1–H.4', H.5'–H.1') supporting a trans C.1'–C.6' arrangement. With this preliminary information, we suspected the C.2' configuration had been incorrectly assigned. In the previous synthesis, this stereocenter was set by an acid-catalyzed ring-opening of an epoxide intermediate. To prepare C-sucrose (1), we needed a diastereoselective synthesis of anti epoxy alcohol 9 (Scheme I). In our earlier account, we had reported that a Ti(*i*-PrO)$_4$/*t*-BuO$_2$H epoxidation could be used to provide this substance, then assigned[5] as the syn epoxy alcohol (i.e., *epi*-2'-9). In spite of numerous efforts, we were unable to define the detailed conditions to reproduce the previously observed results. Other attempts, for example, using Sharpless asymmetric epoxidation,[6] did not succeed in reversing the facial selectivity of the epoxidation. Under these circumstances, we turned our attention to preparation of the requisite anti epoxy alcohol 9 via the triol 8. On the basis of our empirical rule,[7] we anticipated the major stereoisomer produced on osmylation of the allylic alcohol 7 to be 8, which should yield the desired anti epoxy alcohol 9 on selective activation of the primary alcohol followed by base treatment.

The allylic alcohol 7 was prepared by using the previous route with some modification.[8] Osmylation of 7 proceeded quantitatively at −78 °C to produce 8 as a single diaste-

Table I. Steady-State Overhauser Enhancements in Compounds 6, 2, and 4

proton irradiated	enhancement[a] 6[b]	2[c]	4[d]
H_1	$H_{3'}$, $H_{5'}$, H_2, $H_{1'}$	$H_{3'}$, $H_{4'}$, H_2, $H_{1'}$	$H_{4'}$, H_2, H_5, $H_{6'}$, $H_{1'}$
H_3		H_4, H_5, H_2	H_4, H_2,H_5
H_5		$H_{6'}$, H_3, H_4, H_1	H_1, H_3, $H_{4'}$, H_4
$H_{3'}$		H_1, $H_{4'}$, $H_{5'}$, $H_{1'}$	$H_{4'}$, $H_{1'}$, $H_{5'}$
$H_{5'}$		$H_{3'}$, $H_{4'}$, $H_{6'}$, $H_{1'}$	$H_{3'}$, $H_{4'}$, $H_{6'}$
H_α	H_β, H_3, $H_{1'}$, H_5, $H_{3'}$, H_1	H_β, H_3, H_5, $H_{3'}$, H_1	NA
H_β	H_α, H_3, $H_{3'}$, H_2, $H_{5'}$, H_1, H_5 (neg)	H_α, H_3, $H_{3'}$, H_1	NA
$H_{4'}$			H_1, $H_{3'}$, H_5, $H_{6'}$, $H_{5'}$
H_4			H_1 (neg), H_3, H_2, H_5, H_6
			H_1, H_3, H_4

[a] Based on difference measurements utilizing partial saturation. As reported here, enhanced peaks are all greater than ca. 1–2% of the inverted peak area when normalized to −100%. [b] In 4:1 $CDCl_3$/benzene-d_6. [c] In benzene-d_6. [d] In 1:1 $CDCl_3$/benzene-d_6.

(1) For relevant reports, see: (a) Bock, K.; Lemieux, R. U. *Carbohydr. Res.* **1982**, *100*, 63–74. (b) Poppe, L.; Van Halbeek, H. *J. Am. Chem. Soc.* **1992**, *114*, 1092–1094 and references cited therein.
(2) For Part 10 of this series, see: Haneda, T.; Goekjian, P. G.; Kim, S. H.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 490–498.
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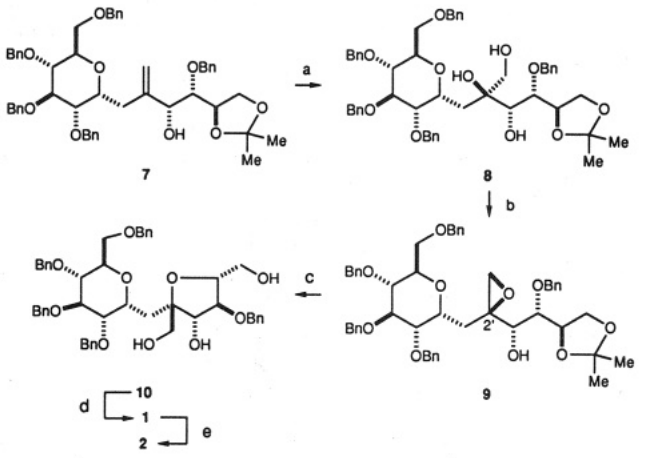
Table II. Comparison of Solid-State Geometries of *C*-Sucrose Octaacetate (2) and Sucrose Octaacetate (4)[11]

parameter	2	4
Linkage Geometry		
Φ(O5–C1–X–C2′), deg	66.0	93.4
Ψ(C1–X–C2′–O2′), deg	−75.9	−21.9
∠(C1–X–C2′), deg	112	118
r(C1–X), Å	1.51	1.42
r(C2′–X), Å	1.58	1.42
r(C1–C2′), Å	2.56	2.44
∠(X–C1–C2–C3), deg	−69.0	−57.4
∠(X–C1–O5–C5), deg	65.3	54.2
∠(X–C2′–C1′), deg	113.3	107.0
Pyranose Bond Lengths, Angles,[a] and Torsional Angles		
C1–C2	1.54, 111.9	1.53, 107.8
C2–C3	1.54, 107.7	1.53, 106.9
C3–C4	1.53, 108.2	1.53, 110.4
C4–C5	1.53, 108.2	1.53, 109.0
C5–O5	1.45, 114.5	1.44, 113.9
O5–C1	1.46, 106.4	1.41, 108.7
C1–C2–C3–C4	−58.0	−60.7
C2–C3–C4–C5	59.3	58.5
C3–C4–C3–O5	−61.7	−56.0
C4–C5–O5–C1	64.5	59.2
C5–O5–C1–C2	−60.0	−62.9
O5–C1–C2–C3	56.2	62.7
Furanose Bond Lengths, Angles,[a] and Torsional Angles		
C2′–C3′	1.54, 104.4	1.56, 102.9
C3′–C4′	1.55, 105.3	1.52, 103.8
C4′–C5′	1.52, 105.9	1.51, 104.0
C5′–O5′	1.45, 112.8	1.43, 111.2
O5′–C2′	1.46, 105.0	1.41, 106.2
C2′–C3′–C4′–C5′	−25.8	27.8
C3′–C4′–C5′–O5′	20.0	−34.6
C4′–C5′–O5′–C2′	−6.5	28.7
C5′–O5′–C2′–C3′	−10.0	−10.6
O5′–C2′–C3′–C4′	21.8	−11.5

[a] Three-atom bond angles follow each internuclear distance (Å), with third atom of next highest increment; e.g., the bond angle for entry C1–C2 is for ∠C1–C2–C3.

Scheme I[a]



[a] Reagents and conditions: (a) OsO_4/Py–THF (2:1)/−78 °C; (b) (i) TsCl/Py/rt, (ii) NaH/cat. imidazole/THF/0 °C; (c) cat. PPTS/MeOH/40 °C; (d) H_2 (1 atm)/10% $Pd(OH)_2$ on C/MeOH/rt; (e) Ac_2O/Py/DMAP/40 °C.

reoisomer. As anticipated, selective activation of the primary alcohol of **8**, followed by base treatment, furnished the desired epoxy alcohol **9**, the structure of which was confirmed on comparison with the previously prepared sample.[5] The epoxy alcohol **9** was cyclized with a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in warm methanol to the penta-*O*-benzyl *C*-sucrose **10**. On a practical note, we were to able convert the allylic alcohol **7** to the cyclized product **10** in 56% yield over four steps with a single chromatographic separation following the final step. Hydrogenolysis of **10** using Pearlman's catalyst gave *C*-sucrose (**1**), which was characterized further as its octaacetate **2**.[9]

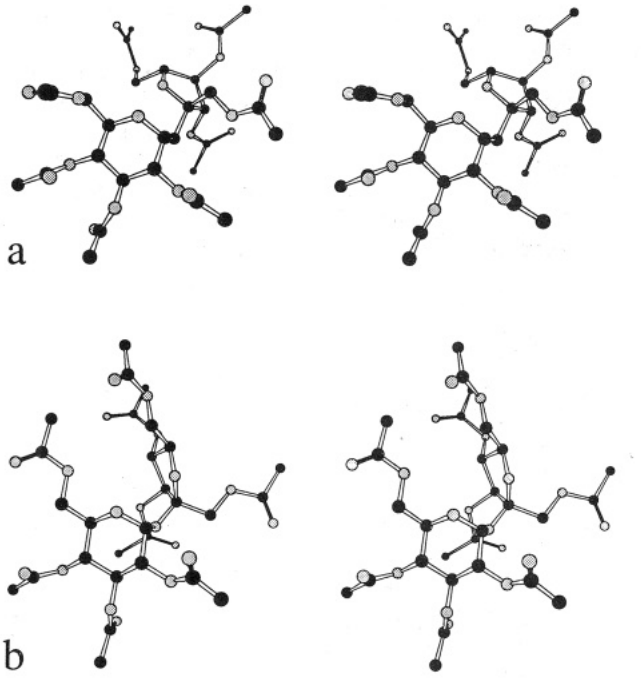


Figure 1. (a) Stereoview of **2** as determined by X-ray diffraction. (b) Stereoview of **4** using atomic coordinates reported in ref 11.

Colorless needles (mp 103–105 °C) of **2** were grown at room temperature in 90% aqueous ethanol. X-ray diffraction data[10] were obtained at ambient temperature, and the structure (Figure 1a) confirmed our suspicion of the misassigned C.2′ stereocenter. This structure also provided an opportunity to compare the structure of **2** with sucrose octaacetate **4**. The features of the solid-state geometry of **2** are discussed in comparison with the known values[11] for **4**, summarized in Table II and illustrated in Figure 1.

The orientations of the glucopyranose and fructofuranose rings with respect to each other in **2** are found to be in approximately ideal "exo-anomeric" geometry. Between **2** and **4**, there are differences in the respective ϕ and ψ values (see **1A**), with the carbon analog having nearly perfectly staggered glycosidic torsional parameters. In **4**, the fructofuranose ring assumes an almost perfect $^{3}_{4}T$ conformation,[12] while a $^{2}T_{3}$ conformation is observed in

(8) A Ni(II)/Cr(II)-mediated coupling reaction was used to assemble the carbon skeleton of **7** (ref 5). In the previous case, a vinyl iodide was used with the Cr(II) reagent containing 0.1% Ni(II). Increasing the Ni(II) content to 1% effected the vinyl bromide coupling in 70% yield.

(9) Compounds **1**, **2**, **8**, and **10** were fully characterized (^{1}H, ^{13}C NMR, HRMS, IR, $[\alpha]_D$). This data and experimental procedures are included as supplementary material.

(10) Crystallographic data for compound **2**: a = 8.107 (3) Å, b = 13.194 (5) Å, c = 31.05 (1) Å, T = 298 K, space group $P2_12_12_1$, Z = 4, $2\theta_{min/max}$ = 3–45°, unique data ($F_0^2 > 3\sigma F_0^2$) 1392, R = 9.21%, R_w = 9.59%. Data were collected with Mo K_α radiation. The structure was solved by standard procedures, and all atoms were refined isotropically. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(11) Oliver, J. D.; Strickland, L. C. *Acta Crystallogr.* **1984**, *C40*, 820–824.

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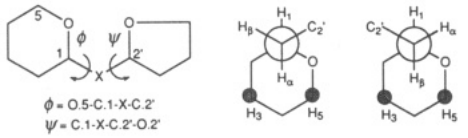
2. As expected, replacing the glycosidic oxygen with a carbon atom results in some bond length and bond angle differences between 2 and 4 (Table II). It is worthwhile noting that these differences, when considered together, may play an antagonistic role in some cases. For example, the longer C.1–X and C.2′–X bonds in 2 are partially compensated by the wider C.1–X–C.2′ bond angle in 4, resulting in a very similar internuclear distance between the anomeric centers.



1A 2A 2B

We have studied the preferred solution conformation of 2 and 4 by ^{1}H NMR spectroscopy. ^3J measurements on 2 yielded information with respect to the rotameric distribution at the ϕ linkage. Values of 8.5 and 3.6 Hz were observed for $^3J_{H.\alpha-H.1}$ and $^3J_{H.\beta-H.1}$, respectively. Using a parameterized Karplus expression,[13] one can rationalize these values with a ca. 80:20 mixture of staggered rotamers **2A** and **2B**, respectively. Steady-state NOE experiments confirmed this unequal distribution of rotamers in solutions. The H.α to H.3 and H.α to H.5 enhancements are approximately equivalent[14] and large. Conversely, when H.β is irradiated, only H.3 shows only a positive enhancement. This asymmetry would be consistent with rotamer **2A**. The seeming absence of a H.β–H.5 dipolar interaction could be due to a competing three-spin effect.[15] At this stage in our studies, we still prefer to use ^3J values to describe the ϕ torsional behavior in 2. In a qualitative sense, the NOE experiments agree with our ^3J analysis; however, quantitative studies of rotamer distributions employing diastereotopic methylene protons are generally not recommended for complex systems.[16]

Intraresidue NOE's in 2 provide a qualitative comparison with 4. In 2, H.1 interacts with the nearby H.1′ protons and H.3′, whereas the H.1–H.3′ interaction is absent in 4. An H.1–H.4′ interaction is detectable, which is also observed in **6**[17] and in sucrose.[18] Recently, this enhancement was used to argue for a flexible sucrose solution conformation.[18] Indeed, the C.1–C.4′ distance (4.9 Å) in the crystal structure of 2 approaches the limit of detection for dipolar interactions in solution, and the H.1–H.4′ enhancement in 2 indicates the range of ϕ/ψ motion in the carbon analog is comparable to that found in 4.

Two coupling constants can be used to compare the fructofuranose rings in 2 and 4. $^3J_{H.4'-H.5'}$ is 5.5 Hz in both 2 and 4, whereas $^3J_{H.3'-H.4'}$ is 3.2 Hz in 2 and 5.5 Hz in 4. This difference could be due to different conformational averaging or could be an amplified β-effect on ^3J produced by the electron-withdrawing acetate protecting group.[19]

Our present studies indicate that the carbon analog prefers an exo-anomeric conformation at the ϕ linkage, in agreement with our earlier studies on other disaccharides. Stereoelectronic stabilization would serve to only reinforce this thermodynamic preference in 4. This preference is recognized in combination with the rotational degrees of freedom at the ϕ and ψ linkage. As with other studies on the naturally occurring substances, the NMR evidence points toward a "flexible" solution structure for *C*-sucrose.[20] Differential behavior for the ϕ vs ψ linkage is possible, although for *O*-disaccharides this eludes direct spectroscopic detection and is usually inferred from molecular modelling. *C*-Glycosides, which allow direct monitoring of the glycosidic preferences via ^3J measurements, offer a unique solution for this particular issue. Preliminary studies[4] on derivatives of 1 indicate that the ϕ linkage adopts a more well-defined exo-anomeric conformation, whereas the ψ linkage is less well-defined and prone to increased conformational averaging. In this sense, we feel the study of *C*-sucrose can further our understanding of conformational issues in sucrose itself.

In summary, we have developed a new, stereospecific, and practical synthesis of *C*-sucrose and have provided unambiguous proof of its structure. Through further studies of 1 and structurally modified derivatives, we hope to gain a better understanding of the ϕ and ψ linkage dynamics in this compound, with analogy to the naturally occurring substance. Preliminary studies are encouraging, and an account will be presented in due course.

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Supplementary Material Available: Preparative procedures and spectral data for compounds 1, 2, 8, and 10 and 1D ^{1}H NOE difference spectra for 2 and 4 (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) The NOE from H.α to H.5 is actually larger than that to H.3, which is consistent with our assignment of the diastereotopic protons.

(15) Indeed, in compound **6**, where the ϕ linkage is predicted to be even more highly populated in the exo-anomeric configuration (^3J's of 10.1 and 1.7 Hz), irradiation of H.β produces a positive H.3 enhancement and a *negative* H.5 enhancement. This could be due to a relayed dipolar interaction mediated by H.α in rotamer **2A**. Therefore, in 2, an admixture of **2A** and **2B** could produce positive and negative enhancements which serve to cancel each other.

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(17) Sanders, J. K. M.; Hunter, B. *Modern NMR Spectroscopy: a Guide for Chemists*; Oxford: Oxford, 1987.

(18) Herve du Penhoat, C.; Imberty, A.; Roques, N.; Michon, V.; Mentech, J.; Descotes, G.; Perez, S. *J. Am. Chem. Soc.* **1991**, *113*, 3720–3727.

(19) For *C*-sucrose (1) in D_2O, $^3J_{H.3'-H.4'}$ and $^3J_{H.4'-H.5'}$ are 7.2 and 8.0 Hz, respectively. In sucrose (3) the corresponding values are 8.0 and 8.6 Hz.

(20) O'Leary, D. J.; Kishi, Y. Unpublished results.