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Preferred Conformation of C-Glycosides. 2. Preferred Conformation of Carbon Analogues of Isomaltose and Gentiobiose

Summary: The preferred conformation of the methyl C-glycosides **1** and **2**, carbon analogues of methyl isomaltoside and methyl gentiobioside, was shown to be **1A** and **2A**, respectively, by ^{1}H NMR spectroscopy.

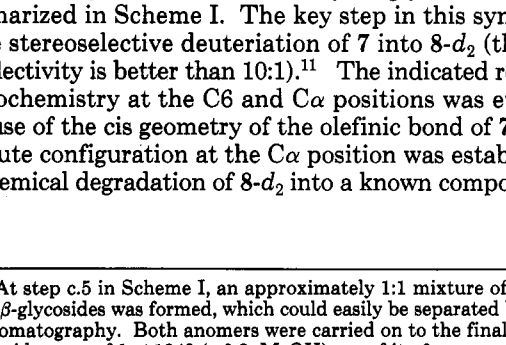
Sir: In the preceding paper, we have demonstrated that both α(axial)- and β(equatorial)-C-glycosides exist predominantly in the conformers bearing the C1′–C2′ bond antiperiplanar to the C1–C2 bond.[1] This conformational preference is very similar to that of corresponding parent glycosides. Obviously, this analysis can be extended to the methyl glycosides **1** and **2** of $\alpha(1'\rightarrow6)$- and $\beta(1'\rightarrow6)$-*C*-diglucoses, which are the carbon analogues of isomaltose (**3**) and gentiobiose (**4**) (Chart I). On the basis of the results reported in the preceding paper, the conformational preference around the C1′–Cα and C5–C6 bonds of **1** and **2** is predicted to be such that the Cα–C6 bond is antiperiplanar to the C1′–C2′ bond and also to the C5–C4 bond. With respect to the Cα–C6 bond, one would expect a priori an extended, zig-zag conformation to be preferred.[2] Thus, we anticipate that **1** and **2** should exist predominantly in the conformers **1A** and **2A**, respectively. In this paper, we would like to present experimental support for this prediction.

For the case of $\alpha(1'\rightarrow6)$-*C*-diglucose, we needed first of all to develop a reliable chemical synthesis and have found that the route summarized in Scheme I meets well with our requirements. The key step in the synthesis is the $NiCl_2/CrCl_2$-mediated coupling[3,4] of the vinyl iodide **5**[5,6] with the aldehyde **6**[7] to yield stereoselectively the allylic alcohol **7** (the stereoselectivity is better than 15:1). The methyl glycoside **1** (α_D +134° in CH_3OH)[8] was isolated and purified by polystyrene gel column chromatography.

The 500-MHz NMR spectrum in CD_3OD–D_2O (9:1) of **1** shows good resolution of all the signals without apparent higher order effects. The C6 and Cα methylene protons appear at 1.59, 1.69, 1.83, and 1.93 ppm. All the spin–spin coupling constants can be measured directly from the spectrum, resulting in the spin relationship summarized in Chart II.[9,10]

The values of spin–spin coupling constants[9] clearly show that both pyranose rings adopt a chair conformation; the vicinal spin–spin coupling constants between the C1′ and Cα protons (J = 11.7 and 3.2 Hz) and also between the C5 and C6 protons (J = 9.5 and 2.2 Hz) demonstrate that one of the two Cα protons is antiperiplanar to the C1′ proton and one of the two C6 protons is antiperiplanar to the C5 proton. The vicinal spin–spin coupling constants between the Cα and C6 protons, i.e., J = 10.8, 10.8, 5.2, and 3.6 Hz, lead to the conclusion that the extended, zig-zag conformation is preferred around the Cα–C6 bond as anticipated. Thus, among 27 ideal staggered conformers possible around the C1′–Cα, Cα–C6, and C6–C5 bonds, only the two conformers **1A** and **1B** are consistent with the observed NMR data.

The differentiation of **1A** from **1B** should be possible by an NMR study with a substrate specifically deuteriated at the Cα or C6 or both positions. Namely, $J_{1',\alpha}$ = 11.7 Hz is attributed to the vicinal spin–spin coupling between the C1′ and Cα *pro-S* protons in the conformer **1A** whereas between the C1′ and Cα *pro-R* protons in the conformer **1B**. A similar analysis can also be applied for $J_{5,6}$ = 9.5 and 2.2 Hz.



1B

Experimentally, this was accomplished by synthesizing the selectively dideuteriated methyl C-glycoside 1-d_2 as summarized in Scheme I. The key step in this synthesis is the stereoselective deuteriation of **7** into 8-d_2 (the stereoselectivity is better than 10:1).[11] The indicated relative stereochemistry at the C6 and Cα positions was evident because of the cis geometry of the olefinic bond of **7**. The absolute configuration at the Cα position was established by chemical degradation of 8-d_2 into a known compound.[12]

(1) Wu, T.-C.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.*, preceding paper in this issue.
(2) The anti conformation of *n*-butane is known to be favored over the gauche conformation by about ΔG = 0.8 kcal/mol.
(3) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, **5644**. Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am.* Chem. *Soc.* **1986**, *108*, 6048.
(4) Attempted couplings utilizing more conventional organometallic reagents including acetylene anion and vinyllithium did not yield the desired products.
(5) This substance was synthesized from 2,3,4,6-tetra-*O*-benzyl-D-glucose *p*-nitrobenzoate in 30% overall yield in six steps: (1) $CH{\equiv}CCH_2TMS/BF_3{\cdot}Et_2O/MeCN/0$ °C → room temperature;[16] (2) $O_3/MeOH{-}CH_2Cl_2/{-}78$ °C, followed by $(Me)_2S$ workup; (3) $CBr_4/(Ph)_3P/CH_2Cl_2/O$ °C; (4) *n*-BuLi/THF/−78 °C; (5) I_2/morpholine/C_6H_6/45 °C; (6) $KO_2CN{=}NCO_2K$/AcOH/dioxane/room temperature.
(6) Satisfactory spectroscopic data were obtained for all the new compounds reported in this paper.
(7) This substance was synthesized from L-xylose diethyl dithioacetal in 75% overall yield in five steps: (1) *p*-MeOPh$(Ph)_2$CCl/py/room temperature; (2) BnBr/NaH/THF–DMF/room temperature; (3) HCl/THF–H_2O/room temperature (4) (*t*-Bu)$(Me)_2$SiCl/imidazole/DMF/room temperature; (5) NBS/$AgNO_3$/collidine/acetone–H_2O/0 °C.
(8) At step c.5 in Scheme I, an approximately 1:1 mixture of methyl α- and β-glycosides was formed, which could easily be separated by silica gel chromatography. Both anomers were carried on to the final methyl C-glycosides: α_D of **1**, +134° (*c* 0.3, MeOH); α_D of its β-anomer, +38.2° (*c* 0.3, MeOH).
(9) The complete table listing chemical shifts and spin–spin coupling constants is included in the supplementary material.
(10) It is worthwhile to note that the hepta-*O*-benzyl derivative of **1** adopts preferentially the conformation corresponding to **1A**, based on the ^{1}H NMR spectrum in $CDCl_3$ (shifts in ppm): H5, 3.60 (ddd, 9.7, 9.7, 2.2 Hz); H6 (*pro-S*), 1.53 (dddd, 13, 11.5, 9.7, 4.1); H6 (*pro-R*), 1.78 (dddd, 13, 11.5, 4.8, 2.2); Hα (*pro-S*), 1.95 (dddd, 14, 11.9, 11.5, 4.1); Hα (*pro-R*), 1.62 (dddd, 14, 11.5, 4.8, 3.2); H1′, 3.99 (ddd, 11.9, 5.7, 3.2).
(11) For examples of hydroxyl group directed heterogeneous hydrogenation, see: Fujimoto, R.; Kishi, Y.; Blount, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7154 and references cited therein.
(12) The summary of this assignment is included in the supplementary material.

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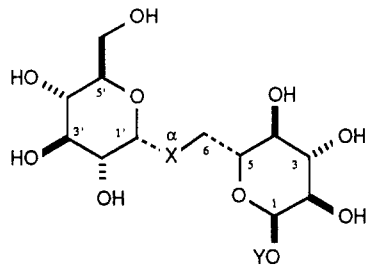
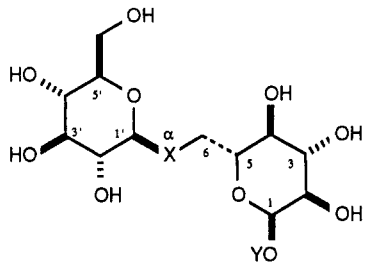
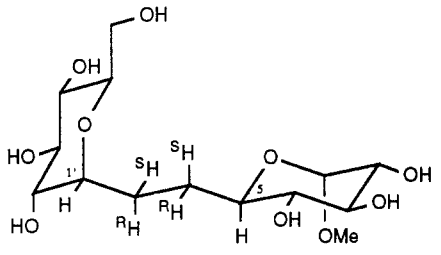
Chart I



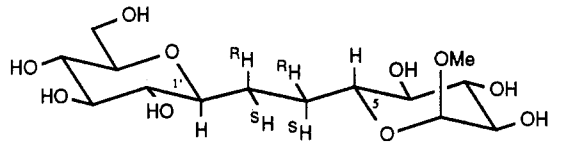
1: X = CH_2, Y = Me
3: X = O, Y = H (isomaltose)



2: X = CH_2, Y = Me
4: X = O, Y = H (gentiobiose)

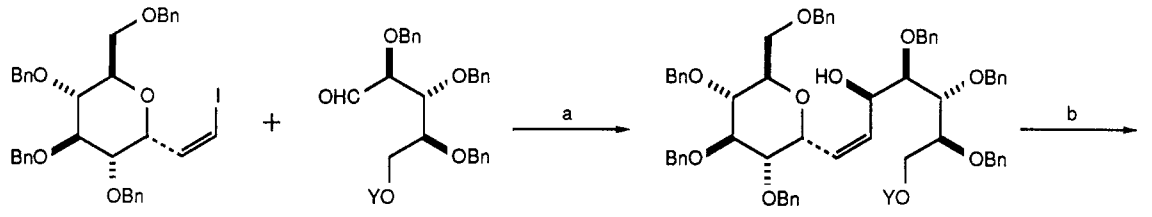


1A

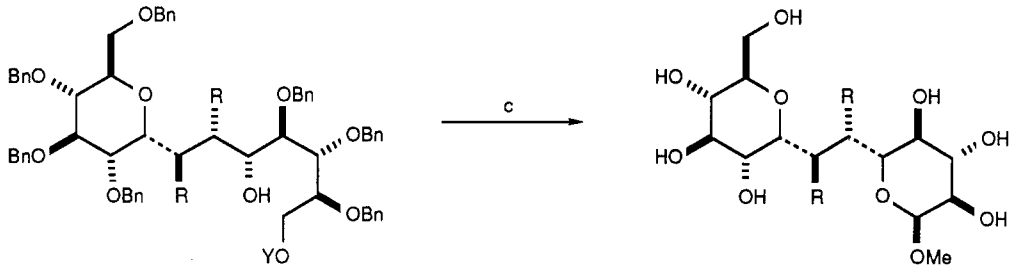


2A

Scheme I[a]



5 6: Y = $Si(Me)_2(t\text{-Bu})$ 7: Y = $Si(Me)_2(t\text{-Bu})$



8: R = H, Y = $Si(Me)_2(t\text{-Bu})$
8-d_2: R = D, Y = $Si(Me)_2(t\text{-Bu})$

1: R = H
1-d_2: R = D

[a] Reagents and conditions: (a) $NiCl_2$(0.1%)–$CrCl_2$/DMSO/room temperature;[3] (b) H_2 or D_2/Pt on Al_2O_3/EtOAc/room temperature; (c) (1) DHP/PPTS/CH_2Cl_2/room temperature, (2) $(n\text{-Bu})_4NF$/THF/room temperature, (3) Swern oxidation,[18] (4) p-TSA/THF–H_2O (5:1)/room temperature, (5) NaH/MeI/THF/room temperature followed by a chromatographic separation,[8] (6) $H_2/Pd(OH)_2$ on C/MeOH–CH_2Cl_2 (4:1)/room temperature.

The NMR spectra of 1-d_2 clearly demonstrates the loss of signals at 1.59 and 1.69 ppm, establishing that methyl α-*C*-isomaltoside exists predominantly in the predicted conformation **1A**. Applying a modified Karplus equation,[13] this conformation can be further refined, to yield the angles of approximately ϕ −70°, ψ −75°, and ω −40°.[14]

The conformational preference of methyl *C*-gentiobiose **2** was studied by using the similar procedure.[15,16] The

(13) For a refinement of the spin–spin coupling constant and dihedral angle correlation, for example, see: Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

(14) The definition of ϕ, ψ, and ω, used by Gagnaire et al. (Gagnaire, D. Y.; Nardin, R.; Taravel, F. R.; Vignon M. R. *Nouv. J. Chim.* **1977**, *1*, 423) was adopted.

Chart II

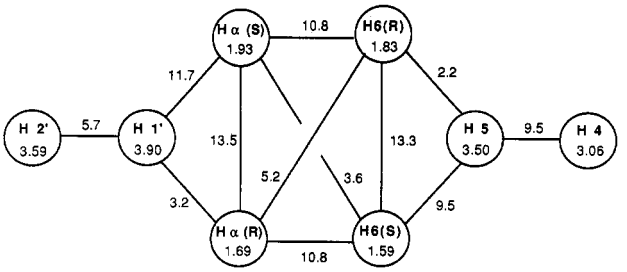
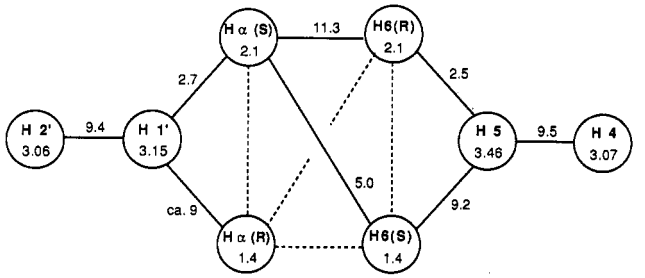


Chart III



spin–spin coupling constants observed (Chart III[9]) demonstrate that **2** exists predominantly in the predicted conformation **2A**. From a modified Karplus equation,[13] the spin-spin coupling constants listed in Table I yield ϕ −35°, ψ −60°, and ω −35°.[14]

The C-disaccharides are, like the corresponding parent disaccharides, not conformationally rigid. Nonetheless, the weighted average of available conformers corresponds extremely well to the one predicted. Comparison of the preferred conformation observed for carbon analogues of 1,6-disaccharides with that of corresponding parent disaccharides is constrained since only limited experimental data is available on the solution conformation of parent substances at this time.[17] We are currently engaged in some experimental work to compare the solution conformations between these two classes of compounds.

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Registry No. **1**, 110352-40-4; 1-d_2, 110316-60-4; **2**, 89160-13-4; **3**, 499-40-1; **4**, 554-91-6; **5**, 110316-55-7; **6**, 110316-56-8; **7**, 110316-57-9; **8**, 110316-58-0; 8-d_2, 110316-59-1.

Supplementary Material Available: The complete tables listing chemical shifts and spin–spin coupling constants of **1** and **2** and the summary for the assignment of absolute configuration of 8-d_2 (3 pages). Ordering information is given on any current masthead page.

(15) Rouzaud, D.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1353.
(16) The details of this study will be published in a full account.
(17) For the conformational analysis of 1,6-disaccharides in solution, for example, see: (a) Ohrui, H.; Nishida, Y.; Watanabe, M.; Hori, H.; Meguro, H. *Tetrahedron Lett.* **1985**, *26*, 3251. (b) Lemieux, R. U.; Wong, T. C.; Thogersen, H. *Can. J. Chem.* **1982**, *60*, 81. (c) Bock, K.; Vignon, M. *Nouv. J. Chim.* **1982**, *6*, 301. (d) Melberg, S.; Rasmussen, K. *Carbohydr. Res.* **1980**, *78*, 215. (e) Gagnaire, D. Y.; Nardin, R.; Taravel, F. R.; Vignon, M. R. *Nouv. J. Chim.* **1977**, *1*, 423.
(18) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

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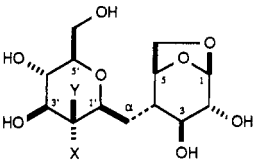
Preferred Conformation of C-Glycosides. 3. Preferred Conformation of Carbon Analogues of 1,4-Disaccharides

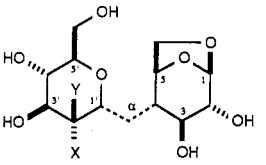
Summary: Through the studies on the carbon analogues of 1,4-disaccharides, a simple but effective method is developed to analyze the conformational preference of disaccharides and related compounds.

Sir: In the preceding papers, we have demonstrated that simple C-glycosides as well as the carbon analogues of 1,6-disaccharides exist predominantly in the predicted conformation.[1] In this paper, we would like to extend this study to the carbon analogues of 1,4-disaccharides. On the basis of the results reported in one of the preceding papers,[1a] the conformational preference around the C1′–Cα bond is predicted to be such that the Cα–C4 bond is antiperiplanar to the C1′–C2′ bond. With respect to the Cα–C4 bond, we have considered the steric interactions around this bond to analyze the problem.

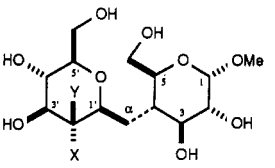
The eight carbon analogues **1**–**8** of 1,4-disaccharides[2] were subjected to NMR studies in CD_3OD–D_2O (9:1) (Table I[3]). The values of spin–spin coupling constants[3]



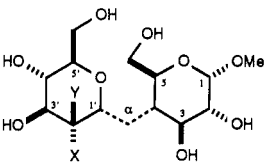
1: X = OH, Y = H
2: X = H, Y = OH



3: X = OH, Y = H
4: X = H, Y = OH



5: X = OH, Y = H
6: X = H, Y = OH



7: X = OH, Y = H
8: X = H, Y = OH

clearly demonstrate that both pyranose rings adopt a chair conformation in all the cases. The assignment of the *pro-R* and *pro-S* protons at the Cα position was unambiguously made through the synthesis of the corresponding specifically monodeuteriated glycosides with known absolute configuration.[4]

No ambiguity remains in specifying the preferred conformation of the carbon analogues **1**–**4** of 1,4-disaccharides belonging to the 1,6-anhydrogluco series. Namely, the spin–spin coupling constants between the C1′ and Cα protons clearly confirm that the C-glycosidic bond adopts preferentially the predicted conformation. Similarly, the spin–spin coupling constants between the C4 and Cα protons establish the preferred conformation around this bond. This conformational preference is straightforwardly explained in terms of steric interactions, which is conveniently recognized by using a diamond lattice. Among the three ideal staggered conformers A–C available for **1** and **2**, conformer C is considered to be least favored be-

(1) (a) Wu, T.-C.; Goekjian, P. G.; Kishi, Y. *J. Org. Chem.* preceding paper in this issue. (b) Goekjian, P. G.; Wu, T.-C.; Kang, H.-Y.; Kishi, Y. *J. Org. Chem.*, second preceding paper in this issue.
(2) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370.
(3) The complete tables listing chemical shifts and spin–spin coupling constants are included in the supplementary material.
(4) The synthetic scheme of specifically monodeuterated substances is included in the supplementary material.

0022-3263/87/1952-4825$01.50/0