CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200700281

Hemicarbasucrose: Turning off the Exoanomeric Effect Induces Less Flexibility

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Abstract: Hemicarbasucrose, a close congener of sucrose in which the endocyclic oxygen atom of the glucose moiety is replaced by a methylene group was synthesized for the first time. The conformational behaviour of hemicarbasucrose was studied by a combination of molecular mechanics and NMR spectroscopy (*J* and NOE data). It was shown that the carbadisaccharide populates two distinct conformational families in solution, the normal *syn*-ψ conformation, which is the predominating conformation of the parent natural O-glycoside, and the *anti*-ψ conformation, which has not been detected for the O-disaccharide. Interestingly, the hemicarbasucrose is less flexible than its natural congener.

Keywords: carbohydrates · conformation analysis · glycomimetics · molecular modeling · NMR spectroscopy

Introduction

Sucrose (**1**) is the sugar par excellence, and the development of analogues has attracted a lot of attention because of clear potential applications in non-nutritive sweeteners, for example. The search for new glycomimetics has led to many families of compounds classified according to the modification of the natural sugar.[1] An important category includes sugar congeners in which an oxygen atom of the acetal function has been replaced by a methylene group, which confers stability towards enzymatic hydrolysis on the analogue. Two subclasses of such mimetics exist: C-glycosides, in which the exocyclic oxygen atom is replaced by a methylene, and carbaglycosides, in which the endocyclic oxygen is replaced by a methylene group. The determination of the three-dimensional structure of these analogues and its comparison with that of O-glycosides is of primary importance to evaluate the potential of the glycomimetics as glycosidase inhibitors or molecular probes.[2] Different studies have addressed this topic and have revealed that the conformational similarity between O-, C-, and carbaglycosides is not a general phenomenon.[3] Subtle differences in conformational behavior have been described for different glycosyl/carbaglycosyl pairs; in general, a higher degree of flexibility is observed for the carba analogues, presumably owing to the absence of electronic effects such as the exoanomeric effect. These findings have encouraged us to extend the comparison to other linkages. Whereas the C-glycoside analogue **2** of sucrose has been prepared and analyzed,[4] carbasucrose has never been investigated. However, sucrose is a nonreducing disaccharide; therefore, replacement of one of the two endocyclic oxygen atoms leads to a hemicarbadisaccharide **3** or **4** in which the glycosidic bond remains part of an acetal, whereas carbasucrose (**5**) would bear two carbocycles (Scheme 1). We now report the first synthesis and conformational analysis of the carbadisaccharide α-carbaGlc-(1→2)-α-Fru (hemicarbasucrose **3**) in water by using NMR spectroscopy in tandem with molecular mechanics calculations and the comparison with the parent O-disaccharide **1**.[5] Su-

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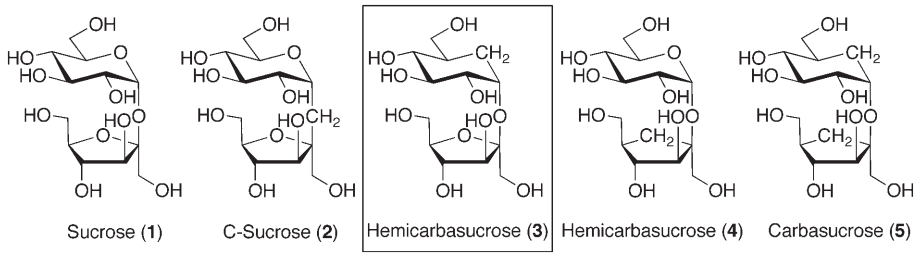
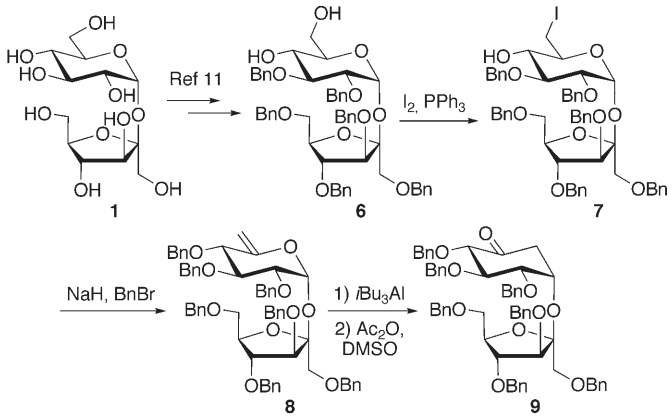


Scheme 1. Sucrose and its carba analogues.

crose has been studied extensively, with rather different conclusions, both in free[6] and protein-bound states.[7]

Results and Discussion

A wide range of synthetic procedures for carbasugars is available;[8] among them we have developed a particularly efficient method that relies on a rearrangement strategy.[9] We have shown that unsaturated hex-5-enopyranoses rearrange to carbocycles under the action of a Lewis acid and with retention of the aglycon, provided that it is sufficiently electron-donating in nature.[10] We applied this strategy to the synthesis of carbamonosaccharides and, more interestingly, to carbadisaccharides starting from the corresponding disaccharide, hence avoiding the coupling of two separately prepared units. Diol **6** is readily available from sucrose (**1**) according to a literature procedure (Scheme 2).[11] This diol



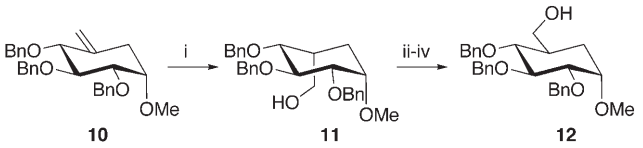
Scheme 2. Synthesis of hex-5-enopyranosidic derivative **8** of sucrose and its rearrangement. Bn = benzyl, DMSO = dimethyl sulfoxide.

Abstract in Chinese:

碳蔗糖是蔗糖的同类物， 其分子中葡萄糖部分的环内氧原子被一个次甲基取代。本文报道了碳蔗糖的首次合成。 用分子力学结合核磁共振光谱 （*J* 和NOE数据）研究了碳蔗糖的构象行为。 实验数据显示，二聚碳糖在溶液中组建了两个显著不同的构象系统： 正常的 *syn*-ψ 构象， 这是母体天然氧糖式的优势构象； *anti*-ψ 构象， 这种构象尚未在二聚氧糖中检测到。 有趣的是， 与它的天然同类物相比， 碳蔗糖较少具有柔性。

was readily converted into alkene **8** by a selective iodination and elimination/alkylation sequence. Alkene **8** was treated with triisobutylaluminum followed by an oxidation to give the cyclohexanone **9** as the major product.[12] We now had to convert this derivative **9** into hemicarbasucrose **3**.

This task involves the conversion of the ketone function into a hydroxymethyl group. We previously carried out this transformation by olefination and subsequent hydroboration of carbocyclic mono- or disaccharides as illustrated in Scheme 3 for cyclohexane **10**.[9a] The outcome of the hydroboration is consistent: the hydrogen atom is always introduced in the equatorial position, regardless of the boron hydride used. We therefore developed an epimerization reaction on this model compound. Swern oxidation of alcohol **11** afforded the corresponding aldehyde, which was epimerized under very mild basic conditions in MeOH/pyr (2:1) at 50 °C for 32 h. The resultant mixture was reduced with $NaBH_4$, and the major equatorial alcohol **12** was isolated in 63 % yield over three steps.



Scheme 3. Hydroboration of alkene **10** and epimerization. Reagents and conditions: i) BH_3·THF, THF, room temperature; then NaOH, H_2O_2, 0 °C→RT, 60 %; ii) $(COCl)_2$, DMSO, −78 °C; then NEt_3; iii) pyridine (pyr), MeOH, 50 °C, 32 h; iv) $NaBH_4$, THF/H_2O, 0 °C, 63 % over three steps.

We then applied this strategy to synthesize hemicarbasucrose **3**. Ketone **9** was converted into alkene **13** by means of a Tebbe reaction[13] in 68 % yield. Hydroboration of **13** afforded the undesired, but expected, axial hydroxymethyl derivative **14**. We then performed the previously described epimerization on **14** which afforded the desired alcohol **15**. Final complete debenzylation of **15** furnished hemicarbasucrose **3** (Scheme 4).

Conformational Behavior

The protocol to deduce the conformational behavior of **1** and **3** was described previously[14] and involves 1) calculation of the conformational energy maps by molecular mechanics calculations, 2) determination of the expected NMR parameters (*J* values and NOE interactions) from the population distribution, and 3) comparison with experimental data to validate the theoretical results. Three staggered conformations around the glycosidic bonds are possible and were pre-

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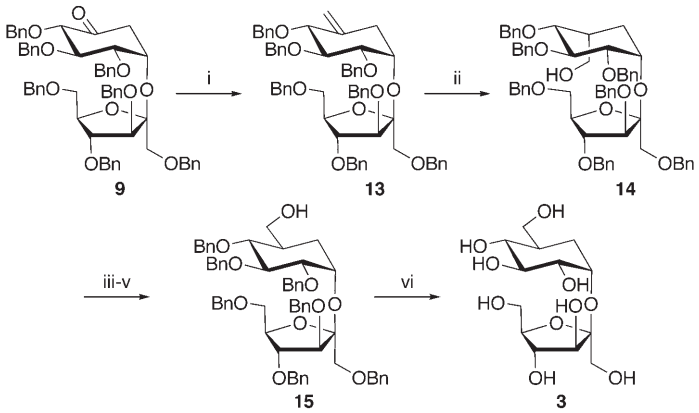

Scheme 4. Final steps toward the synthesis of hemicarbasucrose **3**. Reagents and conditions: i) Tebbe reagent, THF, pyr, −45 °C→RT, 68 %; ii) BH_3·THF, THF, room temperature; then NaOH, H_2O_2, 0 °C→RT, 82 %; iii) $(COCl)_2$, DMSO, −78 °C; then NEt_3, 87 %; iv) pyr, MeOH, 50 °C, 32 h, 70 %; v) $NaBH_4$, THF/H_2O, 0 °C, 88 %; vi) H_2, Pd/C, MeOH, 79 %.

viously termed *exo-syn* (60°), *exo-anti* (180°), and *non-exo* (−60°) in accordance with the *exo*-anomeric geometry and their disposition in a *syn*- or *anti*-type arrangement. Additional possibilities do exist for the three hydroxymethyl groups of the molecule (6, 1′, 6′).[5]

Molecular Mechanics Calculations

The energy maps of **1** and **3** as a function of the glycosidic (ϕ) and aglyconic (ψ) torsions were drawn by using TRIPOS and further minimised with the MM3*[15] force fields. The dihedral angles were defined as ϕ (C7Glc–C1Glc–O–C2Fru) and ψ (C1Glc–O–C2Fru–O5Fru) for **3** and ϕ (O5Glc–C1Glc–O–C2Fru) and ψ (C1Glc–O–C2Fru–O5Fru) for **1**. Eight relaxed energy maps were calculated to take into account different orientations for the hydroxymethyl group.

For the O-glycoside **1**, a detailed conformational analysis[5] showed the existence of five different local minima (Table 1). This molecule has a peculiar feature in that no aglyconic linkage exists, and two glycosidic linkages are present in the molecular framework that provide competing *exo*-anomeric effects[16] around the two glycosidic linkages.[17] In sucrose, the *exo*-anomeric *syn* region is only populated by about 16 % for the Glc-glycosidic linkage and about 28 % for the Fru analogue. For the Glc moiety, a distorted conformer inbetween the pure *exo-syn* and *non-exo syn* conformers appears to be the global minimum, with 60 % population (geometry A). The *non-exo*-anomeric *syn* region is 24 % for the Glc glycosidic torsion, and only populated by 12 % for the Fru torsion, whereas the *anti* conformer is the major one for the Fru torsion, with about 60 % for the corresponding global minimum A. Clearly, the chemical nature of the five-membered ring along with the existence of competing *exo*-anomeric effects, appears, indeed, to be important for these atypical conformational features, with major contributions of nonpure *exo*-anomeric conformers.[18] The dihedral angles exhibit a certain flexibility, as observed in the lowest-energy regions, although the existence of one major conformation was postulated through the detection of a diagnostic hydrogen bond in a partially deuterated sample.[6]

Although the shapes of the potential energy maps for the carbaglycoside **3** are similar to those of **1**, there are noticeable changes in the local minima. In this case, however, the absence of anomeric effects for the Glc moiety strongly modifies the particular features of the minima and reveals the presence of only three low-energy conformations around the glycosidic linkages (Figure 1). The pure *exo*-anomeric conformer around the Glc moiety disappears, and the corresponding Φ torsion is shifted towards essentially eclipsed angles (83 %, conformers B and C, Table 1) The contribution of the *non-exo*-anomeric region slightly decreases to around 17 %. In contrast, for the Fru moiety, the population of the *anti* region strongly diminishes (to only 17 %) and the *exo*-anomeric region is clearly enhanced, passing now from 28 to 78 %. Only 5 % of the population remains in the *non-exo*-anomeric region, according to the molecular mechanics calculations. The enhancement of the *exo*-anomeric region for the Fru linkage of **3** is probably due, at least partially, to the fact that this is now the only glycosidic linkage in the molecule and there is no competition with other *exo*-anomeric effects (for the Glc fragment). The calculations therefore suggest that hemicarbasucrose **3** presents distinct conformational preferences around the glycosidic bonds over its parent O-disaccharide,[5] with distinct conformational diversity around the two bonds.

Table 1. Torsion angle values and relative MM3* energies of the predicted minima and populations (%) of the low-energy regions. The conformational families of the minima are indicated.

Compound	Minima	Torsions (ΦGlc/ΨFru)	Pop. [%]	Type (ΦGlc)	Type (ΨFru)
1	A	120/40	60	distorted *exo-syn*	*anti*
	B	150/5	24	*non-exo-syn*	distorted *exo*
	C	60/−60	1	*exo-syn*	*exo-syn*
	D	70/−160	12	*exo-syn*	*non-exo-syn*
	E	85/−25	3	*exo-syn*	*exo-syn*
3	A	139/39	17	*non-exo-syn*	*anti*
	B	111/−54	78	distorted *exo-syn*	*exo-syn*
	C	111/−171	5	distorted *exo-syn*	*non-exo-syn*

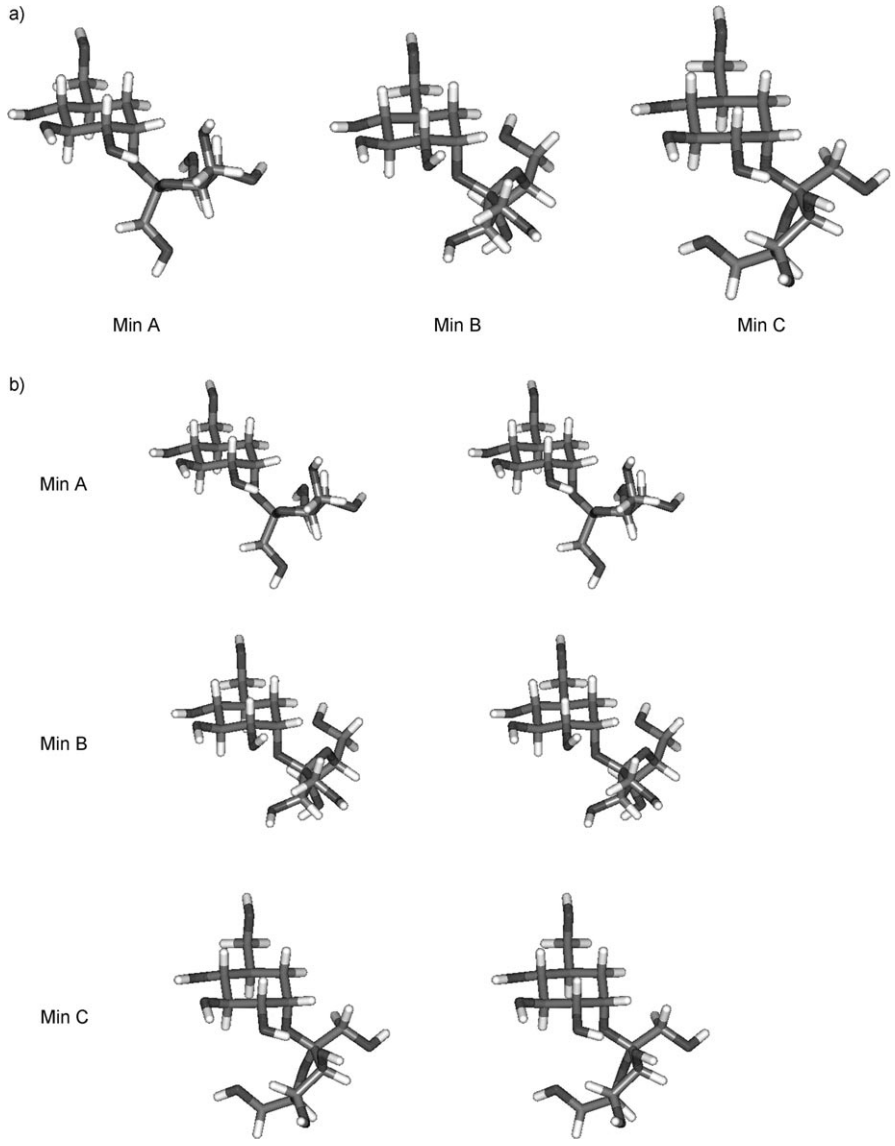

Figure 1. a) Views of the major low-energy conformations obtained by MM3* calculations for hemicarbasucrose **3**. b) Stereoscopic views of the major low-energy conformations obtained by MM3* calculations for hemicarbasucrose **3**.

NMR Spectroscopy

The validity of the theoretical results was verified for **3** through NMR spectroscopy. The ^{1}H NMR spectrum in D_2O was assigned by using a combination of COSY and HSQC experiments (Table 2).[19]

The intra-ring vicinal proton–proton coupling constants proved that the six-membered ring of the carbaGlc moiety adopts the $^{4}C_1$ chair conformation (Table 2). The five-membered ring geometries of the Fru moiety determined by molecular mechanics calculations were used to estimate the 3-H/4-H and 4-H/5-H dihedral angles and converted into proton–proton coupling constants through the well-established Karplus–Altona equation.[20]

The experimental couplings can be compared with the calculated values for minima A–C and for the ensemble average (Table 3). The two observed large values reveal that there is a significant population of a well-defined conformational family. This conclusion is also consistent with the MM3* calculations. A satisfactory matching between the experimental and the theoretical couplings for the distribution is obtained (Table 3). Moreover, the observed values are indeed similar to those for natural sucrose in aqueous solution[5] and, thus, the conformational properties of the two fructofuranose rings in sucrose **1** and hemicarbasucrose **3** are essentially independent of the nature of the Glc moiety.

Further structural information can be extracted from NOESY and ROESY experiments[21] to complement coupling-constant data. The relevant interresidue proton–proton distances in terms of the glycosidic and aglyconic angles are gathered in Table 4 for conformers A, B, and C. It can be observed that 1-H_g is a short distance away from 1-H_f in both C and B conformers and from 4-H_f in conformer A (exclusive close contact). In turn, 4-H_f is exclusively at a medium distance from 5-H_g and 7-$H_{g,eq}$ in global minimum B and two contacts should exclusively characterize minimum conformer C, namely 3-H_f–7-$H_{g,eq}$ and 1-H_f–7-$H_{g,eq}$. All these contacts are, indeed, seen in the NOESY and ROESY spectra, although with different intensities to those predicted by the calculations (Figure 2). The 1-H_g–1-H_f cross-peak is very strong, fivefold stronger than that for 5-H_g–4-H_f, which has a medium intensity, whereas those for minimum conformer C are weak or very weak: 3-H_f–7-$H_{g,eq}$ and 1-H_f–7-$H_{g,eq}$. The 1-H_g–4-H_f cross-peak is also weak. The ensemble average population predicts similar NOE intensities for both 5-H_g–4-H_f (minimum B) and 1-H_g–4-H_f (minimum A), whereas experimentally the close contact corresponding to minimum B is 2.2-fold more intense than that for 1-H_g–4-H_f (minimum A). Moreover, this latter cross-peak displays a similar experimental NOE intensity as that of the 7-H_g–4-H_f cross-peak (3.4 Å proton–proton distance in minimum B) and therefore provides an estimate for the actual average distance in solu-

Table 2. ^{1}H and ^{13}C NMR chemical shifts (δ, ppm), and coupling constants (Hz) of **3** in D_2O at 298 K.

Atom	$\delta(^{1}H)$ ($\delta(^{13}C)$)	$^{3}J_{H,H}$
1-H_g	4.31 (70.3)	3.4 ($J_{1g,2g}$)
2-H_g	3.44 (73.1)	10.0 ($J_{2g,3g}$)
3-H_g	3.67 (74.5)	9.1 ($J_{3g,4g}$)
4-H_g	3.30 (73.1)	9.8 ($J_{4g,5g}$)
5-H_g	1.97 (38.4)	3.4 ($J_{5g,7g(eq)}$)
6-$H_{g,a}$	3.75 (60.9)	
6-$H_{g,b}$	3.75 (60.9)	
7-$H_{g(ax)}$	1.37 (30.0)	
7-$H_{g(eq)}$	2.10 (30.0)	3.4 ($J_{6g(eq),1g}$)
		3.4 ($J_{6g(eq),5g}$)
1-$H_{f,a+b}$	3.72 (62.3)	
3-H_f	4.17 (77.8)	8.5 ($J_{3f,4f}$)
4-H_f	4.04 (74.5)	8.5 ($J_{4f,5f}$)
5-H_f	3.84 (80.6)	
6-$H_{f,a}$, 6-$H_{f,b}$	3.84 (62.3)	

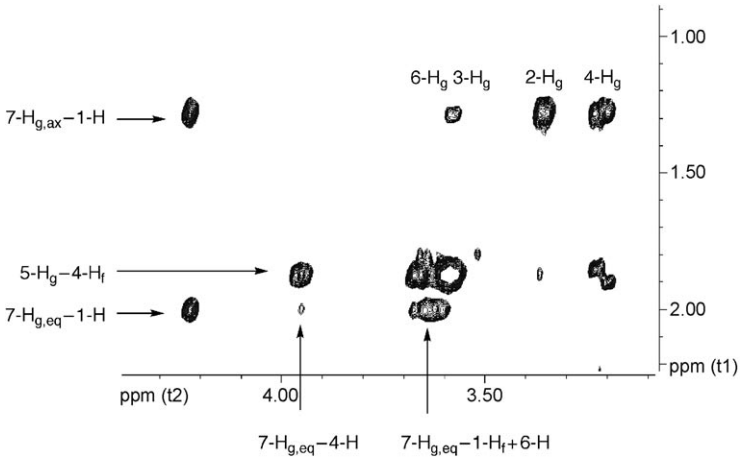

Figure 2. Key sections of the 2D-NOESY spectrum of **3** (500 MHz, 298 K, D_2O, mixing time 600 ms).

Table 3. Experimental vicinal coupling constants ($^{3}J_{H,H}$, Hz) for the five-membered rings of **1** and **3** in D_2O and calculated values for the minima and for the ensemble average.

$^{3}J_{HH}$	Conf. A	Conf. B	Conf. C	Ensemble average (**3**)	Exp. D_2O (**3**)	Exp. sucrose (**1**)
3-H_f–4-H_f	6.7	8.7	8.6	8.3	8.5	8.8
4-H_f–5-H_f	9.1	9.1	8.0	9.0	8.5	8.3

Table 4. Relevant proton–proton distances for major minima A, B, C of **3** and for the ensemble average population distribution ($<r^{-6}>^{-1/6}$), along with the experimental values derived from NOE intensities. The putative hydrogen bonds for each conformer are also given in the last row.

Proton pair	Predicted distances [Å] Conf. A	Conf. B	Conf. C	Dist.	Exp. NOE intensity, estimated distance[a] [Å]
1-H_g–1-H_f	4.3	2.2	2.1	2.3	strong, 2.1–2.3
5-H_g–4-H_f	5.5	2.9	4.8	3.0	medium, 2.8–3.0
7-H_g–3-H_f	4.6	5.2	2.4	3.8	very weak, >3.7
1-H_g–4-H_f	2.3	4.5	3.9	3.0	weak, 3.3–3.7
7-H_g–4-H_f	3.7	3.4	5.4	3.5	weak, 3.3–3.7
7-H_g–1-H_f	4.7	3.4	2.4	3.2	weak, overlap
H bond	$O2_gO1_f$[b]		$O2_gO3_f$		

[a] From a full-matrix relaxation approach. [b] Possible, depending on the C1–C2 rotamer.

tion. Therefore, according to the NOE data, the equilibrium is very much shifted towards minimum B. As the intensity of each NOE interaction is sensitive to the population of the corresponding conformational family, the observations agree, at least semiquantitatively, when using a full-relaxation matrix approach,[22] with a very major (>90%) contribution of the B conformation family. Both A and C regions are overestimated by the calculations, as deduced from the NOE data.

Conclusions

The first synthesis of hemicarbasucrose **3** has been successfully completed. The combination of molecular mechanics and NMR spectroscopic studies has shown that the conformational properties of sucrose (**1**) and its carba analogue **3** are somehow different. When the stereoelectronic stabilization for the Glc glycosidic linkage is absent, as is the case in **3**, the population of the *exo-syn* region in the contiguous Fru linkage is higher than that of its parent O-glycoside. Usually, carba and C-glycosyl compounds display higher flexibility than their parents O-glycosidic compounds.[23] However, this is not the case for hemicarbasucrose **3**, which presents a very high predominance of a unique conformation, B, characterized by an almost eclipsed torsion around ΦGlc and an *exo*-anomeric orientation for ΨFru. This fact is in contrast to the reported data for sucrose,[5] for which controversial data have been reported, although the more rigorous approaches have demonstrated that a major conformational equilibrium does, indeed, exist. It is also notable that the major conformation adopted by hemicarbasucrose **3** is similar to that described in the sucrose crystal structure as well as in some sucrose–lectin complexes.[24]

Nevertheless, the existence of minor orientations around the glycosidic torsions of **3** is also well predicted by the NMR spectroscopic data and molecular mechanics calculations. The conformational differences between carba- and O-glycosides described herein for sucrose, together with those reported for other C-/O-pairs stress that care should be taken when using synthetic analogues as carbohydrate models.[25] The different flexibility of the different families implies differences in entropy upon binding to a given receptor, which may be a limitation for the use of analogues as glycosidase inhibitors. Nevertheless, these compounds are excellent probes to study the active site of proteins.

Experimental Section

General

Optical rotations were measured in a 10-cm, 1-mL cell at 20±2°C with a Perkin–Elmer Model 241 digital polarimeter. Mass spectra (CI (ammonia) and FAB) were obtained with a JMS-700 spectrometer. ^{1}H NMR spectra were recorded at 250 MHz with a Bruker AC-250 or at 400 MHz with a Bruker DRX 400 for solutions in $CDCl_3$, CD_3OD, or C_6D_6 at room temperature. Assignments were confirmed by COSY experiments. ^{13}C NMR spectra were recorded at 63 MHz with a Bruker AC-250 or at 100.6 MHz with a Bruker DRX 400 spectrometer. Assignments were confirmed by using the J-mod technique and HMQC. ^{19}F NMR spectra were recorded at 235 MHz with a Bruker AC-250. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of Silica Gel 60 F_{254} (layer thickness 0.2 mm; Merck, Darmstadt, Germany) and detected by charring with H_2SO_4 or with 0.2% *w/v* cerium sulfate and 5% ammonium molybdate in 2 M H_2SO_4. Flash column chromatography was performed on silica gel 60 (230–400 mesh, Merck). TIBAL was purchased from Aldrich as a 1 M solution in toluene.

12: DMSO (0.17 mL, 2.4 mmol) was diluted in dichloromethane (15 mL) at room temperature under argon and cooled to −78°C. $(COCl)_2$ (0.104 mL, 1.2 mmol) was added dropwise at −78°C under argon. After 10 min a solution of compound **11**[9a] (278 mg, 0.60 mmol) in dichloromethane (15 mL) was added slowly at −78°C. The reaction mixture was stirred at −78°C for 1 h, and Et_3N (0.5 mL) was added at this temperature. After 1.5 h the reaction solution was washed with H_2O, and the organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was submitted to flash column chromatography (cyclohexane/ethyl acetate 4:1). The resulting aldehyde was obtained as a colorless oil (260 mg, 0.57 mmol). This aldehyde was then heated in MeOH/pyr (20 mL/10 mL) at 50°C for 32 h. The reaction solution was then concentrated and dried. The crude residue was dissolved in THF/H_2O (10 mL/2 mL) and cooled to 0°C. A solution of $NaBH_4$ (21 mg, 0.56 mmol) in H_2O (3 mL) was added at this temperature. When analytical TLC showed the absence of starting material the product was extracted with dichloromethane from the reaction mixture. The organic layers were combined, dried with $MgSO_4$, and concentrated. The residue was purified by means of silica-gel flash-column chromatography (toluene/CH_3CN 8:1) to afford carba-5a-methyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**12**) as the major product (175 mg, 0.38 mmol, 63%) and some starting material **11** (60 mg, 0.13 mmol, 21%). $[\alpha]_D^{20}=+28.8$ ($c=1.1$, $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$): $\delta=7.46$–7.35 (m, 15 H_{arom}), 5.10 (d, $J=10.7$ Hz, 1H; CHPh), 5.05 (d, $J=11.2$ Hz, 1H; CHPh), 4.89 (d, $J=10.7$ Hz, 1H; CHPh), 4.80 (s, 2H; CH_2Ph), 4.73 (d, $J=11.2$ Hz, 1H; CHPh), 4.05 (t, $J_{3,2}=J_{3,4}=9.3$ Hz, 1H; 3-H), 3.72–3.67 (m, 2H; 1-H, 6(a)-H), 3.60 (dd, $J_{6(b),5}=4.9$ Hz, $J_{6(b),6(a)}=10.8$ Hz, 1H; 6(b)-H), 3.46 (s, 3H; OCH_3), 3.45–3.42 (m, 1H; 2-H), 3.43 (t, $J_{4,3}=9.0$ Hz, $J_{4,5}=9.0$ Hz, 1H; 4-H), 2.12–1.99 (m, 1H; 5-H), 1.97 (dt, $J_{5a(a),5}=3.7$ Hz, $J_{5a(a),1}=3.7$ Hz, $J_{5a(a),5a(b)}=14.4$ Hz, 1H; 5a(a)-H), 1.14 ppm (ddd, $J_{5a(b),1}=1.8$ Hz, $J_{5a(b),5}=12.9$ Hz, $J_{5a(b),5a(ab)}=14.4$ Hz, 1H; 5a(b)-H); ^{13}C NMR(100 MHz, $CDCl_3$): $\delta=138.9$, 138.4, 138.3 (3 $C_{arom,quat}$), 128.4–127.4 (15 C_{arom}), 83.7 (C3), 83.0 (C2), 82.0 (C4), 77.3 (CH_2Ph), 75.4 (C1), 74.8 (CH_2Ph), 72.4 (CH_2Ph), 64.3 (C6), 56.9 (OCH_3), 37.8 (C5), 26.7 ppm (C5a); HRMS (CI, NH_3): calcd for $C_{29}H_{34}O_5$: 463.2484 $[M+H]^+$; found: 463.2478.

13: A solution of Tebbe reagent (0.5 M in toluene, 0.66 mL, 0.33 mmol) was added to a solution of ketone **9** (110 mg, 0.11 mmol) in THF/pyr (1.6 mL/0.8 mL) protected from light at −50°C under argon. The reaction mixture was continuously protected from light and was stirred and left to heat to room temperature. When analytical TLC showed only traces of starting material, the solution was cooled to −10°C, and aqueous NaOH (10%) was added slowly to quench the reaction. The reaction mixture was filtered through a celite column topped with a $MgSO_4$ pad. The filtrate was concentrated, and the residue was submitted to flash-column chromatography (cyclohexane/ethyl acetate gradient) to afford 1′,3′,4′,6′-tetra-*O*-benzyl-2′-*O*-[(1*S*,2*S*,3*S*,4*R*)-2,3,4-tri-*O*-benzyl-5-methylidene-1,2,3,4-tetrahydroxycyclohexyl]-β-D-fructofuranoside (**13**) as a colorless oil (75 mg, 0.078 mmol) in 68% yield. $[\alpha]_D^{20}=+5$ ($c=0.8$ $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$): $\delta=7.41$–7.29 (m, 35 H_{arom}), 5.19 (s, 1H; 6(a)-H), 4.81 (d, $J=12.3$ Hz, 1H; CHPh), 4.80 (s, 1H; 6(b)-H), 4.78 (d, $J=11.9$ Hz, 1H; CHPh), 4.78 (d, $J=11.7$ Hz, 1H; CHPh),4.74 (d, $J=11.9$ Hz, 1H; CHPh), 4.70 (d, $J=10.9$ Hz, 1H; CHPh), 4.67 (d, $J=11.9$ Hz, 1H; CHPh), 4.66 (d, $J=10.6$ Hz, 1H; CHPh), 4.64 (d, $J=11.7$ Hz, 1H; CHPh), 4.62 (d, $J=11.5$ Hz, 1H; CHPh), 4.56 (d, $J=12.1$ Hz, 1H; CHPh), 4.54 (s, 2H; CH_2Ph), 4.49(d, $J=11.8$ Hz, 1H; CHPh), 4.48 (q, 1H; 1-H), 4.44 (d, $J=8.4$ Hz, 1H; 3′-H), 4.40 (d, $J=12.1$ Hz, 1H; CHPh), 4.17 (t, $J=8.0$ Hz, 1H; 4′-H), 4.06 (ddd, $J_{5',6'(a)}=3.2$ Hz, $J_{5',6'(b)}=5.3$ Hz, $J_{5',4'}=8.4$ Hz, 1H; 5′-H), 3.88–3.80 (m, 2H; 3-H, 4-H), 3.70 (dd, $J_{6'(a),5'}=3.2$ Hz, $J_{6'(a),6'(b)}=10.6$ Hz, 1H; 6′(a)-H), 3.69 (d, $J=11.7$ Hz, 1H; 1×1′-H), 3.65 (d, $J=11.7$ Hz, 1H; 1×1′-H), 3.63 (dd, $J_{6'(b),5'}=5.3$ Hz, $J_{6'(b),6'(a)}=10.6$ Hz, 1H; 6′(b)-H), 3.50 (br d, $J_{2,3}=6.0$ Hz, 1H, 2-H), 2.80 ppm (dd, $J_{5a(a),1}=5.3$ Hz, $J_{5a(a),5a(b)}=13.8$ Hz, 1H; 5a(a)-H), 2.01 ppm (d, $J_{5a(b),5a(a)}=13.8$ Hz, 1H; 5a(b)-H); ^{13}C NMR(100 MHz, $CDCl_3$): $\delta=141.4$ (C5), 139.0 138.9, 138.8, 138.7, 138.2, 138.1, 138.0 (7 $C_{arom,quat}$), 128.3–127.2 (35 C_{arom}), 111.7 (C6), 104.4 (C2′), 83.7 (C3′), 82.5, 82.2 (C3, C4), 81.7 (C2), 81.5 (C4′), 78.1 (C5′), 74.8 (CH_2Ph), 73.2 (CH_2Ph), 73.1 (CH_2Ph), 73.0 (CH_2Ph), 72.7 (CH_2Ph), 72.6 (C6′), 72.4 (CH_2Ph), 71.7 (CH_2Ph), 70.2 (C1′), 68.2 (C1), 35.6 ppm (C5a); HRMS (CI, NH_3): calcd for $C_{62}H_{68}NO_9$: 970.4894 $[M+NH_4]^+$; found: 970.4905.

14: Olefin **13** (65 mg, 0.068 mmol) was dissolved in THF (4 mL), and BH_3·THF (1.0 M, 0.27 mL) was added. The reaction mixture was stirred at room temperature under argon. When TLC showed the absence of starting material, the solution was cooled to 0°C, and EtOH (0.45 mL), aqueous NaOH (10%, 0.15 mL), and H_2O_2 (0.17 mL) were added successively at room temperature. After 30 min, the reaction solution was diluted with ice-cold H_2O, and the product was extracted with dichloromethane. The organic layers were combined, dried, and concentrated. The crude residue was submitted to flash-column chromatography to afford 1′,3′,4′,6′-tetra-*O*-benzyl-2′-*O*-[(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-tri-*O*-benzyl-5-hydroxymethyl-1,2,3,4-tetrahydroxy-cyclohexyl] -β-D-fructofuranoside (**14**) as a colorless oil (54 mg, 0.056 mmol) in 82% yield. $[\alpha]_D^{20}=+16$ ($C=0.9$ $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$): $\delta=7.36$–7.26 (m, 35 H_{arom}), 4.83 (d, $J=11.9$ Hz, 1H; CHPh), 4.81 (d, $J=11.8$ Hz, 1H; CHPh), 4.70 (d, $J=11.7$ Hz, 1H; CHPh),4.69 (d, $J=11.7$ Hz, 1H; CHPh), 4.65 (d, $J=11.8$ Hz, 1H; CHPh), 4.58 (d, $J=11.7$ Hz, 1H; CHPh), 4.57 (d, $J=11.9$ Hz, 1H; CHPh), 4.54–4.37 (m, 7H; 7×CHPh), 4.44–4.41 (m, 1H; 1-H), 4.41 (d, $J_{3',4'}=7.4$ Hz, 1H; 3′-H), 4.15 (t, $J_{4',3'}=7.8$ Hz, $J_{4',5'}=7.8$ Hz, 1H; 4′-H), 4.02 (ddd, $J_{5',6'(a)}=3.0$ Hz, $J_{5',6'(b)}=5.2$ Hz, $J_{5',4'}=8.3$ Hz,1H; 5′-H), 3.90 (t, $J_{3,2}=6.7$ Hz, $J_{3,4}=6.7$ Hz, 1H; 3-H), 3.76 (br s, 2H; 2×6-H), 3.68 (dd, $J_{6'(b),5'}=3.0$ Hz, $J_{6'(a),6'(b)}=10.7$ Hz, 1H; 6′(a)-H), 3.66 (d, $J=10.6$ Hz,1H; 1′-H), 3.60–3.57 (m, 3H; 2-H, 4-H, 6′(b)-H), 3.57 (d, $J=10.6$ Hz, 1H; 1×1′-H), 2.18 (m, 2H; 5-H, 1×5a-H), 1.40–1.30 ppm (m, 1H; 1×5a-H); ^{13}C NMR(100 MHz, $CDCl_3$): $\delta=128.3$–127.2 (35 C_{arom}), 83.9 (C3′), 78.2 (C5′), 73.4 (CH_2Ph), 73.3 (CH_2Ph), 73.2 (CH_2Ph), 72.6 (CH_2Ph), 72.4 (CH_2Ph), 72.3 (C1′), 72.0 (CH_2Ph), 70.0 (C6′), 63.5 (C6), 38.6 ppm (C5); HRMS (CI, NH_3): calcd for $C_{62}H_{70}NO_{10}$: 988.5000 $[M+NH_4]^+$; found: 988.5010.

15: DMSO (15 μL, 0.22 mmol) was diluted in dichloromethane (2.5 mL) at room temperature under argon and cooled to −78°C. $(COCl)_2$ (9 μL, 0.11 mmol) was added at −78°C under argon. After 10 min a solution of alcohol **14** (52 mg, 0.054 mmol) in dichloromethane (2.5 mL) was added at −78°C. The reaction mixture was stirred at this temperature for 1 h, and Et_3N (47 μL) was then added. After 1.5 h, the reaction solution was washed with H_2O and the organic layer was dried with $MgSO_4$ and concentrated. The residue was submitted to flash-column chromatography (cyclohexane/ethyl acetate gradient). The transient aldehyde was obtained as a colourless oil (45 mg, 0.046 mmol) in 87% yield. The resulting axial aldehyde (39 mg, 0.040 mmol) was heated in MeOH/pyr (6 mL/3 mL) at 50°C for 15 h, and the reaction solution was then concentrated and dried. The residue was submitted to flash-column chromatography. Part of the starting aldehyde was recovered (9 mg), and the desired equatorial aldehyde was obtained as a colourless oil (27 mg, 0.028 mmol) in 70% yield. The equatorial aldehyde (26 mg, 0.027 mmol) was dissolved in THF/H_2O (4 mL/1 mL) and cooled to 0°C. A solution of $NaBH_4$ (20 mg/20 mL, 1.0 mL, 0.026 mmol) in H_2O (1 mL) was added dropwise at 0°C. When analytical TLC showed the absence of starting material the product was extracted with dichloromethane from the diluted reaction solution in H_2O. The organic layers were combined, dried with $MgSO_4$,

and concentrated. The residue was purified through a silica-gel column with cyclohexane/ethyl acetate eluant to give 1′,3′,4′,6′-tetra-*O*-benzyl-2′-*O*-[(1*S*,2*S*,3*S*,4*R*,5*R*)-2,3,4-tri-*O*-benzyl-5-hydroxymethyl-1,2,3,4-tetrahydroxycyclohexyl]-β-D-fructofuranoside (**15**) as a colorless oil (23 mg, 0.024 mmol) in 88% yield. $[\alpha]_D^{20} = +37$ ($c = 0.4$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$–7.27 (m, 35 H_{arom}), 4.97 (d, $J = 11.0$ Hz, 1H; CHPh), 4.86 (d, $J = 10.9$ Hz, 1H; CHPh), 4.84 (d, $J = 11.8$ Hz, 1H; CHPh),4.76 (d, $J = 11.4$ Hz, 1H; CHPh), 4.67 (d, $J = 10.8$ Hz, 1H; CHPh), 4.65 (d, $J = 11.0$ Hz, 1H; CHPh), 4.62–4.48 (m, 7H; 7×CHPh), 4.61–4.57 (m, 1H; 1-H), 4.43 (d, $J_{3',4'} = 7.2$ Hz, 1H; 3′-H), 4.43 (d, $J = 11.4$ Hz, 1H; CHPh), 4.17 (t, $J_{4',3'} = 7.2$ Hz, $J_{4',5'} = 7.6$ Hz, 1H; 4′-H), 4.06 (ddd, $J_{5',6'(a)} = 3.0$ Hz, $J_{5',6'(b)} = 5.4$ Hz, $J_{5',4'} = 7.8$ Hz,1H; 5′-H), 3.98 (t, $J_{3,2} = 9.3$ Hz, $J_{3,4} = 9.3$ Hz, 1H; 3-H), 3.75–3.67 (m, 3H; 2×1′-H, 6′(a)-H), 3.61 (dd, $J_{6'(b),5'} = 5.4$ Hz, $J_{6'(b),6'(a)} = 10.6$ Hz, 1H; 6′(b)-H), 3.44 (ddt, 2H; 2×6-H), 3.35 (dd, $J_{4,3} = 9.2$ Hz, $J_{4,5} = 10.5$ Hz, 1H; 4-H), 2.01 (dd, $J_{2,3} = 9.6$ Hz, $J_{2,1} = 2.8$ Hz, 1H; 2-H), 2.26–2.14 (m, 1H; 5-H), 2.11 (dt, $J_{5a(e),\ 1} = 3.7$ Hz, $J_{5a(e),5} = 3.7$ Hz, $J_{5a(e),5a(a)} = 13.9$ Hz, 1H; 5a(e)-H), 1.03 ppm (t, $J = 13.0$ Hz, 1H; 5a(a)-H); ^{13}C NMR(100 MHz, $CDCl_3$): $\delta = 139.0$ 138.9, 138.7, 138.5, 138.2, 138.0, 137.9 (7 $C_{arom,quat}$), 128.4–127.3 (35 C_{arom}), 104.5 (C2′), 83.7 (C3), 83.6 (C3′), 83.0 (C2), 82.6 (C4), 81.7 (C4′), 78.5(C5′), 75.4 (CH_2Ph), 74.9 (CH_2Ph), 73.3 (CH_2Ph), 73.2 (CH_2Ph), 72.4 (CH_2Ph), 72.2 (C1′), 72.0 (CH_2Ph), 71.9 (CH_2Ph), 70.0 (C6), 66.8 (C1), 64.6 (C6), 38.4 (C5), 30.0 ppm (C5a); HRMS (CI, NH_3): calcd for $C_{62}H_{66}NaO_{10}$: 993.4554 [M+Na]$^+$; found: 993.4536.

3: Pd/C (10%) was added to a solution of **15** (9 mg, 9.3 μmol) in MeOH (2 mL). The reaction mixture was stirred under hydrogen at room temperature. When analytical TLC showed the absence of starting material, the reaction solution was filtered through a celite plug. The filtrate was concentrated, and the residue was purified through a sephadex column to afford pure hemicarbasucrose (**3**) as a white foam (2.5 mg, 7.4 μmol, 79%). $[\alpha]_D^{20} = +21.5$ ($c = 0.2$, MeOH); ^{1}H NMR (400 MHz, CD_3OD): $\delta =$ 4.32–4.28 (m, 1H), 4.16 (d, $J = 8.5$ Hz, 1H; 3′-H), 4.03 (t, $J = 8.3$ Hz, 1H), 3.86–3.80 (m, 2H), 3.77–3.63 (m, 6H), 3.43 (dd, $J = 3.2$ Hz, $J = 10.0$ Hz, 1H), 3.29 (dd, $J = 9.1$ Hz, $J = 10.7$ Hz, 1H), 2.09 (dt, $J = 3.8$ Hz, $J =$ 14.4 Hz, 1H; 5a(a)-H), 2.01–1.90 (m, 1H; 5a(e)-H), 1.36 ppm (ddd, 1H; 5-H) ; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 103.7$ (C2′), 80.9, 78.1, 75.03, 74.99, 73.7, 73.4, 70.8, 62.8, 62.6, 61.3, 38.7 (C5), 30.5 ppm (C5a); MALDI-TOF: m/z: 363.11 [M+Na]$^+$.

Molecular Mechanics Calculations

The relaxed (ϕ,ψ) energy maps for compound **3** were generated by systematic rotations around the glycoside and aglyconic bond by using a grid step of 18°, optimization of the geometry at every ϕ,ψ point by using conjugate gradients iterations until the rms derivative was smaller than 0.05 kJ mol^{-1} Å^{-1}, and the energies were calculated by using the TRIPOS force field ($\varepsilon = 80$). The *gg* and *gt* orientations of both Glc and Fru units were taken into account.[18,25] Thus, eight starting structures were considered, and in total 3200 conformers were calculated. From these relaxed energy maps, adiabatic surfaces were built by choosing the lowest-energy structure for a given ϕ,ψ point. The probability distribution was calculated for each point according to a Boltzmann function at 298 K. The local minima were then further refined by using the MM3* force field integrated in the MAESTRO program and further employed for analysis.

J and NOE Calculations

The two vicinal coupling constants of the fructofuranose ring were calculated for each conformational family by using the Karplus–Altona equation.[20] Ensemble average values were calculated from the distribution according to: $J = \Sigma P_{\phi\psi} J_{i\phi\psi}$. Interproton average distances were calculated by using the following expression: $\langle r^{-6} \rangle_{kl} = \Sigma P_{\phi\psi} r^{-6}_{kl(\phi\psi)}$. The NOE intensities were determined according to the complete relaxation matrix, as described previously, by using the NOEPROM program. Isotropic motion and external relaxation of 0.1 s^{-1} were assumed. A correlation time of 70 ps was used to obtain the best matching between experimental and calculated NOE interactions for the intraresidue proton pairs 1-H_{Glc}–2-H_{Glc} and 2-H_{Glc}–4-H_{Glc}.

NMR Spectroscopy

NMR experiments[19] were recorded on a Bruker Avance 500 instrument at 25 °C. A concentration of ≈2 mM of **3** was used. Chemical shifts were referenced to external 2,2-dimethyl-1,2-silapentane-5-sulfonate sodium salt (DSS) in D_2O. 1D spectra were acquired with 32 K data points, which were zero-filled to 64 K data points prior to Fourier transformation. Absolute value COSY, phase-sensitive HSQC spectra, NOESY (mixing times of 100, 200, 400, 600, 800, and 1000 ms), and ROESY (mixing times of 300 and 500 ms) were acquired by standard techniques. Acquisition data matrices were defined by 2 K × 256 points, multiplied by appropriate window functions and zero-filled to 2 K × 512 matrices prior to Fourier transformation. Baseline correction was applied in both dimensions. Spectra were processed by using the Bruker XWIN-NMR program on a PC Linux computer.

Acknowledgements

MS would like to thank Dr. Guillaume Prestat and Dr. Jean-Philippe Goddard for an excellent editorial suggestion.

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Received: September 5, 2007
Published online: November 21, 2007

