reflections 982 assumed as observed with $I > 2\sigma(I)$. Refinement of 134 parameters with anisotropic thermal parameters for non-hydrogen atoms gave $R = 0.037$, $wR = 0.103$ (on F^2), and $S = 0.913$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication no. 100475. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@chemcrys.cam.ac.uk).

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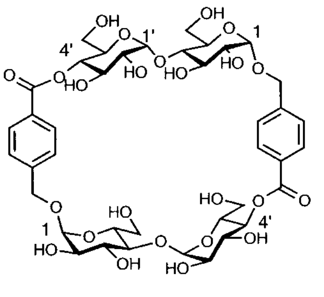
Carbohydrate – Arene Interactions Direct Conformational Equilibrium of a Flexible Glycophane in Water[**]

Juan Carlos Morales and Soledad Penadés*

The confluence of many weak intermolecular forces is crucial for carbohydrate recognition processes. Knowledge about these forces derives mainly from the crystal structure analyses and NMR spectroscopy of complexes between oligosaccharides and lectins, antibodies, or periplasmic binding proteins.[1] These studies show that beyond the expected intermolecular forces always found in biological associations (hydrogen bonding, van der Waals forces, hydrophobic effects), stacking interactions between aromatic side chains and saccharides play an important role in stabilizing the complexes.[1,2] Besides the interactions at atomic level, change in oligosaccharide conformation on binding[3] and desolvation effects[4] are essential in determining the structural and energetic properties associated with carbohydrate recognition. Oligosaccharides observed in solution exist as an ensemble average of all possible conformations, and proteins may select oligosaccharide conformations that pre-exist in solution, or induce changes in the oligosaccharide upon binding. This selection has consequences in the thermodynamics of binding;[5] therefore it is important to assess which factors determine the conformation to be bound. However, the inherent oligosaccharide flexibility and the lack of strong intermolecular interactions places extreme demands on these studies.[3]

Model systems can also help to understand all these molecular aspects of carbohydrate recognition. In previous work we have designed and synthesized a new type of model receptor (glycophanes) to study carbohydrate binding in water.[6] Glycophanes consist of disaccharides and aromatic segments, and may be considered as cyclodextrin – cyclophane hybrids. With these receptors we have shown, for the first time, the existence of lipophilic interactions in water between carbohydrate surfaces.[7] We have now prepared two new glycophanes **1** and **2**, made up from maltose (4-*O*-(α-D-glucopyranosyl)-D-glucopyranose), the constituent disaccharide of cyclodextrins, and (4-hydroxymethyl)benzoic acid as aromatic segment. The linkage of the aromatic ring to either position 4′ or 6′ of the maltose molecule confers different flexibility on the receptors and different topologies than those present in cyclodextrins. This will allow us to compare the influence of the maltose presentation on the interactions of these receptors with a series of common ligands. In this paper we present evidence that carbohydrate – arene stacking is more important that hydrogen-bonding interactions for the dynamic behavior of the more flexible glycophane **2**. This glycophane adopts a folded conformation in water as a result of intramolecular interactions between a glucose moiety and a phenyl ring. This interaction induces a change in the maltose conformer distribution that is not observed in the more rigid glycophane **1**. Water is necessary for this hydrophobic collapse, which is not observed in methanol or dimethylsulfoxide. The conformational properties of **1** and **2** were assessed by NMR spectroscopy, as well as molecular mechanics and dynamics simulations. Model systems for binding carbohydrate in water based on sugar – arene interactions have been previously reported.[8]

Glycophane **1** was synthesized from maltose, and glycophane **2** was obtained in almost quantitative yield by spontaneous transacylation of glycophane **1** in water.[9] Significant upfield shifts (up to $\Delta\delta = 0.4$) were observed for the H1, H2, and H4 protons of **2** relative to the corresponding protons of the reference compounds **1** and **3**, indicating close proximity of the aromatic rings to the β face of the glucose



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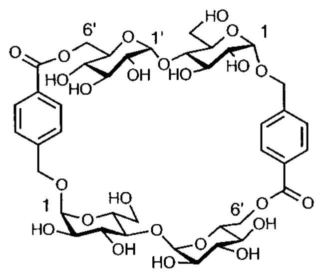

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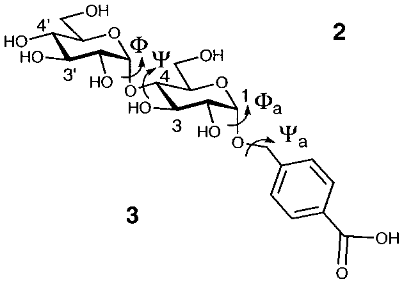

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Table 1. Significant ^{1}H chemical shifts (δ) for **1**, **2**, and **3** at 30°C in different solvents.

	1			**2**			**3**		
Proton	D_2O	MeOH	DMSO	D_2O	MeOH	DMSO	D_2O	MeOH	DMSO
H1	5.08	5.24	4.87	4.67	5.14	4.85	5.04	5.09	4.77
H2	3.63	>3.7	>3.2	3.21	>3.6	>3.2	3.61	3.67	>3.2
H4	3.62	>3.7	>3.2	3.45	>3.6	>3.2	3.67	3.75	>3.2

units. Based on space-filling models, this proximity should force glycophane **2** to adopt a folded conformation that places the maltose molecule in a conformation rather different from that found in the solid state for maltose and cyclodextrins.[10] To test whether the driving force for this conformational change is interaction between sugar and arene units, additional experiments were carried out. Comparison of the ^{1}H NMR spectra of **1**, **2**, and **3** in [D$_4$]methanol, a protic solvent, shows similar chemical shifts for the H1, H2, and H4 protons of the reducing glucose unit in the three compounds. The same result is obtained in [D$_6$]dimethylsulfoxide ([D$_6$]DMSO), where hydrophobic interactions are not favored either (Table 1). In contrast, upon addition of [D$_4$]methanol to a solution of **2** in D_2O, the H1, H2, and H4 protons of the reducing glucose show large deshielding (up to $\Delta\delta = 0.70$), whereas for the rest of the protons regular downfield shifts of about $\Delta\delta = 0.20-0.33$ are observed, indicating an equilibrium between different conformations. Temperature also affects this equilibrium (Figure 1). Decreasing the temperature shifts the equilibrium toward the conformation with sugar–arene interactions, as indicated by the upfield shift of H1, H2, and H4 protons. As the temperature increases, the other conformers are favored. In the case of glycophane **1** or compound **3**, no significant changes in chemical shifts are observed on changing the temperature. Also, neither for **1** nor for **2** or **3** are significant changes in chemical shifts in [D$_4$]methanol solution observed over a broad range of temperatures (−50 to 55°C).

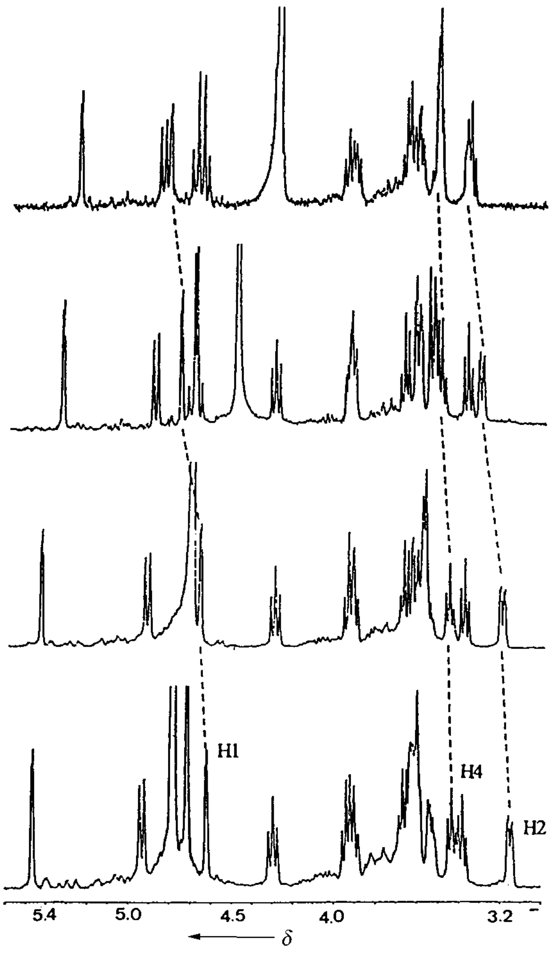

Figure 1. ^{1}H NMR spectra (500 MHz) of glycophane **2** in D_2O at different temperatures.

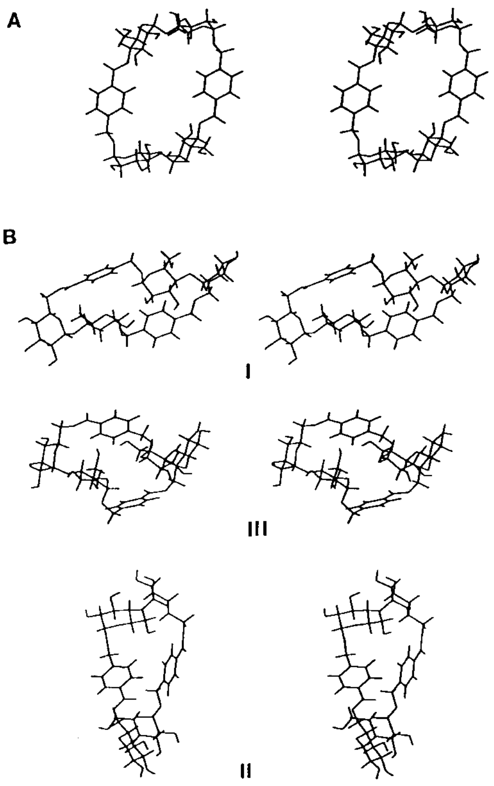

Figure 2. Stereoviews of the global minimun of glycophane **1** (A) and three conformations of glycophane **2** (B) obtained by the Monte Carlo search.

Molecular mechanics simulations by a Monte Carlo (MC) approach[11] show for glycophane **1** only one family of conformers (Figure 2A), in which the glucose moieties adopt the expected $^{4}C_1$ chair conformation and the interglycosidic angles Φ (H1′-C1′-O1′-C4) and ψ (C1′-O1′-C4-H4) are −4 and −30°, respectively. This minimum is similar to the minimum B (−3 and −30°, respectively) found for maltose in solution.[12b] The glycosidic angle Φ_a(H1-C1-O1-CH$_2$) is 68°, in agreement with the *exo*-anomeric effect, and the torsion angle ψ_a(C1-O1-CH$_2$-C$_{Ph}$) is −170°, which allows the receptor to form the cavity. All conformers possess a hydrogen bond between 2′-OH and 3-OH. The structure of this minimum resembles that of cyclodextrins. For glycophane **2**, three

Table 2. Experimental and calculated ROESY data (%) for **1** and **2** in D_2O at 500 MHz at different temperatures.

	1			**2**				
	30 °C T-ROESY [a]	30 °C ROESY	Calcd ROESY	30 °C T-ROESY	25 °C T-ROESY	8 °C T-ROESY	Calcd ROESY [b]	Calcd ROESY [c]
H1′/H2′	4.6 (1.0)[d]	8.5 (1.0)	8.0 (1.0)	4.4 (1.0)	7.0 (1.0)	7.8 (1.0)	9.6 (1.0)	9.21 (1.0)
H1′/H3	< 1.0 (0.1)	< 1.0 (< 0.1)	1.1 (0.12)	1.4 (0.32)	1.2 (0.17)	1.2 (0.15)	3.3 (0.34)	2.92 (0.31)
H1′/H4	7.5 (1.63)	10.7 (1.25)	14.3 (1.8)	7.4 (1.68)	7.0 (1.0)	5.3 (0.68)	2.2 (0.23)	6.94 (0.75)

[a] T-ROESY experiments (350 ms mixing time) were carried out to minimize Hartmann–Hahn effects. T. L. Hwang, A. J. Shaka, *J. Am. Chem. Soc.* **1992**, *114*, 3157–3158. [b] All conformers were taken into account. [c] ROEs calculated for conformers **II** and **III**. [d] The number in brackets is the ratio between ROEs and H1′/H2′ ROE.

different families of conformers were found in the MC search. The global minimum (**I**, Figure 2B) shows a folded structure with a double sugar–arene stacking interaction. The interglycosidic angles Φ/Ψ are approximately $-55°/-60°$, the angle ψ deviating slightly from the minimum A (Φ/Ψ $-60°/-40°$) found for maltose and maltose derivatives in solution.[12] The Φ_a angle is 69°; however, the angle Ψ_a adopts a value of 70° to allow stacking between the aromatic ring and the β face of the reducing glucose (glycophane **1**: $-170°$). In this conformation a hydrogen bond between 2′-OH and 3-OH is not possible. The second family of conformers (**II**, Figure 2B) does not show sugar–arene stacking interactions. The receptor is closed by π–π face-to-edge interactions between the aromatic moieties. The interglycosidic angles Φ/Ψ are 11°/15°, similar to those found for maltose in the solid state.[10] This conformer is 22 kJ mol^{-1} more energetic than the folded family of conformers. A third family (**III**, Figure 2B) of conformers, with a similar energy to the nonfolded conformer was also obtained. All conformers are asymmetric and show sugar–arene stacking in only one of the reducing glucoses. These conformers are intermediates in the equilibrium between conformers **I** and **II** (Figure 2B). Molecular dynamics simulations[11] confirm the stability of the global minima found for **1** and **2** in the MC search. The starting conformations do not change during the 500 ps MD simulations at 300 K. The conformers **II** and **III** of **2** were also stable at this temperature. However, at higher temperatures in the simulation ($T = 500$ K) a transition of the glycosidic linkage conformation, after 300 ps in a maltose unit and after 400 ps in the other one, transforms these conformers into the global minimum **I**, which was stable for the rest of the MD run.

The existence of the folded conformation in **2** was also proven by comparison of the calculated and experimental rotating frame Overhauser enhancements (ROEs) between H1′/H3 and H1′/H4 protons of the maltose moiety. The distance between these interresidue protons reflects the glycosidic linkage conformation. The ROEs have been obtained at different temperature and are referred to the H1′/H2′ intraresidue ROE. The calculated ROEs for **1** and **2** were obtained from the MC calculation employing a quantitative approach with a full relaxation matrix.[13] For glycophane **1** a good agreement between experimental and calculated ROEs was found (Table 2). The calculated ROESY spectrum for **2** corresponds to a high population of the folded conformation; therefore a weak experimental H1′/H4 ROE should be expected. In contrast, the experimental ROEs observed for **2** at 30°C are similar to those for **1**. However, as the temperature decreases, the ratio between H2′ and H4 ROEs decreases, and at 8°C this ratio is smaller than 1 (Table 2), indicating an increase in the H1′–H4 distance, as is to be expected for a greater population of the folded conformation in glycophane **2**. Additionally, the observation of exclusive NOEs between the aromatic protons and the H2, H4, and H6 protons of the reducing glucose moiety at 5°C (Figure 3) definitively confirms the existence of the folded conformation in water as a result of sugar–arene intramolecular interactions.

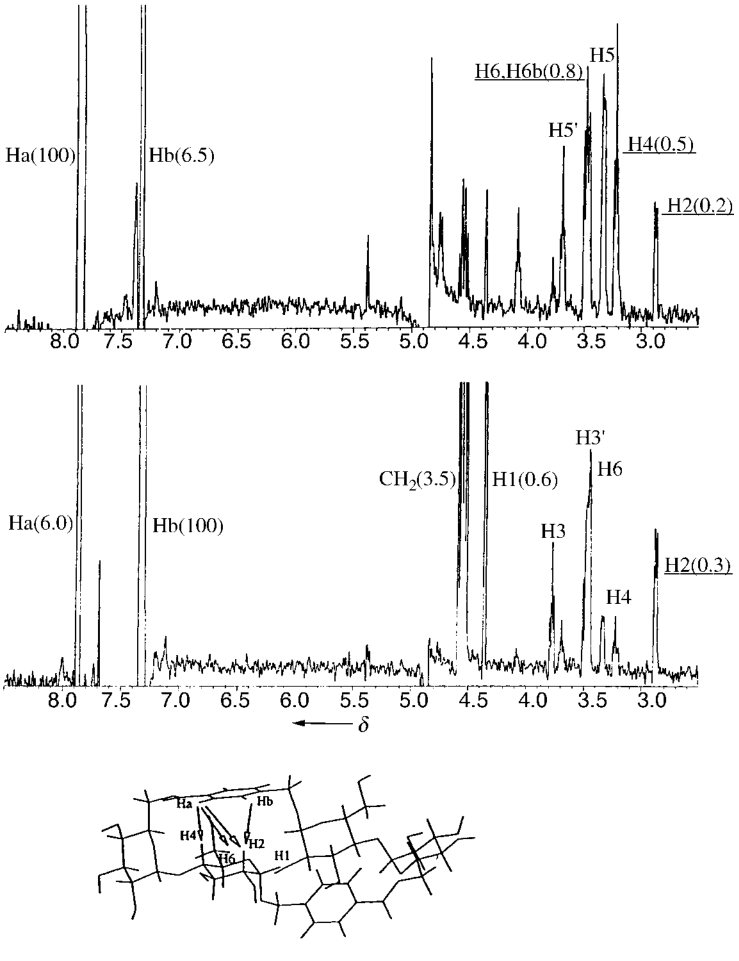

Figure 3. Cross-sections through the signals of the aromatic protons H_a (top spectrum) and H_b (bottom spectrum) from the 2D NOESY spectra (Brucker 600 MHz, 300 ms, 5°C, D_2O) of **2** showing the exclusive NOEs Ha/H2, Ha/H4 and the Hb/H6 of the folded conformation. Below the spectra is the folded conformation of **2** in which the arrows depict the expected NOEs.

The results presented here show that the maltose unit in glycophane **2** is rather flexible and that temperature and solvent, in conjunction with the presence of defined sugar–arene interactions influence its conformational equilibrium. Cyclodextrins together with glycophanes **1** and **2** are good examples of the existence of different conformers of the same disaccharide. It follows that the maltose units in these three compounds should also show different conformational entropies. This may have consequences in the thermodynamics of binding[5] of these maltose-containing compounds to a receptor, for example, the maltose-binding protein.

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$[\mathrm{M^{II}(tcne)_2}]\cdot x\,\mathrm{CH_2Cl_2}$ (M = Mn, Fe, Co, Ni) Molecule-Based Magnets with T_c Values Above 100 K and Coercive Fields up to 6500 Oe**

Jie Zhang, Jürgen Ensling, Vadim Ksenofontov, Philipp Gütlich, Arthur J. Epstein, and Joel S. Miller*

Molecule-based magnets possessing spins on organic radicals is a growing area of increasing contemporary interdisciplinary research.[1, 2] Two classes of organic radicals have been particularly effective in stabilizing molecule-based magnets. These are the strong electron acceptors, such as tetracyanoethylene (TCNE), and dinitroxides. Several classes[2] of magnets are based on these radicals, namely, metallocene and manganoporphyrin electron transfer salts of TCNE (e.g., $[\mathrm{FeCp^*_2}]^{\bullet +}[\mathrm{TCNE}]^{\bullet -}$ (Cp* = pentamethylcyclopentadienyl) and $[\mathrm{Mn(tpp)}]^{+}[\mathrm{TCNE}]^{\bullet -}$ ($\mathrm{H_2TPP}$ = *meso*-tetraphenylporphyrin)), and $[\mathrm{Mn^{II}(hfac)_2}]$ (hfac = hexafluoroacetylacetonate) adducts of dinitroxides (e.g., $\mathrm{(Me_2C_2)_2(NO)_2CR}$, R = Me, Et, *i*Pr, etc.), $[\mathrm{V(tcne)}_x]\cdot y\,$solvent,[3, 4] as well as a few dinitroxides. Unlike the other classes of molecule-based magnets, there is only one example of a room temperature magnet $[\mathrm{V(tcne)}_x]\cdot y\,$solvent, and due to its high ordering temperatures ($T_c \sim 400$ K) and unknown structure, more examples of this class of materials are necessary to understand the chemistry and physics. Herein, we report the preparation and preliminary magnetic properties of $[\mathrm{M(tcne)_2}]\cdot x\,\mathrm{CH_2Cl_2}$ (M = Fe (**1**), Mn (**2**), Co (**3**), Ni (**4**)) magnets.[5]

$[\mathrm{Fe(tcne)_2}]\cdot x\,\mathrm{CH_2Cl_2}$ (**1**) is prepared from the reaction of iron(II) iodide,[3] which was used in the form of the MeCN solvate, and TCNE. Both reactants were dissolved in $\mathrm{CH_2Cl_2}$, and upon mixing the product rapidly precipitated. After washing with $\mathrm{CH_2Cl_2}$ the material was dried in vacuo at 30 °C overnight.[6] The IR spectrum of compound **1** exhibits three sharp ν_{CN} bands at 2221 (m), 2277 (s), and 2174 (s) cm^{-1} (Table 1); the width of these absorptions may depend on the precursors and other conditions.[6] These absorptions are consistent with those for the coordinated radical anion $[\mathrm{TCNE}]^{\bullet -}$. They are similar to the ν_{CN} bands for $[\mathrm{V(tcne)}_x]\cdot y\,\mathrm{CH_2Cl_2}$, but are sharper and occur at higher energies. In contrast, however, to the amorphous $[\mathrm{V(tcne)}_x]\cdot y\,\mathrm{CH_2Cl_2}$, **1** is partly crystalline according to the X-ray powder pattern (Figure 1). Indexing of this pattern has been thwarted as the

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