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Crown Ethers as Building Blocks for Carbohydrate Receptors

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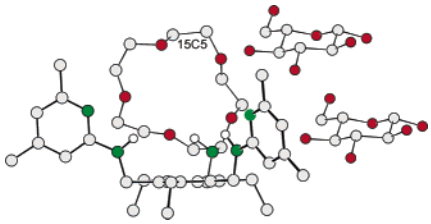
ABSTRACT



Acyclic receptors containing neutral hydrogen bonding sites, such as amino-pyridine groups and a crown unit, perform effective recognition of neutral sugar molecules through multiple interactions. Receptor 1 has been shown to be a particularly effective and highly selective receptor for β-glucopyranoside.

Crown ethers are a particularly widely used class of receptor molecules in supramolecular chemistry.[1] In the area of biomimetic sugar recognition,[2] however, the crown-based receptors have received less study. The crown units have mostly been incorporated into different boronic acid-based receptor systems,[3,5b] using covalent interactions for sugar binding. The design of both selective and effective carbohydrate receptors operating through noncovalent interactions still represents a significant challenge.[4,5]

Our previous studies established that acyclic receptors containing neutral hydrogen bonding sites, such as 2-aminopyridine, -pyrimidine, or -naphthyridine units, perform effective recognition of carbohydrates through multiple interactions.[4c−e,6] Aminopyridine receptors based on a 2,4,6-trimethyl- or 2,4,6-triethylbenzene frame show high β versus α anomer selectivity in the recognition of glucopyranosides in organic media.[4d,6c] Remarkable changes in the binding

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affinity and selectivity of pyridine-based receptors are observed when the degree of steric hindrance at the pyridine nitrogen atom decreases. *N*,*N*′,*N*″-Tris(4-methylpyridin-2-yl)benzene-1,3,5-tricarbonamide, for example, shows both an enhanced affinity and an inverse selectivity since it binds the α-glucopyranoside better than the *β*-anomer.[4e]

The development of effective receptors required frameworks able to fully encapsulate a carbohydrate molecule, surrounding it with various recognition units capable of engaging in multiple interactions.[2] Molecular modeling indicated that acyclic receptors containing both heterocyclic recognition groups and crown units should be able to form complexes, in which the sugar substrate is bound in the receptor cleft and almost completely encapsulated (see below, Figure 2). In this paper we describe the synthesis and binding

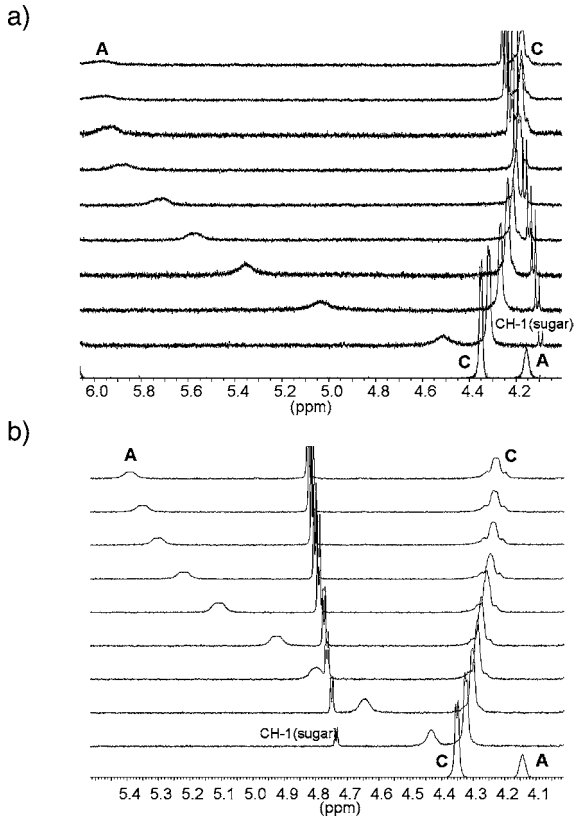

Figure 1. (a) Partial ^{1}H NMR spectra ($CDCl_3$, 25 °C) of receptor **1** after addition of (from bottom to top) 0.00−3.47 equiv of **3a** ([**1**] = 0.87 mmol). (b) Partial ^{1}H NMR spectra of receptor **1** after addition of 0.00−6.22 equiv of **4a** ([**1**] = 0.85 mmol).

properties of two representatives, **1** and **2**, of the new series of sugar-binding receptors (the two receptors were prepared

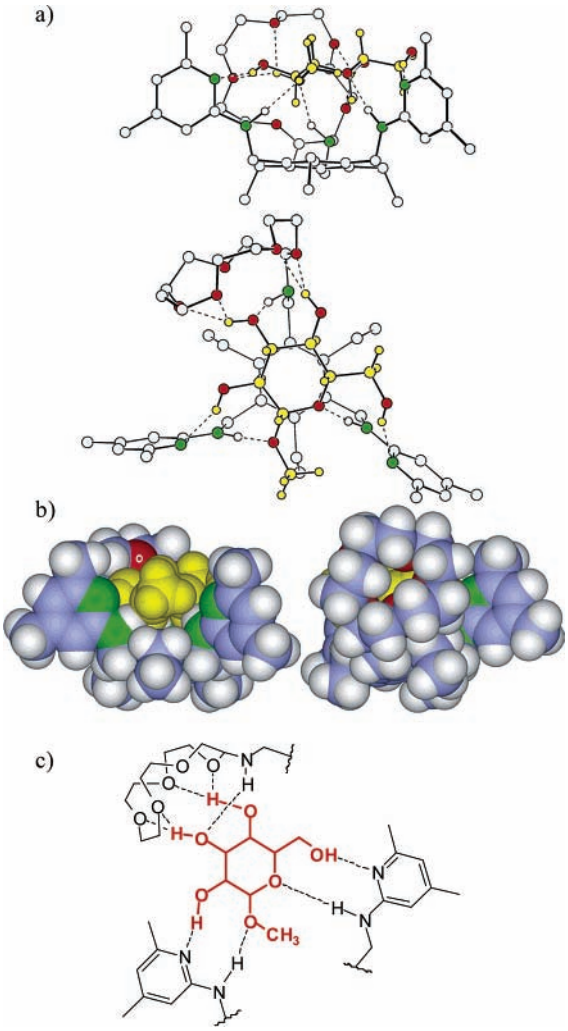

Figure 2. (a) Energy-minimized structure of the 1:1 complex formed between receptor **1** and methyl *β*-D-glucopyranoside (**3b**) (MacroModel V.6.5, Amber* force field, Monte Carlo conformational searches, 50 000 steps): (a) Side and top views (CH hydrogens of the receptor are omitted for clarity)—sugar C and H, yellow; O, red; N, green; receptor C, gray; (b) Space-filling representation, two different side views (the sugar molecule is highlighted in yellow). (c) Schematic representation of the hydrogen bonds in this complex.

as described in the Supporting Information).[7] To compare their binding properties with the properties of the previously studied receptors, the glucopyranosides **3a**, **3b**, **4a**, and **4b** were selected as substrates for the studies in organic media.

Quiocho has shown that in the crystal structures of protein/sugar complexes, the bound sugar substrates and all of the

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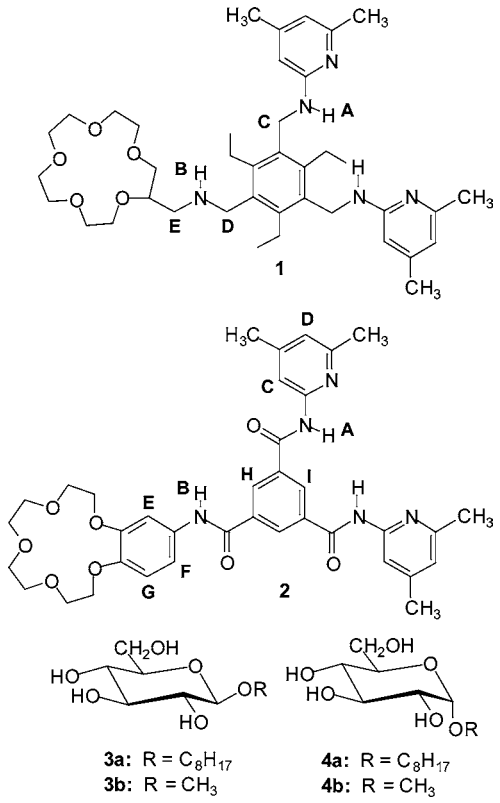
groups directly associated with sugar binding are buried deep in the cleft and are rendered inaccessible to the bulk solvent.[2a] The lower dielectric constant, relative to the bulk solvent, within the cleft is likely to strengthen hydrogen bonds and van der Waals contacts.[2a−c] Thus, studies with synthetic receptors in an aprotic environment provide a base for a deeper understanding of the basic molecular features of sugar recognition, and facilitate the search for effective recognition motifs for carbohydrates.

The interactions of hosts **1** and **2** and glucopyranosides were investigated by ^{1}H NMR binding titrations[8−10] and extraction experiments. The complexation between the two receptors and pyranosides was evidenced by several changes in the NMR spectra. During the titration of **1** with β-glucopyranoside **3a** the signal due to the amine NH (protons A; for labeling, see Formula 1) moved downfield by 1.82 ppm ($\Delta\delta_{max}$; see Figure 1a). Furthermore, the ^{1}H NMR spectra showed changes in the chemical shifts of the CH_3 and CH_2 resonances, as well as the pyridine CH protons of **1**. The signal for the protons C moved upfield by 0.17 ppm with broadening, whereas those for the CH_3 and pyridine CH protons shifted in the range 0.03−0.07 ppm (see the Supporting Information, Figure S1). The signals for the protons D, E, and B were overlapping during the titration. The NH^A, $CH_2{}^C$, CH_3, and pyridine CH signals were monitored for the determination of the binding constants; the typical titration curves are shown in Figure S3.

The spectroscopic changes indicated very strong 1:1 binding followed by weaker association of the second sugar molecule. The best fit of the titration data was obtained with the mixed 1:1 and 1:2 receptor/sugar binding model; this model was further supported by the mole ratio plots.

The binding constants were found to be $K_{a1} = 584\,300$ M^{-1} and $K_{a2} = 13\,800$ M^{-1} (Table 1).[11,12] These results indicate that the receptor **1** exhibits about 10-fold higher affinity for β-glucopyranoside **3a** than the previously described triarmed pyridine-based receptor [1,3,5-tris[(4,6-dimethyl-pyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene; the binding constants for this receptor and sugar **3a** were found to be $K_{a1} = 48\,630$ M^{-1} and $K_{a2} = 1\,310$ M^{-1}, mixed 1:1/1:2 receptor/sugar binding model].[4d]



Molecular modeling studies suggested that all OH groups and the ring oxygen atom of the bound sugar in the complex **1·3b** are involved in the formation of hydrogen bonds (pyr-NH···O-1, pyr-NH···O-5, 2-OH···N-pyr, 6-OH···N-pyr, crown-NH···OH-3, two 3-OH···O-crown, and two 4-OH···O-crown interactions), including cooperative and bidentate hydrogen bonds. The 3- and 4-hydroxy groups of **3b** can participate in three-center bonds[13] with the oxygen atoms of the crown unit, as shown in Figure 2.[14] Interactions of sugar C−H bonds with the central phenyl ring of **1** provide additional stabilization of the complex.

In contrast to the strong binding of **1** with β-glucopyranoside **3a**, the binding of the α-anomer **4a** is relatively weak. After the addition of 6 equiv of **4a** the NH^A of **1** shifted by

Table 1. Association Constants for Receptors **1** and **2** and Glucopyranosides **3a** and **4a**[a]

host−guest complex	K_{a1} [M^{-1}]	K_{a2} [M^{-1}]	$\Delta\delta^d$ [ppm]
1·3a	584 300	13 800[b]	NH^A: 1.82; $CH_2{}^C$: −0.17
1·4a	1 400		NH^A: 1.24; $CH_2{}^C$: −0.13
2·3a	10 950	48 680[c]	NH^A: 0.92
2·4a	7 430	13 740[c]	NH^A: 0.89

[a] In $CDCl_3$ (stored over activated molecular sieves and deacidified with Al_2O_3). Average K_a values from multiple titrations (for each system at least 3 titrations were carried out). The reproducibility of the K_a values was ±10−25%. Error in a single K_a estimation was <10%. [b] 1:2 receptor/pyranoside complex. [c] 2:1 receptor/pyranoside complex. [d] Largest change in chemical shift of the receptor resonances observed during the titration.

(8) The binding constants were determined in chloroform at 25 °C by titration experiments and the titration data were analyzed by nonlinear regression analysis, using the program HOSTEST 5.6 (see ref 9). The stoichiometry of receptor−sugar complexes was determined by mole ratio plots (see ref 10) and by the curve-fitting analysis of the titration data. Dilution experiments show that receptors **1** and **2** do not self-aggregate in the used concentration range.

(9) Wilcox, C. S.; Glagovich, N. M. Program HOSTEST 5.6; University of Pittsburgh: Pittsburgh, PA, 1994. This program is designed to fit data to different binding models, which include both "pure" binding models, taking into consideration the formation of only one type of complex in solution, and "mixed" binding models containing more than one type of complex in solution.

(10) For examples on the use of the mole ratio method, see: (a) Tsukube, H.; Furuta, H.; Odani, A.; Takeda, Y.; Kudo, Y.; Inoue, Y.; Liu, Y.; Sakamoto, H.; Kimura, K. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davis, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, UK, **1996**; Vol. 8, p 425. (b) Liu, M. T. H.; Bonneau, R. *J. Am. Chem. Soc.* **1990**, *112*, 3915−3919.

(11) In a strong binding equilibrium, the ideal data set is difficult to obtain because of the limitation of the NMR spectroscopic sensitivity (see, refs 10a and 12). In the case of **1** such a data set could be obtained at concentrations below 0.9 mmol/L.

(12) For a review discussing the limitations of the NMR method, see: Fielding, L. *Tetrahedron* **2000**, *56*, 6151−6170.

1.24 ppm, without saturation. The signal for the protons C moved upfield by 0.13 ppm (the shifts of the CH_3 and pyridine CH protons are shown in Figure S2). The motions of the NH^A, $CH_2{}^C$, and CH signals (see Figure 1b) were consistent with 1:1 binding (see Figure S3a), providing association constants of 1400 M^{-1}. Thus, **1** shows a β/α anomer selectivity, which is significantly higher than that observed previously.[4d,6c]

Additional evidence for the preferred complexation of the β-anomer was obtained from extraction experiments, where β- and α-methyl-glucopyranoside, **3b** and **4b**, were extracted from the solid state into a $CDCl_3$ solution of receptor **1** (see the Supporting Information, Figure S4).

Receptor **2**, based on the 1,3,5-benzene-tricarbonyl frame, exhibits a similar level of affinity toward α- and β-glucopyranoside (see Table 1). This receptor has the tendency to form 2:1 receptor/glucopyranoside complexes; the addition of only 0.5 equiv of sugar led to practically complete complexation of **2** (see, for example, Figure S6a). The ^1H NMR titrations of **2** with α- and β-glucopyranoside produced similar spectral changes. Addition of glucopyranoside to a $CDCl_3$ solution of **2** led to both a broadening and a downfield shifting of the NH protons of **2**. The complexation induced shifts observed for the amide NH of **2**, protons A and B, amount to 0.92 and 1.30 ppm, respectively. The signal for the protons of the central phenyl ring, H and I, moved upfield by 0.34 ppm, whereas those for the protons E and F shifted downfield by 0.30 and 0.25 ppm, respectively. The pyridine CH's, protons D, moved upfield by 0.25 ppm with strong broadening, as shown in Figure S5.

The signals NH^A, H/I, and E were monitored for the determination of the binding constants (the NH^B resonances strongly broaden during the titration and become distinct near saturation; these signals could not be monitored for the determination of the binding constants); the typical titration curve is shown in Figure S6a. The best fit of the titration data was obtained with the mixed 1:1 and 2:1 receptor/sugar binding model; the formation of 2:1 receptor/sugar complexes was further supported by the mole ratio plots (see, for example, Figure S6b). The binding constants of β-glucopyranoside **3a** and receptor **2** were found to be 10 950 (K_{a1}) and 48 680 M^{-1} (K_{a2}), those for α-glucopyranoside **4a** and **2** amount to 10 430 (K_{a1}) and 13 740 M^{-1} (K_{a2}) (see Table 1). Thus, the affinity of **2** toward glucopyranosides is much higher than that of the previously described triarmed amidopyridine receptor [*N*,*N*′,*N*″-tris(6-methylpyridin-2-yl)benzene-1,3,5-tricarbonamide].[6a]

Modeling studies indicated that in the 2:1 receptor/sugar complexes the two receptor molecules almost completely enclose the sugar, leading to involvement of all sugar hydroxyl groups in interactions with the receptor molecules. Typical hydrogen-bonding motifs found by molecular modeling are shown in Figure 3.

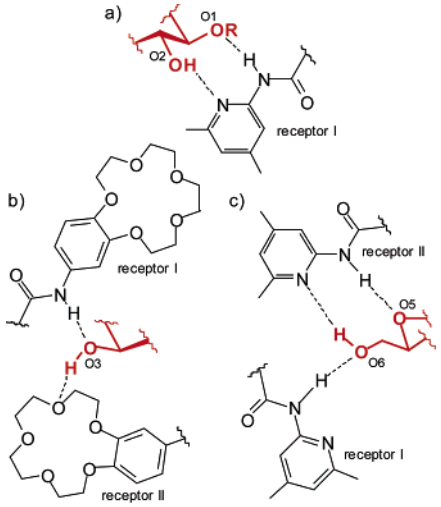


Figure 3. Examples of hydrogen-bonding motifs found by molecular modeling studies in the 2:1 complex between receptor **2** and sugar **3a** (MacroModel V.6.5, Amber* force field, Monte Carlo conformational searches, 50 000 steps).

The results obtained with the receptors **1** and **2** show that acyclic receptors containing both amino-/amidopyridine binding subunits and a crown unit perform effective recognition of neutral carbohydrates through multiple interactions. The comparison of the binding properties of the receptors **1** and **2** with those of the previously described triarmed pyridine-based analogues shows that the incorporation of a suitable crown unit into the acyclic receptor structure significantly affects the binding affinity and selectivity of the new receptors. The recognition units in receptor **1**, based on the 2,4,6-triethylbenzene-frame, are particularly favorably positioned for the binding of β-glucopyranoside. This receptor displays remarkable β vs α anomer selectivity, which is significantly higher than observed previously. Such acyclic receptors are effective, simple, and readily accessible. The simple acyclic structure offers the possibility of an easy variation of the receptor structure, providing a base for systematic studies toward recognition motifs for carbohydrates.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft.

Supporting Information Available: Experimental details for the syntheses and analyses; ^1H NMR titration data (Figures S1−S3, S5, S6) and extraction experiments (Figure S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) In comparison to the previously described tri-armed pyridine-based receptor (see ref 4d), the new receptor **1** may form three additional hydrogen bonds with the β-glucopyranoside. The studies in the area of drug design found that a neutral−neutral hydrogen bond is worth up to about 1.5 kcal mol^{-1}, which is equivalent to a maximum 15-fold increase in binding, see: (a) Davis, A. M.; Teague, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 736−749. (b) Fersht, A. R.; Shi, J.-P.; Knill-Jones, J.; Lowe, D. M.; Wilkinson, A. J.; Blow, D. M.; Brick, P.; Carter, P.; Waye, M. M. Y.; Winter, G. *Nature* **1985**, *314*, 845−851. (c) Williams, D. H.; Searle, M. S.; Mackay, J. P.; Gerhard, U.; Maplestone, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 1172−1178.