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Novel Porphyrin–Cryptand Cyclic Systems: Receptors for Saccharide Recognition in Water

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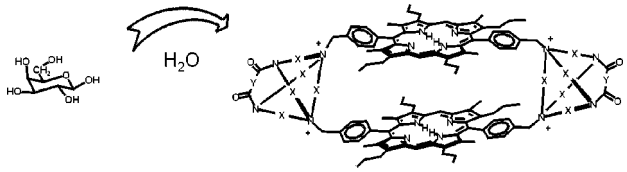
ABSTRACT



Two macrocyclic porphyrin sandwich systems, 4 and 5, together with the linear compound 6 have been prepared and examined as saccharide receptors. The cyclic porphyrin–cryptand conjugates 4 and 5 bind saccharides efficiently in highly competitive media with a preference for trisaccharides probably due to a complementary topology of hydrophobic and hydrophilic solvating regimes with respect to the sugar guests.

Among the biologically important compounds, carbohydrates represent particularly attractive molecular guests, which, however, also belong to the most difficult classes to be selectively recognized in their natural environment. The most recent work and a current review[1] list examples of successful saccharide receptors comprising the resorcinol−aldehyde−cyclotetramer, polyaza clefts, amino cyclodextrins, boronic acid based receptors, cyclophanes, capped porphyrins, polypyridine macrocycles, and phosphonates supplementing the very successful but probably less organized oligosaccharide−resorcinarene conjugates.[2] Though water-soluble porphyrins have been studied extensively, mainly with respect to their utility for electron-transfer studies in photosynthesis and artificial enzymes models[3−5] and their potential for medicinal applications,[6,7] this versatile building block has just recently been probed for saccharide complexation.[8] From the literature precedence, we concluded that the combination of porphyrin building blocks and quasi tetrahedral amido−azonia cryptands to form the macrocyclic compounds **4** and **5** might set the stage for saccharide binding in competitive solvents.

Molecular modeling clearly demonstrated the presence of a molecular cavity of the size required for encapsulation of a trisaccharide (Figure 1). The host−guest attraction should originate from the hydrophobic lining in the porphyrin sandwich interacting with the upper and lower hydrophobic faces of the sugar units and may be assisted by hydrogen bonding from their hydroxyl groups to the well-hydrated tertiary amide and azonia functions creating a special polar medium intermittent between the porphyrin planes. This

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(1) (a) Bahr, A.; Felber, B.; Schneider, K.; Diederich, F. *Helv. Chim. Acta* **2000**, *83*, 1346. (b) Davis, A. P.; Wareham, R. S. *Angew. Chem.* **1999**, *20*, 2978.
(2) (a) Fujimoto, K.; Miyata, T.; Aoyama, Y. *J. Am. Chem. Soc.* **2000**, *122*, 3558. (b) Matsuda, Y.; Chuleeraruk, J.; Nishiyama, K.; Fujimoto, K.; Fujimoto, T.; Shimizu, T.; Hayashida, O.; Aoyama, Y. *Pure Appl. Chem.* **1998**, *70*, 2379.
(3) Zhang, H.-Y.; Yu, J.-Q.; Bruice, T. C. *Tetrahedron* **1994**, *50*, 11339R.
(4) Coleman, J. P.; Wagenknecht, P. S.; Hutchison, J. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1537.
(5) Karaman, R.; Bruice, T. C. *J. Org. Chem.* **1991**, *56*, 3470.
(6) Bonnett, R. *Chem. Soc. Rev.* **1995**, 19.
(7) Cannon, J. B. *J. Pharm. Sci.* **1993**, *82*, 435.
(8) Sugasaki, A.; Ikeda, M.; Takeuchi, M.; Koumoto, K.; Shinkai, S. *Tetrahedron* **2000**, *56*, 4717.

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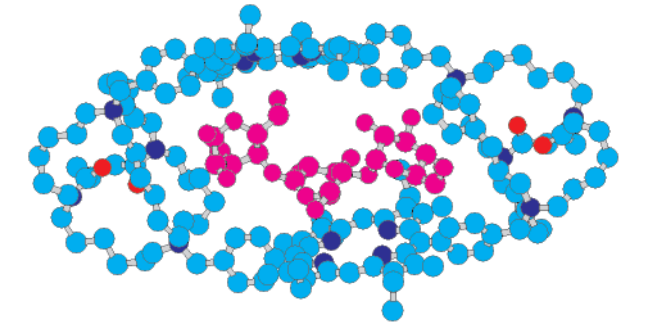
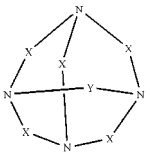


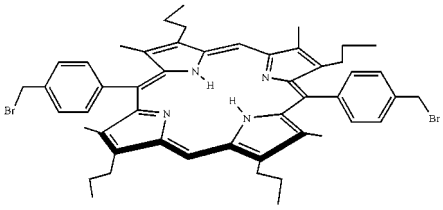
Figure 1. Energy-minimized structure of the {maltotriose⊂**4**} molecular complex (Hyperchem).

topology is nicely complementary to the distribution of hydrophobic and hydrophilic parts of the sugar molecules. Owing to the high and pH independent positive charge, these compounds were expected to be soluble in water while their tendency for aggregation, which frequently haunts porphyrinic host−guest systems, is minimized. In addition to their role as tectones, the porphyrin moieties should feel the accommodation of a sugar guest molecule inside the cavity and respond by tuning their optical/fluorescence properties accordingly, thereby easing the analysis of the guest binding event. Furthermore, they open the option to modify the spacing and accessibility of the binding site by prudent choice of the peripheral and/or meso substituents that can be introduced in the synthesis quite easily. For comparison and to assess the potential advantages of guest encapsulation into a molecular cavity, the open-chain analogue **6** containing the same number of positively charged sites at physiological pH was prepared.

Analoguous compounds consisting of porphyrin (**2**) and tetrahedral tetraamine (**1a**) building blocks had been obtained previously, and these conjugates were shown to successfully bind nucleotides in water.[9] However, the preparation starting



1a X = Y = $(CH_2)_6$
1b X = $(CH_2)_6$, Y = $CO(CH_2)_4CO$



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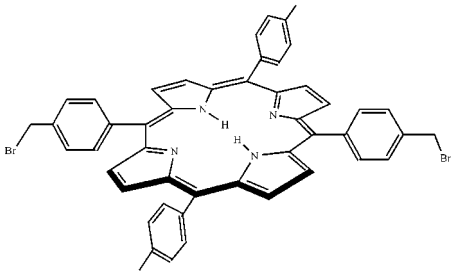

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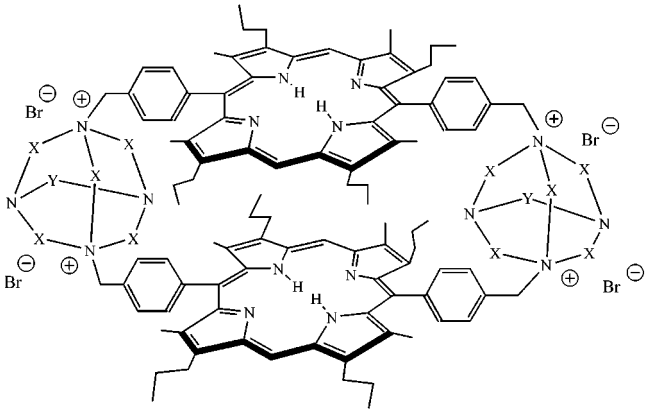
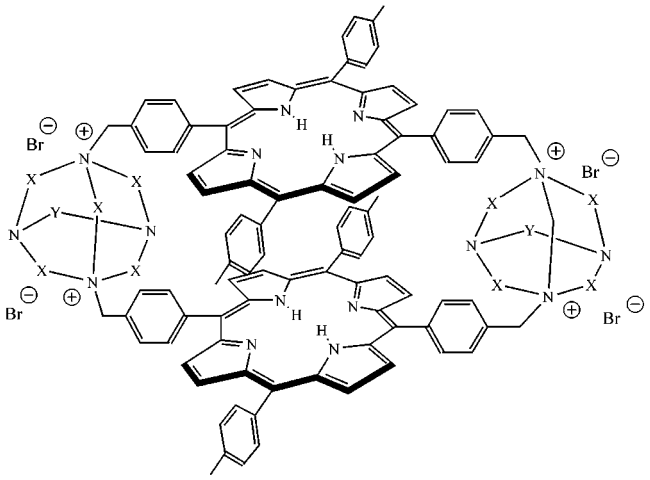
from benzylic bromides **2** or **3** and amine **1a** could not be elaborated to furnish the bisporphyrinic sandwich compounds. Instead, the multitude of reactive sites preferentially gave polymers as evidenced by TLC and MALDI-TOF analysis. More favorable results were obtained by employing **2** or **3** with the macrotricyclic amide **1b** in a 1:1 stoichiometric ratio. This moiety contains only two tertiary N atoms that are reactive in Menshutkin-type alkylations and therefore are less prone to resinification. In the optimized synthetic protocol, a chloroform solution of bis(bromomethyl)porphyrin (**2** or **3**)[9] was slowly added to an acetonitrile solution of **1b**[10] with heating over a period of 8 h followed by reflux for 24 h. This method generated high dilution conditions which favored the formation of cyclic systems over linear alkylation products, while the remaining starting compound (conversion was typically around 50%) could easily be removed by crystallization (dichloromethane−hexane). Linear conjugate **6** was obtained under similar conditions, but using 5 molar equiv of bisamide **1b**.[11]

Many water-soluble porphyrins containing polar solubilizing groups exhibit strong intermolecular aggregation[12−14] which is detectable in the UV spectrum from inspection of the Soret band and complicates the quantitative evaluation of the guest binding event. The novel host compounds **4**, **5**, and **6** showed no irregular dependence of the position and magnitude of their Soret absorptions at 407 nm (**4**) or 420

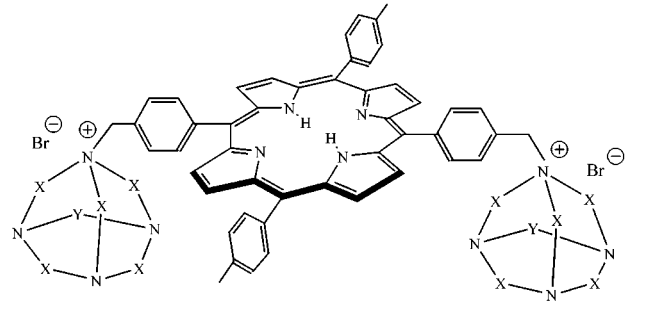
(9) Král, V.; Cattani, A.; Sinica, A.; Schmidtchen, F. P. *Tetrahedron* **1999**, *55*, 7829.
(10) Schmidtchen, F. P. *J. Org. Chem.* **1986**, *51*, 5161.
(11) **Conjugate 4:** yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$, 5% CD_3OD): 10.23 (methine, s, 4H); 8.2−7.9 (phenyl, m, 16H); 5.16 (Ar-CH_2-N, s, 8H); 4.19−3.38 (CH_2, m, 168H); 2.68−2.21 (CH_3, m, 24H); 1.54 (CH_3, m, 24H); −2.5 (NH, s, 4H). MALDI-TOF MS: for $C_{172}H_{248}Br_4N_{16}O_4$ calcd 2920; found 2940 ($MH^+ + H_2O$), 2921 (MH^+), 2876 (M −Br + $2H_2O$), 2858 (M −Br + H_2O), 2840 (M − Br), 1425 (M − Br + H^+)/2, 1301 (M − 4Br)/2. Anal. $C_{172}H_{248}Br_4N_{16}O_4$ (2923.5). Calcd: C 70.66, H 8.55, N 7.67. Found: C 70.58, H 8.52, N 7.59. **Conjugate 5:** yield 42%. ^{1}H NMR (400 MHz, $CDCl_3$, 5% CD_3OD): 8.98−7.56 (phenyl, β-pyrrole, m, 48H); 5.29 (Ar-CH_2-N, s, 8H); 4.20−3.09 (CH_2, m, 136H); 2.69−2.30 (CH_3, m, 12H); −2.8 (NH, s, 4H). MALDI-TOF MS: for $C_{168}H_{208}Br_4N_{16}O_4$ calcd 2832; found 1416 (M + $2H^+$)/2, 1373 (M −2Br + $2H^+$ + $4H_2O$)/2, 1355 (M − 2Br + $2H^+$ + $2H_2O$)/2, 1337 (M − 2Br)/2, 1428 (M + $2H^+$ + $2H_2O$)/2. Anal. $C_{168}H_{208}Br_4N_{16}O_4$ (2835.2). Calcd: C 71.17, H 7.39, N 7.90. Found: C 71.08, H 7.22, N 7.78. **Conjugate 6:** yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$, 10% CD_3OD): 8.87−7.54 (phenyl, β-pyrrole, m, 24H); 5.25 (Ar-CH_2-N, s, 4H); 3.90−3.18 (CH_2, m, 136H); 2.68−2.31 (CH_3, s, 6H); −2.82 (NH, s, 2H). MALDI-TOF MS: for $C_{120}H_{172}Br_2N_{12}O_4$ calcd 2004, found 2005 (MH^+), 940 (M − 2Br + $2H_2O$)/2. Anal. $C_{120}H_{172}Br_2N_{12}O_4$ (2006.5). Calcd: C 71.83, H 8.64, N 8.38. Found: C 71.58, H 8.52, N 8.28.
(12) Rubries, R.; Crustas, J.; El-Hachemi, Z.; Jaramillo, T.; Lopez, M.; Valls, E, Farrera, J.-A.; Ribo, J. M. *New J. Chem.* **1999**, 189.
(13) Pasternack, R. F.; Huber, P. R.; Boyd, P.; Engasser, G.; Francesconi, L.; Gibbs, E.; Fasella, P.; Venturo, G. C.,. Hinds, L. C. *J. Am. Chem. Soc.* **1972**, *94*, 4511.
(14) Pasternack, R. F. *Ann. N.Y. Acad. Sci.* **1973**, *206*, 614.O.



4 X = $(CH_2)_6$, Y = $CO(CH_2)_4CO$



5 X = $(CH_2)_6$, Y = $CO(CH_2)_4CO$



6 X = $(CH_2)_6$, Y = $CO(CH_2)_4CO$

nm (**5**, **6**), respectively, and cleanly followed Beer's law in the concentration range required in the measurements with the saccharide guests (10^{-5}−10^{-6} M). The addition of commercially available saccharides and glycosides to aqueous solutions of the novel receptors changed the intensity but not the position of the Soret band maximum. The concentration dependence of the peak diminution can be fit by nonlinear regression to a 1:1 host−guest binding model (Figure 2).

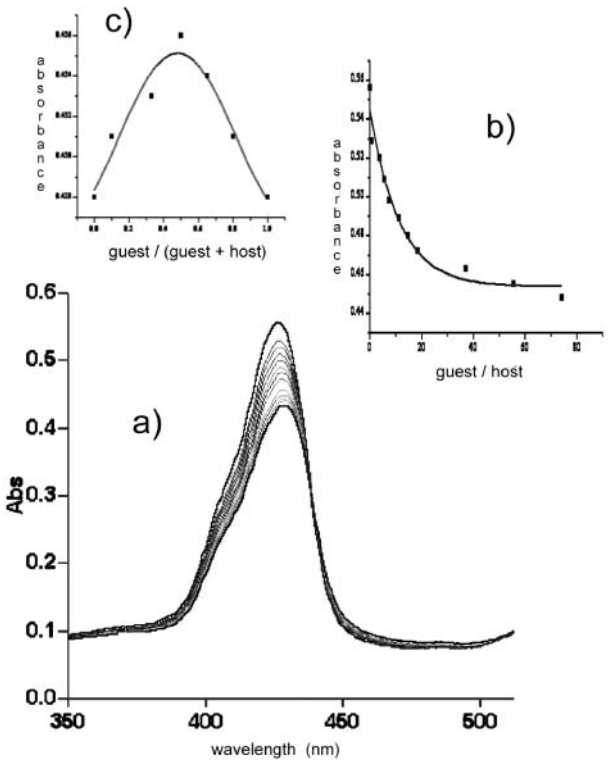


Figure 2. (a) Typical spectral UV−vis changes upon the incremental addition of glucose to receptor **6** in water at room temperature, 2.4×10^{-6} M of **6** in H_2O/5% MeOH; $\lambda_{max} = 420$ nm. (b) Plot of the extinction changes vs guest/host ratio. The solid line represents the fitted curve. (c) Job plot indicating a maximum at a mol fraction of 0.5 (i.e., 1:1 stoichiometry).

This stoichiometry was also corroborated by an independent Job plot (Figure 2c). Analogous data evaluation was also performed with the corresponding fluorescence spectra. The association constants agreed within experimental error. The efficacy of sugar binding with hosts **4** and **5** is considerably higher than in the systems recently reported by us[15] and sets a new mark for small artificial saccharide receptors binding their guests in water.

A peculiar selectivity feature is worthy of note: The association constants increase from mono- to di- (threhalose, lactose) and further to the trisaccharide, but diminish again with higher oligomers of glucose (Table 1). Maltotriose is the most preferred substrate for receptors **4** and **5**, possessing a well-defined cavity while this trend was not observed, as expected, for the open-chain receptor **6** lacking this structural feature. The alkyl substituent of alkyl-α-D-glucopyranosides enhanced the association constant in comparison to glucose. Interestingly, the novel receptors are able to discriminate between α- and β-anomers by a factor of 4. Obviously, the recognition process is governed by substrate geometry and size. However, a significant shift in the IR amide carbonyl streching vibration band from 1613 cm^{-1} in the uncomplexed host **4** to 1630 cm^{-1} in the presence of glucose testifies to

(15) Rusin, O.; Král, V. *J. Chem. Soc., Chem. Commun.* **1999**, 2367.

Table 1. Association Constants for Binding of Saccharides to Receptors **4**−**6** in Water monitored by UV−Vis[a]

	association constant log $K_a \pm$ exp error range		
saccharide	**4**	**5**	**6**
D-galactose	3.10 ± 0.14	3.52 ± 0.07	3.32 ± 0.06
D-glucose	3.14 ± 0.13	3.63 ± 0.06	3.08 ± 0.17
methyl-α-D-glucoside	3.75 ± 0.06	3.89 ± 0.06	3.77 ± 0.08
methyl-β-D-glucoside	3.14 ± 0.15	3.36 ± 0.08	3.04 ± 0.11
octyl-α-D-glucoside	3.20 ± 0.11	3.86 ± 0.03	3.74 ± 0.11
D-trehalose	3.96 ± 0.05	3.98 ± 0.07	3.62 ± 0.06
D-lactose	4.45 ± 0.16	3.81 ± 0.07	3.74 ± 0.04
maltotriose	4.72 ± 0.06	4.24 ± 0.10	3.78 ± 0.12

[a] The formation constants (UV−vis determination) of sugar−receptor complexes. In a 1 cm square quartz cuvette was placed a 2.4×10^{-6} M solution of macrocycle **4**, **5**, or **6** in H_2O containing 5% of MeOH (v/v). Saccharide was added in aliquots of a stock solution (0−100 equiv; the solution contained the same concentration of receptor as in the cuvette). The absorbance changes at the position of the Soret band were measured (room temperature), and the data were evaluated with the aid of least squares curve fitting. The K_a was calculated for 1:1 complexes and averaged over four independent determinations.

the participation of hydrogen-bonding interactions to the amide groups in the binding process as well. Although the individual contributions to saccharide binding are less clear at present, the distinct advantage for guest inclusion into the molecular cavity of **4** and **5** is evident from the CD spectra: Glucose binding to the porphyrin sandwich receptors results in a very weak induction of a CD band at the Soret absorption position whereas a much more dramatic effect was observed with the more flexible linear host **6**. In this case the amplification might also originate from a saccharide-mediated intermolecular chiral aggregation which is impossible on inclusion complex formation of **4** and **5**.

In conclusion, the novel cyclic receptors **4** and **5** showed selective binding of saccharides in water solution, revealing a trend increasing from mono- to trisaccharide. The binding strength appears to derive from a matched complementarity in the pattern of hydrophilic and hydrophobic areas of host and guest. The selectivity is most likely based on relative size since the best bound trisaccharide molecule just fills the receptor cavity. Interestingly, *O*-alkyl-glucopyranosides also showed diastereoselective binding discriminating α- and β-anomers of glucopyranosides by a factor of 4.

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