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Phenanthroline Unit as a Building Block for Carbohydrate Receptors

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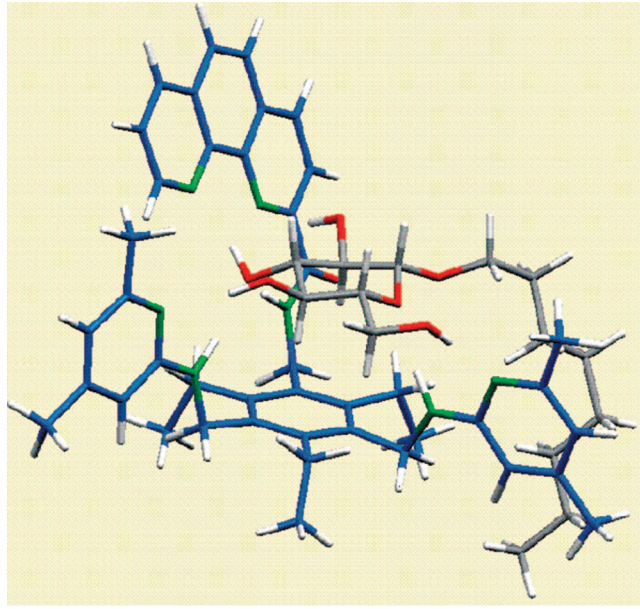

An acyclic receptor **1**, containing phenanthroline- and aminopyridine-based recognition sites, has been established as a powerful carbohydrate receptor. Compared to the previously described acyclic receptors, compound **1** shows significantly higher binding affinities as well as selectivities, which are quite different from those of the earlier systems. The phenanthroline unit has been established as a valuable building block for the construction of effective and selective carbohydrate receptors.

Introduction

Synthetic carbohydrate receptors operating through noncovalent interactions[1–4] provide valuable model systems to study the underlying principles of carbohydrate-based molecular recognition processes. Advances in this area are likely not only to provide insight into the molecular recognition phenomena, but also to facilitate the development of new therapeutics or chemosensors. As part of our program aimed at the development of effective and selective carbohydrate receptors, we have already analyzed the binding properties of receptors consisting of pyridine-, pyrimidine-, indole-, imidazole-, benzimidazole-, guanidinium-, carboxylate-, crown ether-, hydroxy-, amino-, amide-, and oxime-based recognition groups.[4] Depending on the nature and number of recognition units and connecting bridges used as the building blocks, a variety of structures with

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(1) (a) Davis, A. P.; James, T. D. In *Functional Synthetic Receptors*; Schrader, T., Hamilton, A. D., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 45−109. (b) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2979–2996. (c) Mazik, M., *ChemBioChem* **2008**, *9*, 1015−1017.

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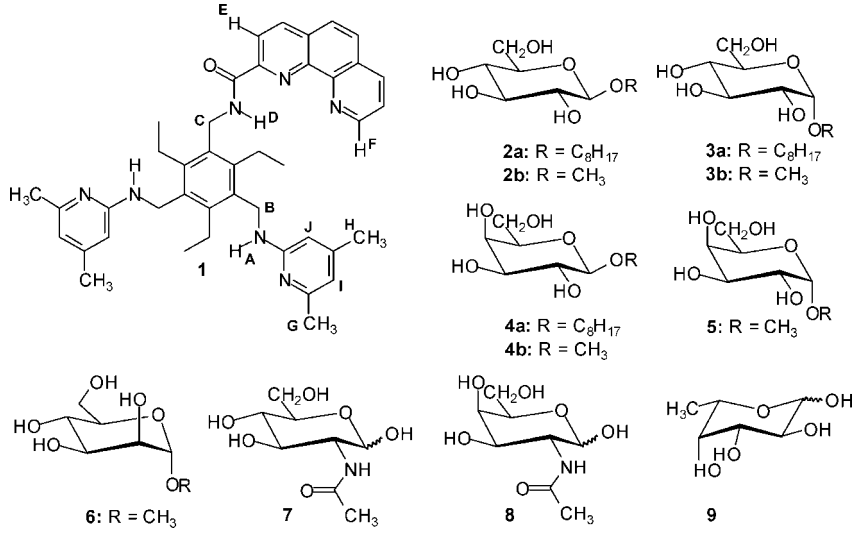

FIGURE 1. Receptor **1** and structures of sugars **2**−**9**.

different binding properties could be obtained. The aim of this study was to evaluate the potential of the phenanthroline unit in the recognition of neutral carbohydrates. The potential of phenanthroline-based receptors in the recognition of saccharides through noncovalent interactions has not been explored so far. The phenanthroline unit has mostly been incorporated into different boronic acid-based receptors,[3,5] using covalent interactions for sugar binding. It should be noted that hydrogen-bonding phenanthroline-based receptors have been designed to bind diols. Complexation properties of such receptors toward cyclohexane diols have been described by Anslyn and co-workers.[6]

As a starting point, we have examined the binding properties of an acyclic phenanthroline/aminopyridine-based receptor **1** (see Figure 1). To evaluate the recognition capabilities of this receptor several sugars were selected as substrates, such as octyl β-D-glucopyranoside (**2a**), methyl β-D-glucopyranoside (**2b**), octyl α-D-glucopyranoside (**3a**), methyl α-D-glucopyranoside (**3b**), octyl β-D-galactopyranoside (**4a**), methyl β-D-galactopyranoside (**4b**), methyl α-D-galactopyranoside (**5**), methyl α-D-mannopyranoside (**6**), *N*-acetyl-D-glucosamine (**7**), *N*-acetyl-D-galactosamine (**8**), and L-fucose (**9**). The binding properties of **1** were compared with those of the symmetrical aminopyridine-based analogue **10** (1,3,5-tris[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene[4l]).[7] The interactions of the receptor **1** and the corresponding saccharides were investigated by ^{1}H NMR titrations and extraction experiments. The studies showed that the incorporation of a suitably positioned phenanthroline unit into the receptor structure significantly affects the binding properties of the new receptor.

Results and Discussion

The synthesis of compound **1** is outlined in Scheme 1. The synthesis started from 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**11**),[8] which was converted into compound **13**[4b] via a reaction with 2 equiv of 2-amino-4,6-dimethylpyridine (**12**). The treatment of **13** with aqueous ammonia gave the amino derivative **14**,[4b] which was converted into compound **1** through a reaction with 1,10-phenanthroline-2-carbonyl chloride (**19**).[9] The carbonyl chloride **19** was prepared via a reaction of 1,10-phenanthroline-2-carboxylic acid (**18**) with thionyl chloride. The synthesis of **18** started from phenanthroline (**15**), which was oxidized with hydrogen peroxide to form 1,10-phenanthroline

(2) For some examples of carbohydrate receptors operating through noncovalent interactions, see (further examples are cited in refs 4a−c): (a) Ferrand, Y.; Crump, M. P.; Davis, A. P. *Science* **2007**, *318*, 619−622, and references cited therein. (b) Klein, E.; Crump, M. P.; Davis, A. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 298–302. (c) Abe, H.; Aoyagi, Y.; Inouye, M. *Org. Lett.* **2005**, *7*, 59–61. (d) Welti, R.; Abel, Y.; Gramlich, V.; Diederich, F. *Helv. Chim. Acta* **2003**, *86*, 548–562. (e) Welti, R.; Diederich, F. *Helv. Chim. Acta* **2003**, *86*, 494–503. (f) Wada, K.; Mizutani, T.; Kitagawa, S. *J. Org. Chem.* **2003**, *68*, 5123–5131. (g) Segura, M.; Bricoli, B.; Casnati, A.; Muñoz, E. M.; Sansone, F.; Ungaro, R.; Vicent, C. *J. Org. Chem.* **2003**, *68*, 6296–6303. (h) Ishi-I, T.; Mateos-Timoneda, M. A.; Timmerman, P.; Crego-Calama, M.; Reinhoudt, D. N.; Shinkai, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2300–2305. (i) Cho, H.-K.; Kim, H.-J.; Lee, K. H.; Hong, J.-I. *Bull. Korean Chem. Soc.* **2004**, *25*, 1714–1716. (j) Tamaru, S.-i.; Shinkai, S.; Khasanov, A. B.; Bell, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4972–4976. (k) Ladomenou, K.; Bonar-Law, R. P. *Chem. Commun.* **2002**, 2108–2109. (l) Bitta, J.; Kubik, S. *Org. Lett.* **2001**, *3*, 2637–2640. (m) Král, V.; Rusin, O.; Schmidtchen, F. P. *Org. Lett.* **2001**, *3*, 873–876. (n) Eblinger, F.; Schneider, H.-J. *Collect. Czech. Chem. Commun.* **2000**, *65*, 667–672.

(3) Another strategy, which has been employed for the design of synthetic carbohydrate receptors, involves exploitation of non-natural bonding interactions; this strategy relies on the reversible formation of covalent bonds from diol units and boronic acid. For reviews on boronic acid-based receptors, see: (a) James, T. D.; Shinkai, S. *Top. Curr. Chem.* **2002**, *218*, 159–200. (b) Striegler, S. *Curr. Org. Chem.* **2003**, *7*, 81–102. (c) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Angew. Chem., Int. Ed.* **1996**, *35*, 1910–1922.

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(5) (a) For fluorescent sensing of uronic acids based on a cooperative action of boronic acid and metal chelate, see: Takeuch, M.; Yamamoto, M.; Shinkai, S. *Chem. Commun.* **1997**, 1731–1732. For an example of metal-containing phenanthroline-based chemosensor based on 1,3,5-triethylbenzene frame, see: (b) Cabell, L. A.; Best, M. D.; Lavigne, J. J.; Schneider, S. E.; Perreault, D. M.; Monahan, M.-K.; Anslyn, E. V. *J. Chem. Soc., Perkin Trans. 2* **2001**, 315–323.

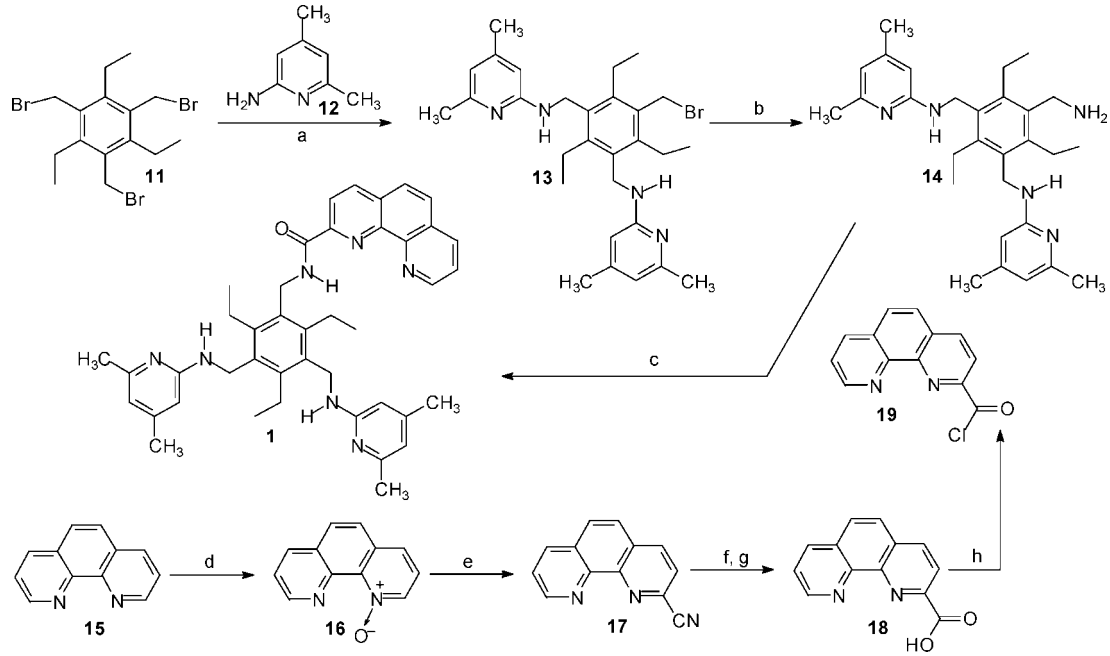
(6) Bell, D. A.; Diaz, S. G.; Lynch, V. M.; Anslyn, E. V. *Tetrahedron Lett.* **1995**, *36*, 4155–4158.

(7) Our previous studies showed that receptors based on the 2,4,6-triethylbenzene frame display about 2-fold higher binding affinity toward neutral monosaccharides than those based on the 2,4,6-trimethylbenzene unit, see ref 4l.

(8) Wallace, K. J.; Hanes, R.; Anslyn, E.; Morey, J.; Kilway, K. V.; Siegel, J. J. *Synthesis* **2005**, 2080–2083.

(9) (a) Corey, E. J.; Borror, A. L.; Foglia, T. *J. Org. Chem.* **1965**, *30*, 288–289. (b) Su, W.-H.; Jie, S.; Zhang, W.; Song, Y.; Ma, H.; Chen, J.; Wedeking, K.; Fröhlich, R. *Organometallics* **2006**, *25*, 666–677.

SCHEME 1. Synthesis of Receptor 1[a]



[a] Reagents and conditions: (a) 2 equiv of **12**, CH_3CN/THF, K_2CO_3;[4b] (b) NH_3/H_2O;[4b] (c) $N(Et)_3$, THF; (d) H_2O_2;[9] (e) PhCOCl; KCN;[9] (f) NaOH, H_2O/EtOH; (g) HCl;[9] (h) $SOCl_2$.

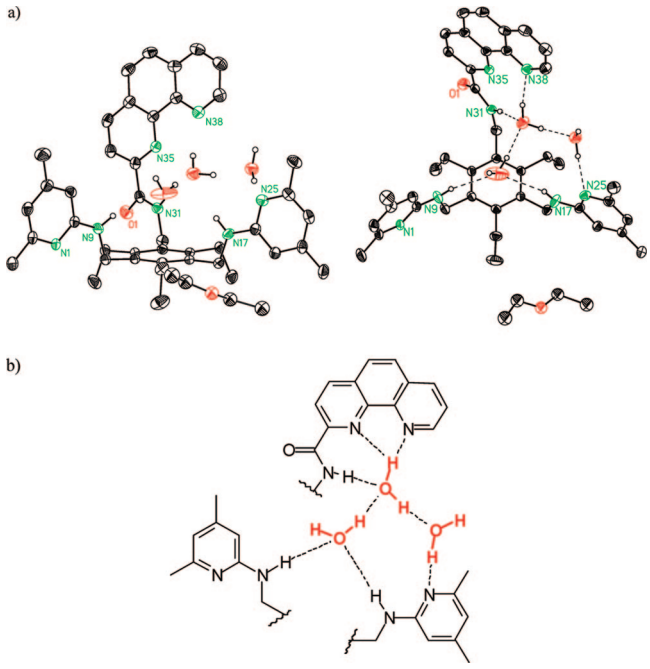


FIGURE 2. (a) Crystal structure of **1** (two different representations, C−Hs are omitted for clarity); three hydrogen-bonded water molecules and one diethyl ether molecule are shown. (b) Schematic representation of the hydrogen-bonding motifs in the binding pocket of **1**.

1-oxide[9] (**16**). The reaction of **16** with potassium cyanide and benzoyl chloride gave 2-cyano-1,10-phenantroline (**17**), which was further converted to the 1,10-phenanthroline-2-carboxylic acid (**18**).

The crystal structure of **1** is shown in Figure 2a (crystals were grown by slow evaporation of the solvent from a diethyl ether−chloroform solution of compound **1**). The crystal structure revealed the presence of three water molecules in the binding pocket of **1**; the receptor−water aggregate is stabilized by eight hydrogen bonds ($H_2O\cdots HN^D$, HOH···N-pyridine, 2 × $H_2O\cdots HN^A$, 2 × HOH···*N*-phenanthroline, and 2 × $H_2O\cdots$HOH), as shown in Figure 2b.

The ^{1}H NMR titration experiments with β- and α-glucopyranoside, **2a** and **3a**, were carried out by adding increasing amounts of the sugar to a solution of receptor **1**. In addition, inverse titrations were performed in which the concentration of sugar **2a** or **3a** was held constant and that of the receptor was varied. The interactions of receptor **1** with carbohydrates were investigated in $CDCl_3$, water-containing $CDCl_3$, DMSO-d_6/$CDCl_3$, and $CD_3OD/CDCl_3$ mixtures (0.1:9.9, 0.5:9.5, and 1:9 v/v). The complexation between receptor **1** and the glucopyranosides was evidenced by several changes in the NMR spectra (see Figures 3 and 4, as well as Figures S1−S5 in the Supporting Information).

The addition of β-glucopyranoside **2a** to a $CDCl_3$ solution of receptor **1** caused significant downfield shift of the amine NH^A and amide NH^D signals of **1** (indicating the participation of these groups in the formation of intermolecular hydrogen bonds; see Table 1), as well as changes of the chemical shifts of the $CH_3^{G,H}$, $CH_2^{B,C}$, pyridine $CH^{I,J}$, and phenantroline CH resonances (for labeling, see Figure 1). The NH^A and NH^D signals broadened significantly, became almost indistinguishable from the baseline after the addition of only 0.1 equiv of **2a**, and finally became distinctly visible near the saturation that occurred after the addition of about 1 equiv of sugar **2a**. The $CH_3^{G,H}$ signals of **1** moved up- and downfield, as shown in Figure S1, Supporting Information, whereas the CH_2^B signal moved upfield with broadening and splitting. Splitting of the CH_2^C signal of **1** was observed after the addition of about 0.1 equiv of **2a** (see Figure S1b in the Supporting Information).

The addition of α-glucopyranoside **3a** to a $CDCl_3$ solution of **1** yielded similar NMR effects (see Figures 3, 4a, and S2, Supporting Information); however, the spectral changes observed in the titrations with the α-anomer **3a** were more substantial than those seen in the titrations with the β-anomer **2a** (for comparison, see Figure S1a in the Supporting Information and

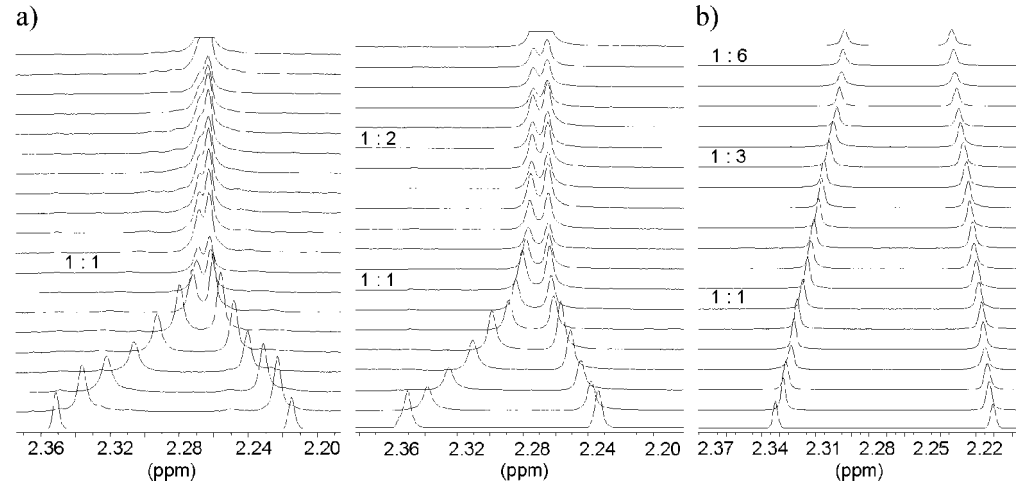


FIGURE 3. (a) Partial ^{1}H NMR spectra (400 MHz) of receptor **1** after addition of (from bottom to top) 0.00−2.49 equiv of α-glucopyranoside **3a** ([**1**] = 1.02 mM): left, $CDCl_3$; right, water-containing $CDCl_3$ (0.04% H_2O). (b) Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$) of receptor **10** after addition of 0.00−7.25 equiv of **3a** ([**10**] = 0.70 mM). Shown are chemical shifts of the pyridine methyl groups.

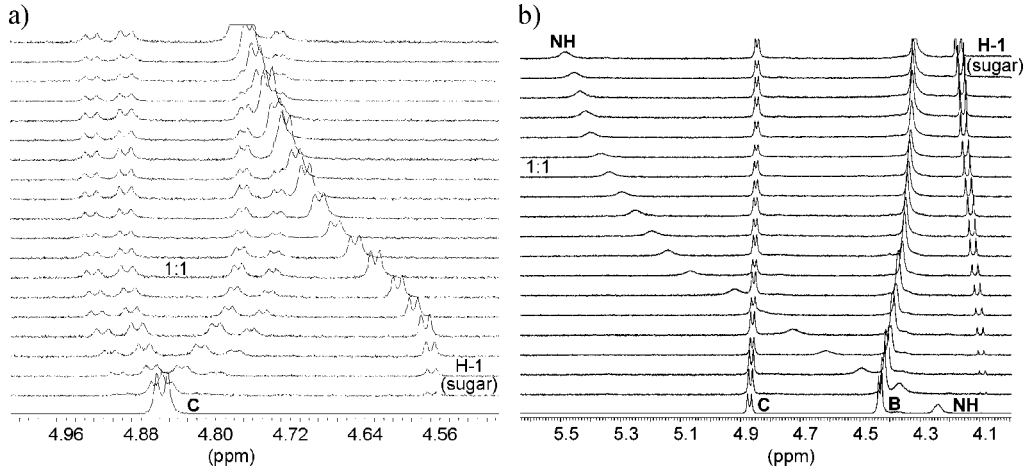


FIGURE 4. Partial ^{1}H NMR spectra (400 MHz; $CDCl_3$) of receptor **1** after addition of (a) 0.00−2.67 equiv of α-glucopyranoside **3a** ([**1**] = 0.86 mM) and (b) 0.00−1.80 equiv of β-galactopyranoside **4a** ([**1**] = 0.90 mM).

Figure 3a). In both cases, **1**·**2a** and **1**·**3a**, the shifts of the aromatic CH's and the CH_3 protons were monitored for the determination of the binding constants. The curve fitting of all the titration data suggested the existence of 1:1 and 2:1 receptor−sugar complexes in chloroform solutions (this binding model was further supported by the mole ratio plots; see Figure S6 in the Supporting Information), with a stronger association constant for the 1:1 binding and a weaker association constant for the 2:1 receptor−sugar complex.[10,11] The binding constants, however, were too large to be accurately determined by the NMR method[12] (the association constants[10b,11] for **1**·**2a** amounted to 334 600 (K_{11}) and 13 970 M^{-1} (K_{21}), those for **1**·**3a** were found to be $K_{11} > 10^5$ and $K_{21} \approx 10^4$ M^{-1}; see Table 1). Similar complexation behavior of receptor **1** could also be observed in water-containing $CDCl_3$ (0.04% H_2O, see Table 1 and Figure 3a, as well as Figure S2b in the Supporting Information).

Compared with the previously described symmetrical receptor **10**,[41] receptor **1** shows significantly increased affinity to the both anomers **2a** and **3a** (for comparison of the binding constants, see Table 1). Receptor **1** displays not only higher efficiency, but also an inverse selectivity since it binds the α-glucopyranoside better than the β-anomer. Comparison of parts a and b of Figure 3 clearly reflects the strong differences in the complexation ability of **1** and **10**.

The binding studies in DMSO-d_6/$CDCl_3$ and CD_3OD/$CDCl_3$ mixtures showed that affinities of **1** for the glucopyranosides **2a** and **3a** decrease as solvent polarity increases. The motions of the signals observed during the titrations of **1** with **2a** or **3a** in 1%, 5%, and 10% DMSO-d_6 in $CDCl_3$ (see Figures S2 and S3a, Supporting Information) were consistent with 1:1 and 2:1 receptor−sugar binding. After the addition of 1% DMSO-d_6 the binding constants for **1**·**3a** were still too large to be accurately determined by the NMR method ($K_{11} > 10^5$ and $K_{21} \approx 10^4$ M^{-1}; see Table 1). The binding constants for **1**·**3a** in 5% DMSO-d_6 in $CDCl_3$ were determined to be 107 700 (K_{11}) and 8 540 M^{-1} (K_{21}),[10b] whereas those for **1**·**2a** amounted to 36 530

(10) (a) The binding studies were carried out in $CDCl_3$, water-containing $CDCl_3$, CD_3OD/$CDCl_3$, and DMSO-d_6/$CDCl_3$ mixtures at 25°C. The titration data were analyzed by nonlinear regression analysis, using the program HOSTEST 5.6 (see ref 11). The stoichiometry of receptor−-sugar complexes was determined by the mole ratio method and by the curve-fitting analysis of the titration data. For each system at least 3 titrations were carried out; for each titration 16−20 samples were prepared. Dilution experiments show that receptor **1** does not self-aggregate in the used concentration range. (b) K_{11} corresponds to the 1:1 association constant. K_{21} corresponds to the 2:1 receptor−sugar association constant. K_{12} corresponds to the 1:2 receptor−sugar association constant. $\beta_{21} = K_{11} \times K_{21}$, $\beta_{12} = K_{11} \times K_{12}$.

(11) Wilcox, C. S.; Glagovich, N. M. Program HOSTEST 5.6; University of Pittsburgh: Pittsburgh, PA, 1994.

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

TABLE 1. Association Constants[a,b] for Receptors 1 and 10 and Sugars 2a, 3a, and 4a

receptor–sugar complex	solvent	K_{11} [M^{-1}]	K_{21}[j] or K_{12}[k] [M^{-1}]	$\beta_{21} = K_{11}K_{21}$ or $\beta_{12} = K_{11}K_{12}$ [M^{-2}]	$\Delta\delta_{obs}$[n] ($\Delta\delta_{max}$)[o] [ppm]
1·2a	$CDCl_3$[c]	10^5	10^4; *j,l*	10^9	NH^A: 1.50; NH^D: 1.40; $CH_3{}^G$: −0.06 (−0.06); $CH_3{}^H$: 0.04 (0.04); CH^E: 0.09 (0.09); CH^F: −0.04; CH^J: 0.05
	5% DMSO-d_6/$CDCl_3$[c,f]	36530	2600; *j*	9.50×10^7	NH^A: 1.56; NH^D: 1.21; $CH_3{}^G$: −0.06 (−0.06); $CH_3{}^H$: 0.05 (0.05); CH^E: 0.10 (0.10); CH^F: −0.04; CH^J: 0.06
1·3a	$CDCl_3$[c]	$>10^5$	*j, m*		NH^A: 1.90; NH^D: 2.14; $CH_3{}^G$: −0.09 (−0.09); $CH_3{}^H$: 0.05; CH^E: 0.09 (0.09); CH^F: 0.12 (0.12); CH^J: 0.07
	H_2O-containing[d] $CDCl_3$	$>10^5$	*j, m*		NH^A: 0.90; NH^D: 1.20; $CH_3{}^G$:−0.09 (−0.09); CH^F: 0.15 (0.15); CH^E: 0.07
	1% DMSO-d_6/$CDCl_3$[c,e]	$>10^5$	*j,m*		NH^A: 1.90; NH^D: 2.12; $CH_3{}^G$: −0.09 (−0.09); $CH_3{}^H$: 0.05; CH^E: 0.09; CH^F: 0.12 (0.12); CH^J: 0.07
	5% DMSO-d_6/$CDCl_3$[c,f]	107700	8540; *j*	9.20×10^8	NH^A: 1.75; NH^D: 2.05; $CH_3{}^G$: −0.08 (−0.08); $CH_3{}^H$: 0.05; CH^E: 0.08 (0.08); CH^F: 0.12; CH^J: 0.07
	10% DMSO-d_6/$CDCl_3$[c,g]	10500	840; *j*	8.82×10^6	NH^A: 1.50; NH^D: 1.93; $CH_3{}^G$: −0.08 (−0.08); $CH_3{}^H$: 0.05 (0.05); CH^E: 0.07; CH^F: 0.13; CH^J: 0.07
	1% CD_3OD/$CDCl_3$[c,h]	41200	4900; *j*	2.01×10^8	NH^D: 0.78 (0.80); $CH_3{}^G$: −0.07 (−0.07); $CH_3{}^H$: 0.04; CH^E: 0.04, CH^F: 0.14 (0.14)
	5% CD_3OD/$CDCl_3$[c,i]	1390			NH^D: 0.50 (0.67); $CH_3{}^G$: −0.05 (−0.07); $CH_3{}^H$: 0.05; CH^E: 0.03, CH^F: 0.12
1·4a	$CDCl_3$[c]	9550	1030; *j*	9.83×10^6	NH^A: 1.24; NH^D: 1.14; $CH_3{}^G$: −0.04 (−0.05); $CH_3{}^H$: 0.03; CH^E: 0.06; CH^F: 0.01; CH^J: 0.08
10·2a[p]	$CDCl_3$[c]	48630	1320; *k*	6.42×10^7	NH: 1.31 (1.35)
10·3a[p]	$CDCl_3$[c]	1310			NH: 1.16 (1.44)
10·4a[p]	$CDCl_3$[c]	3070	470; *k*	1.44×10^6	NH: 1.15 (1.33)

[a] Average K_a values from multiple titrations. [b] Errors in K_a are less than 10%. [c] $CDCl_3$ was stored over activated molecular sieves and deacidified with Al_2O_3. [d] ~0.04% H_2O. [e] DMSO-d_6/$CDCl_3$, 0.1:9.9 v/v. [f] DMSO-d_6/$CDCl_3$, 0.5:9.5 v/v. [g] DMSO-d_6/$CDCl_3$, 1:9 v/v. [h] CD_3OD/$CDCl_3$, 0.1:9.9 v/v. [i] CD_3OD/$CDCl_3$, 0.5:9.5 v/v. [j] K_{21} corresponds to 2:1 receptor–sugar association constant. [k] K_{12} corresponds to 1:2 receptor–sugar association constant. [l] Hostest program indicated "mixed" 1:1 and 2:1 receptor–sugar binding model with $K_{11} = 334600$ and $K_{21} = 13970$ M^{-1}($\beta_{21} = 4.67 \times 10^9$ M^{-2}). [m] Hostest program indicated "mixed" 1:1 and 2:1 receptor–sugar binding model with $K_{11} > 10^5$ and $K_{21} \approx 10^4$; however, the binding constants were too large to be accurately determined by the NMR method. [n] Largest change in chemical shift observed during the titration for receptor signals (the concentration of receptor was kept constant and that of sugar varied). [o] Change in chemical shift at saturation binding, values provided by HOSTEST. [p] Results from ref 4l. Compound **10**: 1,3,5-tris[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene.

(K_{11}) and 2 600 M^{-1} (K_{21}). Studies performed with the α-anomer **3a** in 10% DMSO-d_6 in $CDCl_3$ revealed $K_{11} = 10\,500$ M^{-1} and $K_{21} = 840$ M^{-1} (the complexation-induced shifts of the receptor signals are given in Table 1). The spectral changes observed during the titrations of **1** with **3a** in methanol/chloroform mixtures (see Figure S4 in the Supporting Information) were less substantial than those observed during the titrations in dimethyl sulfoxide-containing chloroform solutions (see Figure S2, Supporting Information). The motions of the signals observed during the titrations of **1** with **3a** in 1% CD_3OD in $CDCl_3$ (see Figure S4, Supporting Information) were again consistent with 1:1 and 2:1 receptor–sugar binding; the binding constants for **1·3a** were determined to be 41 200 (K_{11}) and 4 900 M^{-1} (K_{21}). The curve fitting of the titration data obtained in the presence of 5% CD_3OD indicated the formation of complexes with 1:1 receptor–sugar stoichiometry with $K_{11} = 1390$ M^{-1}. Thus, the interactions between **1** and **3a** in CD_3OD/$CDCl_3$ mixtures are significantly weaker than those observed in the presence of DMSO-d_6.

In addition, the interactions between receptor **1** and glucopyranosides **2a** and **3a** were investigated on the base of inverse titrations in which the concentration of sugar **2a** or **3a** was held constant and that of the receptor varied. During the titrations of **2a** or **3a** with **1** the signals due to the OH protons of the sugar shifted downfield with strong broadening and were unobservable after the addition of only 0.1 equiv of the receptor, indicating an important contribution of the OH groups to the complex formation. The complexation between **2a**/**3a** and **1** was further evidenced by significant chemical shift changes of the CH units of the sugar (upfield shifts, as shown for CH-1 in Figure S5, Supporting Information). The results of the NMR spectroscopic titrations indicate the participation of the sugar CH units in the CH···π interactions with the aromatic core of **1**.

In both cases, **2a·1** and **3a·1**, the best fit of the titration data was obtained with the "mixed" 1:1 and 1:2 sugar–receptor binding model; thus, the inverse titrations supported the existence of 1:1 and 2:1 receptor–sugar complexes in chloroform solution, with a stronger association constant for the 1:1 binding and a weaker association constant for the 2:1 receptor–sugar complex. The association constants obtained on the basis of these titrations are identical within the limits of uncertainty to those determined from titrations where the role of receptor and substrat was reversed.

Molecular modeling calculations (see Figure 5) also showed that the binding pocket of **1** has the correct shape and size for the encapsulation of glucopyranoside **2a** or **3a**; examples of binding motifs indicated by molecular modeling are shown in Figure 5, as well as Figure S8 in the Supporting Information. The hydrogen-bonding motif shown in Figure 5c is similar to that observed between the phenanthroline group and a water molecule in the crystal structure of **1** (see Figure 2b).

Binding studies with β-galactopyranoside **4a** showed that the interactions of receptor **1** with this monosaccharide are less favorable than those with glucopyranosides **2a** and **3a**. During the titrations of **1** with **4a** in $CDCl_3$ the signals due to the amine NH^A and amide NH^D of receptor **1** moved downfield and, in contrast to the titrations with **2a** and **3a**, were still observable even after the addition of 3 equiv of **4a** (see Figure 4b and in the Supporting Information Figure S3b). Furthermore, the ^1H NMR titrations of **1** with **4a** produced chemical shift changes of the $CH_2{}^{B,C,E}$, $CH_3{}^{F,G}$, pyridine $CH^{H,I}$, as well as phenanthro-

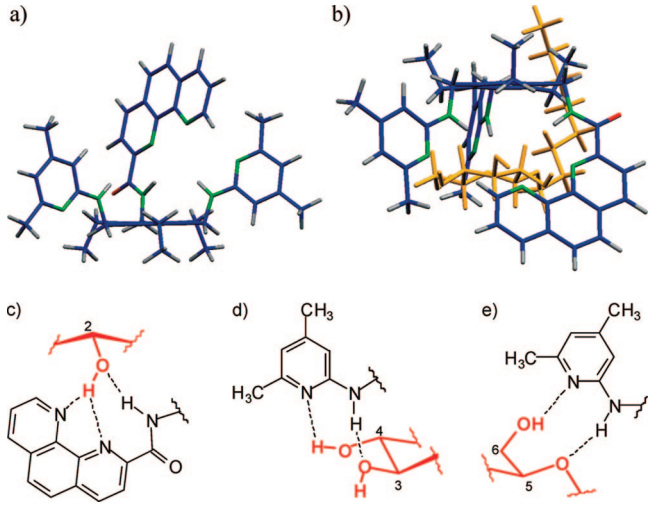


FIGURE 5. (a, b) Energy-minimized structure of the receptor **1** and the 1:1 complex formed between receptor **1** and β-glucopyranoside **2a** (MacroModel V.8.5, OPLS-AA force field, MCMM, 50000 steps). Color code: receptor C, blue; O, red; N, green; the sugar molecule is highlighted in orange. (c−e) Examples of hydrogen-bonding motifs indicated by molecular modeling studies in the 1:1 complex between receptor **1** and α-glucopyranoside **3a**.

line CH groups (see Table 1). In contrast to the titrations with β- and α-glucopyranoside, **2a** and **3a**, no splitting of the CH_2^B and CH_2^C signals of **1** was observed after the addition of the β-galactopyranoside **4a**, as shown in Figure 4b. The curve fitting of the titration data indicated again the formation of complexes with 1:1 and 2:1 receptor−sugar stoichiometry (this binding model was further supported by the mole ratio method); the binding constants were determined to be 9550 (K_{11}) and 1030 (K_{21}) M^{-1} (see Table 1). Thus, the complexes formed between receptor **1** and glucopyranosides **2a** and **3a** are much more stable than those formed with the β-galactopyranoside **4a**.

Further evidence for the strong complexation of α- and β-glucoside and a weaker binding of β-galactoside by receptor **1** was provided by extraction experiments (extraction of sugars from the solid state into a 1.1 mM $CDCl_3$ solution of receptor **1**; see Figure 6). Furthermore, these experiments indicated the formation of strong complexes with α-galactoside and L-fucose.

Receptor **1** solubilized the tested sugars **2b**, **3b**, **4b**, and **5**−**9** in $CDCl_3$ to different extents (the ^{1}H NMR signals of the corresponding sugar were integrated with respect to the receptor's signals to provide the sugar−receptor ratio); the extractability decreased in the sequence α-glucoside **3b** > α-galactoside **5** > β-glucoside **2b** > fucose **9** > β-galactoside **4b** > *N*-acetylgalactosamine **8** > α-mannoside **6** > *N*-acetylglucosamine **7** (control experiments were performed in the absence of **1**). Receptor **1** was able to dissolve 1 equiv of α-glucoside **3b** and α-galactoside **5**, 0.5 equiv of β-galactoside **4b**, and about 0.2 equiv of α-mannoside **6**. The preference of **1** for α-glucoside vs the β-anomer indicated by ^{1}H NMR spectroscopic titrations was also suggested by the extraction experiments. These experiments indicated not only the α- vs β-anomer preference in the recognition of glucopyranosides (**3b** vs **2b**) but also that in the recognition of galactopyranosides (**5** vs **4b**).

Conclusions

The binding studies showed that acyclic receptor **1**, containing phenanthroline- and aminopyridine-based binding subunits,

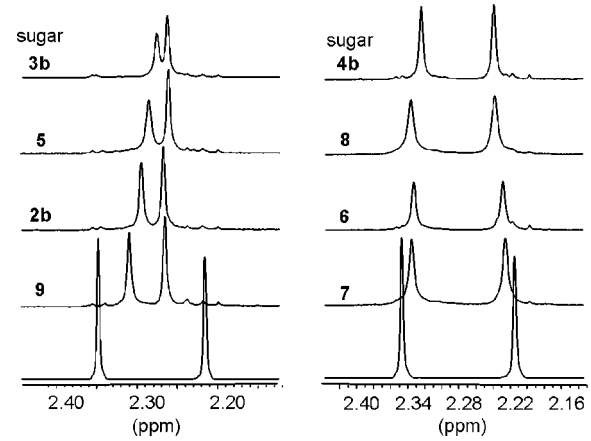


FIGURE 6. Partial ^{1}H NMR spectra (400 MHz) of receptor **1** before (bottom) and after the extraction of solid methyl β-D-glucopyranoside (**2b**), methyl α-D-glucopyranoside (**3b**), methyl β-D-galactopyranoside (**4b**), methyl α-D-galactopyranoside (**5**), methyl α-D-mannopyranoside (**6**), *N*-acetyl-D-glucosamine (**7**), *N*-acetyl-D-galactosamine (**8**), and L-fucose (**9**) by a $CDCl_3$-solution of receptor **1** (1.10 mM). Shown are chemical shifts of the $CH_3^{G,H}$ signals of **1**.

performs effective recognition of neutral carbohydrates through multiple interactions. Both hydrogen bonding and interactions of the sugar CH's with the phenyl rings of the receptor[13,14] (as characterized by ^{1}H NMR spectroscopy) contribute to the stabilization of the receptor−sugar complexes. The comparison of the binding properties of receptor **1** with those of the previously described symmetrical pyridine-based analogue **10**[41] shows that combining phenanthroline- and aminopyridine-based recognition units significantly affects the binding affinity and selectivity of the new receptor (for comparison of the binding constants, see Table 1). Compared to **10**,[41] receptor **1** exhibits not only significantly higher binding affinities but also different binding preferences. The phenanthroline unit has been established as a valuable building block for the construction of carbohydrate receptors. The results obtained with receptor **1** serve as a basis for the development of new phenantroline-based receptors, incorporating both neutral and ionic hydrogen-bonding sites for the recognition of saccharides in organic and aqueous media.

Experimental Section

1-[*N*-(1,10-Phenanthrolin-2-ylcarbonyl)aminomethyl]-3,5-bis[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (1). (a) Synthesis of 19: A mixture of 1,10-phenantroline-2-carboxylic acid (**18**)[9] (0.30 g, 1.34 mmol) and thionyl chloride (20 mL) was refluxed for 6 h. The thionyl chloride was then removed in vacuum. Afterward, THF (3 × 20 mL) was added and the solvent was removed in vacuum. The crude product was used directly for further reaction. **(b) Synthesis of 1:** A solution of **19** in THF/CH_2Cl_2 (1:1, v/v; 40 mL) was added dropwise to a solution of 1-aminomethyl-3,5-bis[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-trieth-

(13) For some discussions on carbohydrate−aromatic interactions, see: (a) Terraneo, G.; Potenza, D.; Canales, A.; Jiménez-Barbero, J.; Baldridge, K. K.; Bernardi, A. *J. Am. Chem. Soc.* **2007**, *129*, 2890–2900. (b) Chávez, M. I.; Andreu, C.; Vidal, P.; Aboitiz, N.; Freire, F.; Groves, P.; Asensio, J. L.; Asensio, G.; Muraki, M.; Cañada, F. J.; Jiménez-Barbero, J. *Chem. Eur. J.* **2005**, *11*, 7060–7074. (c) Kiehna, S. H.; Laughrey, Z. R.; Waters, M. L. *Chem. Commun.* **2007**, 4026–4028. (d) Screen, J.; Stanca-Kaposta, E. C.; Gamblin, D. P.; Liu, B.; Macleod, N. A.; Snoek, L. C.; Davis, B. G.; Simons, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3644–3648. (e) Morales, J. C.; Penadés, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 654–657.

(14) For examples of CH−π interactions in the crystal structures of the complexes formed between artificial receptors and carbohydrates, see ref 4k.

ylbenzene (**14**)[4b] (0.473 g, 1.03 mmol) and triethylamine (0.28 mL) in THF/CH_2Cl_2 (50 mL). After complete addition, the mixture was stirred at room temperature for 48 h. The reaction mixture was then treated with water (15 mL) and stirred for 15 min, then the organic solvents were removed in vacuum. The resulting precipitate was filtered, washed with water, dried, and recrystallized from THF/hexane. Yield 93%. Mp 129−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7.6 Hz, 3H), 1.22 (t, J = 7.6 Hz, 6H), 2.14 (s, 6H), 2.26 (s, 6H), 2.71 (q, J = 7.6 Hz, 2H), 2.82 (q, J = 7.6 Hz, 4H), 4.34 (d, J = 2.3 Hz, 4H), 4.55 (br s, 2H), 4.78 (d, J = 4.6 Hz, 2H), 6.04 (s, 2H), 6.22 (s, 2H), 7.58 (m, 1H), 7.75 (s, 2H), 8.18 (dd, J = 8.1/1.5 Hz, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 9.06 (dd, J = 4.5/1.5 Hz, 1H), 9.22 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 16.9, 21.1, 22.9, 23.2, 23.9, 38.5, 40.7, 103.7, 113.7, 121.6, 123.4, 126.5, 127.8, 128.9, 130.0, 131.9, 132.9, 136.5, 137.4, 143.7, 144.1, 144.4, 145.6, 148.9, 149.9, 150.1, 156.3, 158.2, 164.5. HR-MS calcd for $C_{42}H_{47}N_7O$ 665.3837, found 665.3836. R_f 0.44 (aluminum oxide, diethyl ether/chloroform 15:1 v/v).

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Supporting Information Available: Further examples of ^{1}H NMR titrations (Figures S1−S5), representative mole ratio plots (Figure S6), copies of the ^{1}H and ^{13}C NMR spectra of **1** (Figures S9 and S10), and crystal data and structure refinement for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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