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Oxime-Based Receptors for Mono- and Disaccharides

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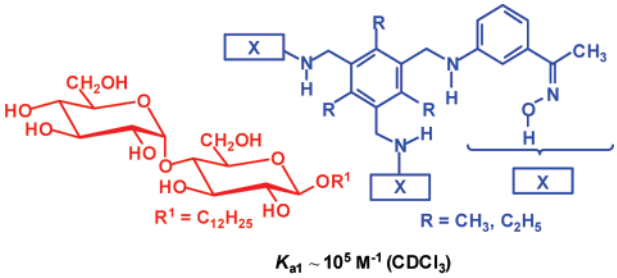

Representatives of a new series of acyclic oxime-based receptors were prepared and their binding properties toward neutral sugar molecules studied. ^{1}H NMR and fluorescence titrations revealed that receptors **2a** and **2b**, incorporating suitable positioned amine and oxime moieties, are able to form strong 1:1 complexes ($K_{a1} \sim 10^5$ M^{-1}) with dodecyl α- and β-maltoside in chloroform solutions. Furthermore, the binding studies with β-glucopyranoside indicated the formation of complexes with 1:1 and 1:2 receptor−monosaccharide binding stoichiometry (with overall binding constant $\beta_2 \sim 10^5$ M^{-2}). Both hydrogen bonding and interactions of the sugar CH's with the phenyl rings of the receptor contribute to the stabilization of the receptor−sugar complexes. Molecular modeling calculations, synthesis, and binding studies are described.

Introduction

X-ray crystallographic data revealed that a number of interactions contribute to the stabilization of protein−carbohydrate complexes, including neutral and ionic hydrogen bonds, metal coordination, and packing of aromatic side chains against the sugar rings.[1] An excellent example of the extensive use of polar and aromatic residues in binding oligosaccharides can be observed in the crystal structure of the maltose-binding protein (MBP) containing the bound maltose.[1i] As reported by Quiocho et al.,[1i] the maltose is buried in the binding groove and almost completely inaccessible to the bulk solvent. The binding of maltose results in the formation of eleven direct hydrogen bonds with eight residues of MBP and five indirect hydrogen bonds via water molecules. A large number of aromatic residues are in or close to the maltose-binding groove and play an important role in maltose binding. Quiocho et al. pointed out that "the maltose is wedged between four aromatic side chains and the resulting stacking of these aromatic residues on the faces of the glucosyl units provides a majority of the van der Waals contacts in the complex."[1i]

Recently, we have shown that acyclic biphenyl-based receptor, incorporating four heterocyclic recognition groups based on 2-aminopyridine unit, is able to bind dodecyl β-D-maltoside in chloroform and water-containing chloroform solutions with remarkable affinity.[2] The hydrogen-bonding receptor has the tendency to form strong 2:1 receptor−maltoside complexes (K_a

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$> 10^6\ M^{-1}$) in which the biphenyl units of the both receptors stack on the sugar rings. Furthermore, this receptor shows β versus α binding selectivity in the recognition of maltosides as well as di- versus monosaccharide selectivity[2] (for examples of other carbohydrate receptors reported by our group, see ref 3; for reviews on carbohydrate recognition with artificial receptors, see ref 4; for some recent examples of carbohydrate receptors operating through noncovalent interactions, see ref 5).

Quiochio has shown that the hydrogen bonds between sugar-binding proteins and essential recognition determinants on sugars are shielded from bulk solvent, meaning that they exist in a lower dielectric environment.[1b−d,i] Thus, investigations with synthetic receptors in organic media (see also refs 6 and 7) can make an important contribution to our understanding of the complex carbohydrate binding processes in nature (recognition of neutral sugars in aqueous solution through noncovalent interactions remains an important challenge in artificial receptor chemistry; for some examples, see refs 3d, 5e, 8).

In this study, we focused on interactions of receptors **2a** and **2b**, incorporating suitably positioned amine and oxime moieties, with neutral carbohydrates in organic media. The receptor molecules were expected to complex carbohydrates through hydrogen bonds in combination with the interactions between the faces of the sugars and the four aromatic rings of the receptors (similar to the complex between MBP and maltose, in which the maltose is wedged between four aromatic side chains, see above; for recent discussions on the importance of carbohydrate-aromatic interactions, see ref 9). The interactions involving pairs of OH···N hydrogen bonds, which are observed between oxime functionalities in the crystal structures,[10,11] have inspired the using of the oxime groups as hydrogen-bonding sites for carbohydrates. The three oxime groups of the receptors **2a** and **2b** were expected to participate in oxime−N···HO−sugar, ═N−OH···OH−sugar, and ═N−OH···O−ring hydrogen bonds with the essential recognition determinants on sugars. Furthermore, the hydrogen bonds between the suitable positioned amine groups of the receptors and the hydroxy groups of the sugars were expected to provide further stabilization of the receptor−sugar complexes. The formation of the above-mentioned interactions was also indicated by molecular modeling studies.

The potential of oxime-based receptors in carbohydrate recognition has not been explored so far. It should be also noted that oximes[10] have received far less attention in supramolecular chemistry than other compounds such as carboxylic acids and amides.[11]

Results and Discussion

To evaluate the recognition capabilities of receptors **2a** and **2b** in aprotic solvents, such as chloroform, and compare the binding properties with the properties of the previously published receptors, the dodecyl β-D-maltoside (**3**), dodecyl α-D-maltoside (**4**) and octyl β-D-glucopyranoside (**5**) were selected as substrates.

Molecular modeling calculations indicated that the acyclic scaffold of **2a** and **2b** provides a cavity of the correct shape and size for disaccharide encapsulation (see Figure 1a). In the case of monosaccharide, two molecules can be bound into the cavity of the receptors (see Figure 1b).

Compounds **2a** and **2b** were obtained by oximation of the corresponding ketones **1a** and **1b**, which were prepared via a

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(6) The importance of the model studies in organic media has been pointed out by Gokel et al.: Pajewski, R.; Ferdani, R.; Pajewska, J.; Li, R.; Gokel, G. W. *J. Am. Chem. Soc.* **2005**, *127*, 18281−18295: "In a recent and excellent review by Kubik and co-workers titled 'Recognition of Anions by Synthetic Receptors in Aqueous Solution,' the authors state that 'the chemistry of life mainly takes place in water...' While this is true in the broadest sense, relatively little biological chemistry takes place in bulk water per se. Instead, biological reactions and interactions occur in or between proteins or membranes or both. Assuredly, cytosolic proteins interact with numerous species, but most recognition, catalysis, signaling, and other processes occur in enzyme pockets or in or on membranes. This contradiction in medium requirements presents the organic chemist with the challenge of developing a model system that is truly suitable for the study of biological phenomena."

(7) Many biological interactions occur in enzyme pockets or in membranes, meaning that they occur in an environment with a lower dielectric constant relative to the bulk solvent. For this reason, many theoretical studies on different enzyme model systems have been performed in a medium with a lower dielectric constant (mostly $\epsilon = 5.7$). See, for example: (a) Cho, K.-B.; Moreau, Y.; Kumar, D.; Rock, D. A.; Jones, J. P.; Shaik, S. *Chem. Eur. J.* **2007**, *13*, 4103−4115. (b) de Visser, S. P.; Shaik, S.; Sharma, P. K.; Kumar, D.; Thiel, W. *J. Am. Chem. Soc.* **2003**, *125*, 15779−15788. (c) de Visser, S. P. *J. Phys. Chem. A.* **2005**, *109*, 11050−11057.

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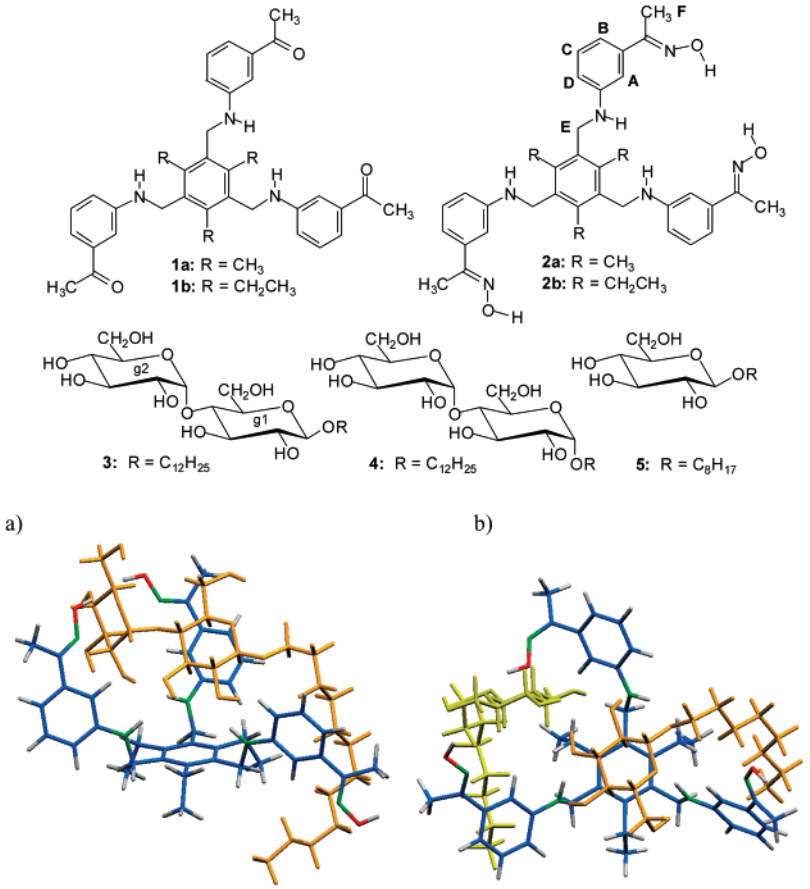

FIGURE 1. (a) Energy-minimized structure of the 1:1 complex formed between receptor **2b** and β-maltoside **3**. (b) Energy-minimized structure of the 1:2 receptor−sugar complex formed between receptor **2b** and β-glucopyranoside **5**. MacroModel V.6.5, Amber* force field, Monte Carlo conformational searches, 100000 steps. Color code: receptor C, blue; receptor N, green; receptor O, red; the sugar molecules are highlighted in yellow or orange.

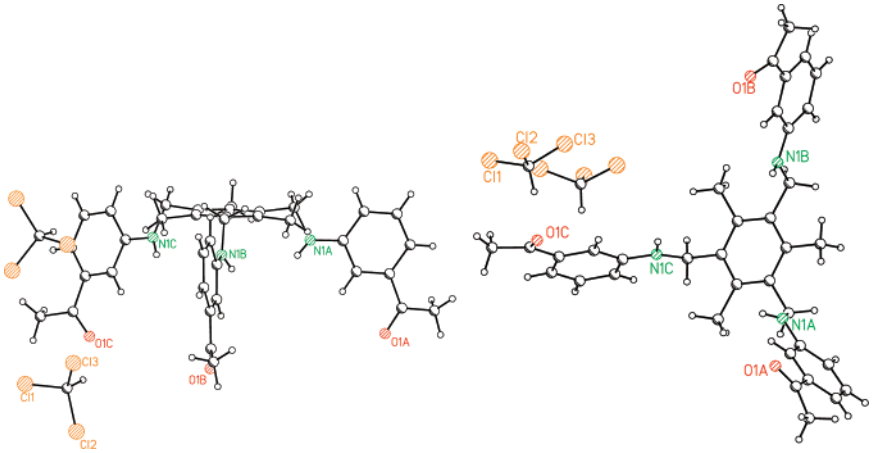

FIGURE 2. Molecular structure of **1a** in the crystal ($CHCl_3$ molecules are included in the crystal), top and side views.

reaction of 1,3,5-tris(bromomethyl)-2,4,6-trimethyl-[12] or -2,4,6-triethylbenzene[13] with 3-aminoacetophenone (see the Experimental Section). The crystal structures of **1a** and **1b** are shown in Figures 2 and 3, respectively (the crystals of **1a** were obtained from methanol/chloroform solution, those of **1b** from toluene/ethyl acetate solution). It should be noted that the three $CH_3C(=O)$-substituted phenyl rings of **1a** and **1b** point to the same face of the central phenyl ring.

The interactions of the receptors and carbohydrates were investigated by ^{1}H NMR and fluorescence spectroscopy.[14,15] The ^{1}H NMR binding titration data were analyzed using the Hostest 5.6[16] and the HypNMR 2006 programs[17] (stoichiometry of the receptor-sugar complexes was determined by mole ratio plots

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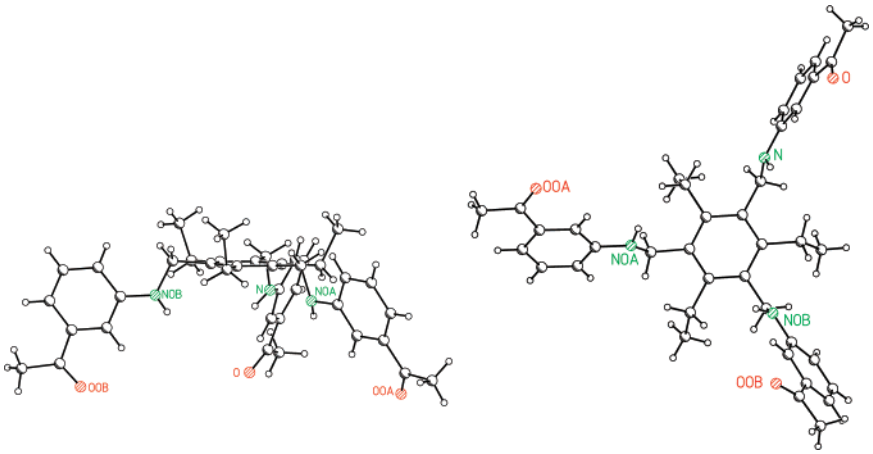

FIGURE 3. Molecular structure of **1b** in the crystal, top and side views.

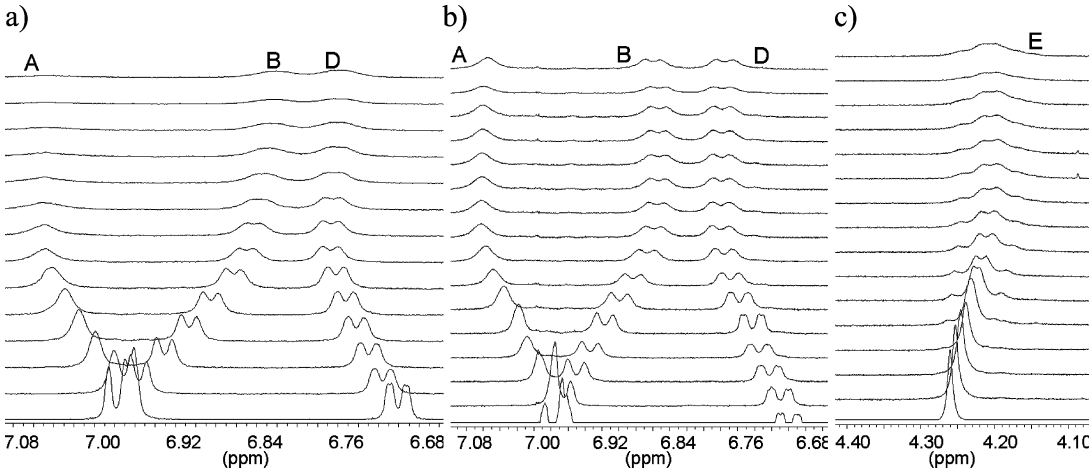

FIGURE 4. (a) Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$) of **2b** after addition of (from bottom to top) 0.00, 0.15, 0.30, 0.46, 0.60, 0.81, 1.01, 1.31, 1.66, 2.17, 2.78, 3.13, 3.63, and 4.04 equiv of β-maltoside **3** ([**2b**] = 0.93 mM). Shown are chemical shifts of the phenyl CH resonances of **2b** (protons A, B, and D; for labeling, see formula **2b**). (b and c) Partial ^{1}H NMR spectra of **2b** after addition of (from bottom to top) 0.00, 0.15, 0.30, 0.45, 0.61, 0.82, 1.02, 1.32, 1.68, 2.19, 2.81, 3.16, 3.67, 4.08, 4.34 and 4.59 equiv of α-maltoside **4** ([**2b**] = 0.93 mM). Shown are chemical shifts of the phenyl CH and CH_2 resonances of **2b** (protons A, B, D, and E; for labeling, see formula **2b**).

and by the curve-fitting analysis of the titration data). The fluorescence binding titration data were analyzed using the Hyperquad 2006 program.[17]

Binding Studies with Disaccharides 3 and 4. β-Maltoside **3** is poorly soluble in $CDCl_3$ but could be solubilized in this solvent in the presence of the receptor **2a** or **2b**, indicating favorable interactions between **3** and **2a**/**2b**. Thus, the receptor in $CDCl_3$ was titrated with a solution of maltoside dissolved in the same receptor solution. The complexation between **2a**/**2b** and disaccharide **3** was evidenced by several changes in the NMR spectra. During the titrations of **2a** and **2b** with **3** the signal due to the amine NH moved downfield with strong broadening and was almost unobservable after the addition of only 0.4 equiv of β-maltoside **3**. The oxime OH signal shifted downfield by about 1.8 ppm with broadening; the addition of 1 equiv of sugar **3** led to practically complete complexation of **2a** or **2b**. Furthermore, the ^{1}H NMR spectra showed changes in the chemical shifts of the CH_3 (protons F), CH_2 (protons E), and phenyl CH resonances of **2a** and **2b** (Figure 4). The signals of the CH_2 and CH_3 protons moved upfield by ~0.07 and 0.08 ppm, respectively (splitting of the CH_2 signal of **2a** and **2b** was observed after the addition of about 0.6 equiv of **3**). The signals due to the phenyl CH protons shifted up- (protons B) or downfield (protons A, C, D) in the range of 0.05−0.16 ppm with broadening, as shown in Figure 4a. The shifts of the CH_2, CH_3 and aromatic CH protons of **2a** or **2b** were monitored as a function of sugar concentration. A typical titration plot is shown in Figure 5a. Both the fitting the titration data and the mole ratio plots (see Figure S11, Supporting Information) indicated the formation of complexes with 1:1 binding stoichiometry. The association constant of 96400 M^{-1} (K_{a1}) was determined for **2a**·**3**, whereas that for **2b**·**3** amounted to 100500

(14) (a) The binding constants were determined in chloroform at 25 °C by titration experiments. Dilution experiments show that receptors do not self-aggregate in the used concentration range. For each system, at least three ^{1}H NMR titrations were carried out; for each titration 15−20 samples were prepared (for a description of titration experiments with maltoside **3** and glucopyranoside **5**, see the Supporting Information). (b) Error in a single K_a estimation was <10%. (c) K_{a1} corresponds to the 1:1 association constant. K_{a2} corresponds to the 1:2 receptor/sugar association constant. $\beta_2 = K_{a1}K_{a2}$.

(15) (a) For each system at least two fluorescence titrations were carried out; for each titration 20 samples were prepared. (b) Error in a single K_a estimation was <15%.

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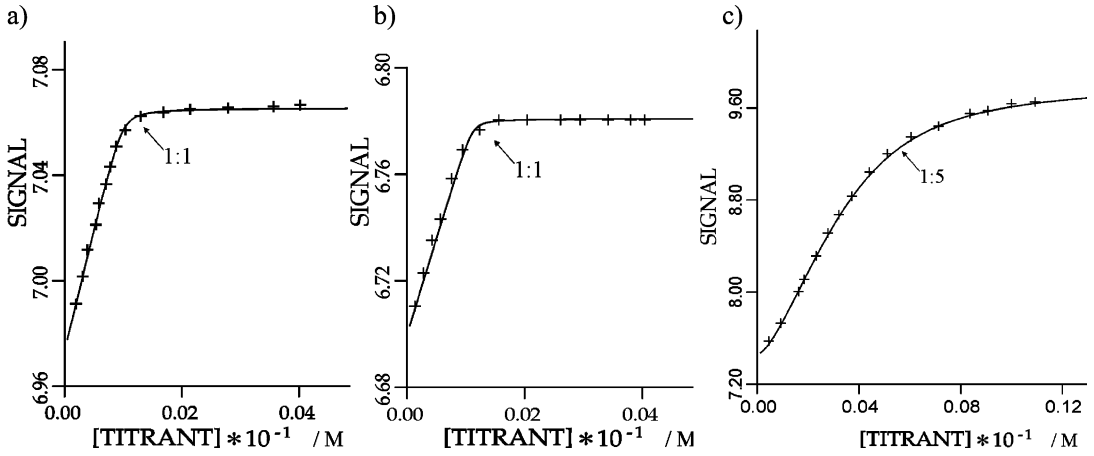

FIGURE 5. Plot of the observed (x) and calculated (−) chemical shifts of the phenyl CH resonances of **2a** (0.90 mM) as a function of added *β*-maltoside **3** (a), phenyl CH resonances of **2b** (0.93 mM) as a function of added α-maltoside **4** (b), and oxime OH resonances of **2b** (1.00 mM) as a function of added *β*-glucopyranoside **5** (c). The [receptor]/[sugar] ratio is marked.

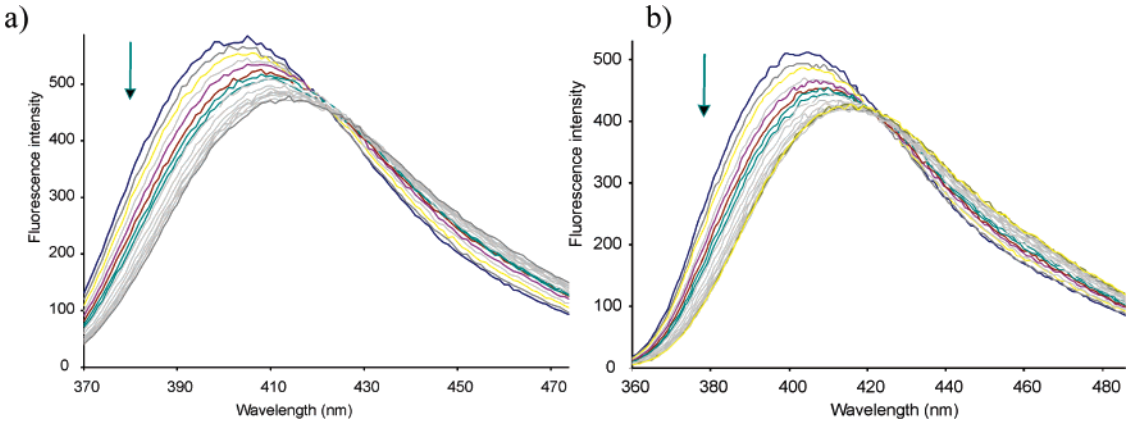

FIGURE 6. Fluorescence titration of receptor **2b** with *β*-maltoside **3** (a) and α-maltoside **4** (b) in $CHCl_3$; [**2b**] = 0.22 and 0.18 mM; equiv of **3** = 0.00, 0.10, 0.21, 0.31, 0.42, 0.52, 0.63, 0.73, 0.84, 0.94, 1.05, 1.26, 1.47, 1.68, 1.89, 2.10, 2.53, 2.95, 3.37, 3.58; equiv of **4** = 0.00, 0.11, 0.22, 0.33, 0.43, 0.54, 0.65, 0.76, 0.87, 0.98, 1.09, 1.30, 1.52, 1.73, 1.95, 2.17, 2.60, 3.04, 3.47, 3.69.

M^{-1} (the binding constants are almost too high to measure by NMR technique[18]).

α-Maltoside **4** is almost insoluble in $CDCl_3$ but could also be solubilized in this solvent in the presence of the receptor **2b** (in contrast to our previously described studies with the biphenyl-based receptor[2]). The ^{1}H NMR titrations of **2b** with α-maltoside **4** produced similar spectral changes as those with *β*-maltoside **3**. The amine NH resonances of **2b** broaden during the titration and were almost unobservable after the addition of about 0.4 equiv of α-maltoside **4**. The signal due to the oxime OH of **2b** moved downfield by ∼1.60 ppm with strong broadening; after the addition of 1 equiv of sugar **4** almost no more change was observed in the NMR spectra. In addition, the signals due to the CH_2 and CH_3 protons shifted upfield by ∼0.06 and 0.10 ppm, respectively (splitting of the CH_2 signal of **2b** was observed after the addition of about 0.6 equiv of **4**; see Figure 4c**)**. Similar to the titration with *β*-maltoside **3,** the signals of the phenyl CH protons of **2b** shifted up- and downfield (in the range of 0.08−0.12 ppm) during the titration with α-maltoside **4**, as shown in Figure 4b. The fit of NMR shift changes of the methyl, methylene and phenyl CH resonances agreed again with 1:1 receptor−sugar binding model (for example, see Figure 5b); The binding constant for **2b·4** was found to be 65300 M^{-1} (K_{a1}).[14b,c] Thus, ^{1}H NMR titrations indicated that the receptor **2b** exhibited about 1.5-fold higher affinity for *β*-maltoside **3** than for the α-anomer **4**.

The formation of strong complexes between the receptors **2a** or **2b** and disaccharides **3** or **4** was also confirmed by fluorescence spectroscopy. The fluorescence titration experiments were carried out by adding increasing amounts of the sugar **3** or **4** (both disaccharides are soluble in $CHCl_3$ in the concentration range required for fluorescence titrations) to a $CHCl_3$ solution of the receptor **2a** or **2b** (for example, see Figure 6). The best fit of the titration data (at 396 nm) was obtained with 1:1 binding model; the formation of the 1:1 complexes was further supported by the mole ratio plots. The binding constant for **2a·3** was found to be 93000 M^{-1}, that for **2b·3** amounted to 98900 M^{-1}. The binding constants for **2a·4** and **2b·4** were found to be 58600 and 62000 M^{-1}, respectively. Thus, the binding constants are comparable with those determined on the base of the NMR spectroscopic titrations.

According to molecular modeling calculations the 1:1 receptor−maltoside complexes can potentially be stabilized by several hydrogen bonds between the OH groups of the sugar and the amine-NH, oxime-OH, and oxime-N of the receptor **2a** or **2b**. Furthermore, CH···N/O hydrogen bonds and interactions of

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

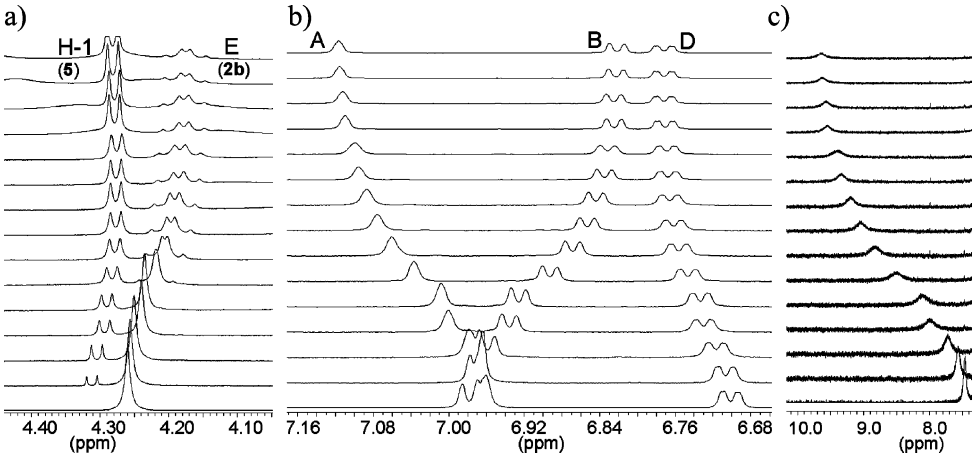

FIGURE 7. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$) of **2b** after addition of (from bottom to top) 0.00, 0.46, 0.92, 1.61, 1.84, 2.77, 3.69, 4.39, 5.08, 6.01, 7.16, 8.32, 9.01, 9.94, and 10.86 equiv of **5** ([**2b**] = 1.01 mM). Shown are chemical shifts of the CH_2 (a), phenyl CH (b), and oxime OH (c) resonances of **2b** (for labeling, see formula **2b**).

sugar CHs with the phenyl groups of the receptor molecule should provide an additional stabilization of the receptor−sugar complex. In the case of **2b·3**, the 2- and 4-OH groups and the ring oxygen atom of the glucosyl unit g2 (for labeling see formula **3**) participate in NH···OH-2, =N−OH···OH-4, and =N−OH···O-ring hydrogen bonds, respectively. The 2- and 3-OH groups of the g1 unit are involved in hydrogen bonds with two NH groups of the receptor (NH···OH-2, NH···OH-3). In addition, the 3-OH group of the g1 unit participates in OH··· Ph interaction. The CH-3 and -5 of the g2 unit are involved in CH···N interactions with the oxime-N, whereas the CHs in the positions 1, 3 and 5 of the g1 unit participate in CH-π interactions (CH−π distances, 2.6−2.9 Å) with the phenyl ring of the receptor **2b** (see Figure 1a).

Binding Studies with β-Glucopyranoside 5. The ^{1}H NMR titration experiments with β-glucopyranoside **5** were carried out by adding increasing amounts of the sugar to a $CDCl_3$ solution of the receptor **2a** or **2b**. Similar to the binding studies between **2a**/**2b** and sugars **3** or **4**, the complexation between **2a**/**2b** and glucopyranoside **5** was evidenced by several changes in the NMR spectra. However, whereas after the addition of 1 equiv of β- or α-maltoside almost no more change was observed in the chemical shift of the receptor signals, with the monosaccharide **5** chemical shift changes continue to higher [sugar]/[receptor] ratios. During the titration with **5** the signal due to the amine NH of **2a**/**2b** moved downfield by about 1.5 ppm (after the addition of 5 equiv of sugar). In contrast to the titrations with disaccharides **3** and **4**, the NH signal of **2a** or **2b** was still observable even after the addition of 10 equiv of **5**. The oxime OH signal shifted significantly downfield by about 2.2 ppm with broadening (see Figure 7c). Furthermore, the ^{1}H NMR spectra showed changes in the chemical shifts of the phenyl CH's (up- or downfield shifts in the range of 0.07−0.16 ppm), CH_2 and the CH_3 protons (upfield shifts, in the range of 0.04−0.09 ppm), as illustrated in Figure 7a,b. The curve fitting of the titration data suggested the existence of 1:1 and 1:2 receptor−monosaccharide complexes in the chloroform solution (typical titration curve is shown in Figure 5c). The binding constants for **2a·5** were found to be 140 (K_{a1}) and 1380 (K_{a2}) M^{-1} ($\beta_2 = 1.93 \times 10^5$ M^{-2}), whereas those for **2b·5** amounted to 170 (K_{a1}) and 1730 (K_{a2}) M^{-1} ($\beta_2 = 2.98 \times 10^5$ M^{-2}).[14c] Thus, the receptor **2b**, based on 2,4,6-triethylbenzene

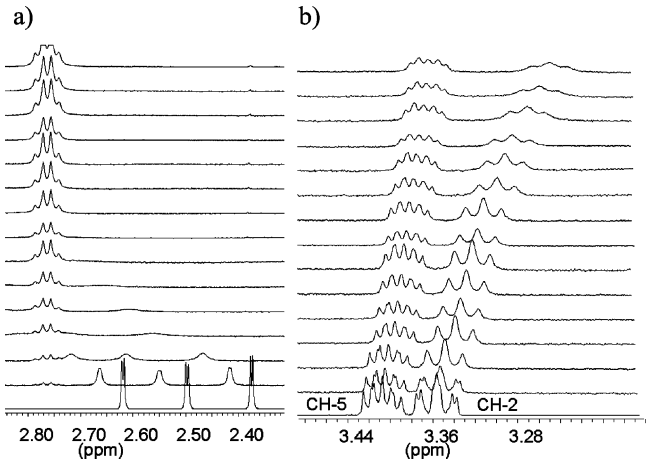

FIGURE 8. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$) of β-glucopyranoside **5** after addition of (from bottom to top) 0.04, 0.09, 0.19, 0.24, 0.29, 0.33, 0.38, 0.43, 0.55, 0.62, 0.70, 0.84, 0.96, and 1.08 equiv of receptor **2b** ([**5**] = 1.20 mM). Shown are chemical shifts of the OH (a) and CH-2 and CH-5 (b) resonances of **5** (in Figure 8a the signals due to CH_2CH_3 of **2b** are also shown).

frame, exhibits about 1.5-fold higher affinity for sugar **5** than the receptor **2**a, based on 2,4,6-trimethylbenzene unit.

In addition, the interactions between **5** and **2b** were investigated on the base of inverse titrations in which the concentration of pyranoside **5** was held constant and that of receptor **2b** varied. During the titration of **5** with **2b** the signals due to the OH protons of **5** shifted downfield with strong broadening and were almost unobservable after the addition of only 0.2 equiv of **2b** (see Figure 8a), indicating important contribution of the OH groups of **5** to the complex formation. The complexation between **5** and **2b** was further evidenced by chemical shift changes of the CH units of **5**. Among the CH signals, the signal of the CH-2 proton **5** shows the largest shift (upfield shift by 0.12 ppm, after the addition of 1 equiv of **2b**, see Figure 8b). Interestingly, the participation of the CH-2 in CH−π interactions was also indicated by molecular modeling (see Figure 1b).

Interaction between **2a** or **2b** and glucopyranoside **5** could also be detected by fluorescence (fluorescence intensity decreased with increasing monosaccharide concentration); however, the spectral changes observed during the fluorescence titrations with glucopyranoside **5** were less substantial than those

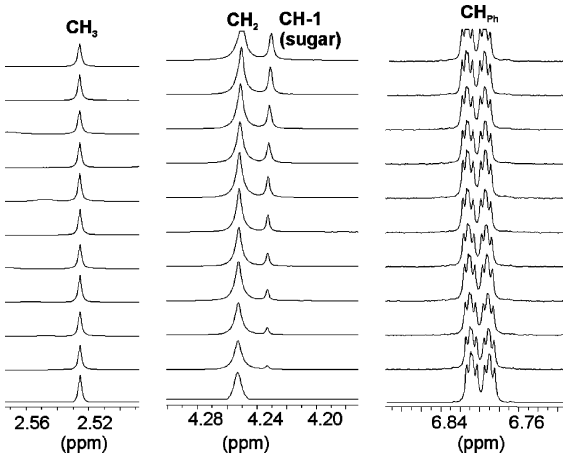

FIGURE 9. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$) of **1a** after addition of (from bottom to top) 0.00−6.11 equiv of **5** ([**1a**] = 0.87 mM).

observed during the titrations with disaccharides **3** and **4**. The analysis of the titration data confirmed the mixed 1:1 and 1:2 receptor−glucopyranoside binding model; the binding constants determined on the base of fluorescence titrations in $CHCl_3$ were comparable with those determined on the base of the NMR spectroscopic titrations.

Comparative binding studies between the ketone **1a** and β-glucopyranoside **5** confirmed the expected very weak interactions between the binding partners. During the ^{1}H NMR titrations of the compound **1a** with β-glucopyranoside **5** the signal due to the NH of **1a** shifted downfield by only 0.05 ppm, whereas the CH, CH_2 and CH_3 signals of **1a** almost did not move ($\Delta\delta < 0.01$ ppm; in contrast to the marked spectral changes observed during the titrations of the oxime-based **2a** with **5**), as shown in Figure 9. Thus, the results of the NMR titrations indicate that the corresponding ketones are not suitable receptors for the recognition of carbohydrates.

Conclusion

Representatives of a new series of acyclic receptors containing neutral hydrogen-bonding sites, such as amine and oxime groups, were prepared and their binding properties toward neutral sugar molecules studied. The formation of complexes has been characterized by ^{1}H NMR spectroscopy and confirmed by a second, independent technique, namely fluorescence spectroscopy. The artificial receptors **2a** and **2b** have been established as highly effective receptors for β- and α-maltosides **3** and **4**.[19] In $CDCl_3$ the binding constants for **2a·3** and **2b·3** were found to be 96400 and 100500 M^{-1}, respectively; those for **2a·4** and **2b·4** amounted to 58600 and 62000 M^{-1}, respectively. ^{1}H NMR titrations indicated that the receptors exhibited about 1.5-fold higher affinity for β-maltoside **3** than for the α-anomer **4.** The binding constants determined on the base of fluorescence titrations in $CHCl_3$ are comparable with those determined on the base of the NMR spectroscopic titrations. Both receptors **2a** and **2b** have the tendency to form strong 1:1 receptor−sugar complexes with β- and α-maltoside (the both glucose units of the disaccharide have the possibility to interact with four phenyl rings of the receptor, these interactions seem to be responsible for the 1:1 binding stoichiometry, as indicated also by molecular modeling calculations), in contrast to the previously described biphenyl-based receptor,[2] which has the tendency to form strong 2:1 receptor−sugar complexes with β-maltoside **3** (the biphenyl units of the both receptors stack on the disaccharide rings).

The NMR and fluorescence spectroscopic binding studies with β-glucopyranoside **5** suggested the formation of complexes with 1:1 and 1:2 receptor−glucopyranoside binding stoichiometry (with overall binding constant $\beta_2 \sim 10^5$ M^{-2}). The binding constants for **2a·5** were found to be 140 (K_{a1}) and 1380 (K_{a2}) M^{-1} ($\beta_2 = 1.93 \times 10^5$ M^{-2}), whereas those for **2b·5** amounted to 170 (K_{a1}) and 1730 (K_{a2}) M^{-1} ($\beta_2 = 2.98 \times 10^5$ M^{-2}). Thus, the receptor **2b**, based on 2,4,6-triethylbenzene frame, exhibits about 1.5-fold higher affinity for sugar **5** than the receptor **2**a, based on 2,4,6-trimethylbenzene unit.

Both hydrogen bonding (for example, NH···OH−sugar, =N−OH···OH−sugar, oxime−N···HC−sugar, phenyl−CH···O−sugar) and interactions of the sugar CH's with the phenyl rings[9,20] of the receptor **2a** or **2b** contribute to the stabilization of the receptor−sugar complexes (the phenyl groups of **2a** and **2b** provide apolar contacts to a saccharide, similar to sugar-binding proteins, which commonly place aromatic surfaces against patches of sugar CH groups).

The selective recognition of neutral carbohydrates by synthetic receptors still represents a significant challenge; thus, artificial carbohydrate receptors operating through noncovalent interactions provide valuable model systems to study the basic molecular features of carbohydrate recognition.

Experimental Section

Analytical TLC was carried out on silica gel 60 F_{254} plates employing ethyl acetate/toluene (3:1, v/v) as the mobile phase. Melting points are uncorrected. Dodecyl β-D-maltoside (**3**), dodecyl α-D-maltoside (**4**), and octyl β-D-glucopyranoside (**5**) are commercially available.

General Procedure for the Synthesis of 1a and 1b. To a mixture of 1,3,5-tris(bromomethyl)-2,4,6-trimethyl- or -2,4,6-triethylbenzene (3.50 mmol) and K_2CO_3 (11 mmol) in CH_3CN (100 mL) was added dropwise a CH_3CN (20 mL) solution of 3-aminoacetophenone (14 mmol). The mixture was heated under reflux for 36 h. After filtration and evaporation of solvent, the crude product was crystallized from chloroform/ethanol or chloroform/methanol.

1,3,5-Tris[(3-acetylphenyl)aminomethyl]-2,4,6-trimethylbenzene (1a). Yield: 63%. Mp: 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 9 H), 2.59 (s, 9 H), 3.64 (br s, 3 H), 4.32 (s, 6 H), 6.80 (dt, J = 7.4 Hz/1.9 Hz, 3 H), 7.30 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8, 26.7, 43.4, 110.9, 117.6, 118.2, 129.4, 133.8, 137.1, 138.3, 148.4, 198.6. HRMS: calcd for $C_{36}H_{39}N_3O_3$ 561.2986, found 561.2991. $R_f = 0.70$.

1,3,5-Tris[(3-acetylphenyl)aminomethyl]-2,4,6-triethylbenzene (1b). Yield: 60%. Mp: 240−241 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J = 7.4 Hz, 9 H), 2.59 (s, 9 H), 2.76 (q, J = 7.4 Hz, 6 H), 3.66 (br s, 3 H), 4.29 (s, 6 H), 6.86 (dt, J = 7.2 Hz/1.9 Hz, 3 H), 7.32 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 22.9, 26.8, 42.3, 110.8, 117.5, 118.2, 129.4, 133.1, 138.3,

(19) (a) For an example of macrocyclic receptor, which is able to distinguish between the octyl β-D-maltoside and octyl β-D-glucopyranoside in organic media (CD_3CN/CD_3OD, 88:12 v/v), see: Neidlein, U.; Diederich, F. *Chem. Commun.* **1996**, 1493−1494. (b) Selective recognition of oligosaccharides is still rare; for a recent review, see ref 4a; for recent examples, see refs 2 and 5a.

(20) For examples of CH−π interactions in the crystal structures of the complexes formed between artificial receptors and carbohydrates, see ref 3f.

143.9, 148.2, 198.7. HRMS: calcd for $C_{39}H_{45}N_3O_3$ 603.3455, found 603.3449. $R_f = 0.67$.

General Procedure for the Synthesis of 2a and 2b. The mixture of compound **1a** or **1b** (0.5 mmol), hydroxylamine hydrochloride (6 mmol), and sodium hydroxide (5 mmol, added as a 20% aqueous solution) in aqueous ethanol (30 mL) was refluxed for 8 h (the solution was monitored by TLC). After the reaction mixture was cooled, sodium hydroxide (1 mmol) was added, and the reaction mixture was stirred for 1 h. After the addition of water (15 mL) and evaporation of ethanol, the precipitate was filtered off and crystallized from ethanol.

1,3,5-Tris[(3-acetylphenyl)aminomethyl]-2,4,6-trimethylbenzene Trioxime (2a). Yield: 67%. Mp: 170−171 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.11 (s, 9 H), 2.36 (s, 9 H), 4.16 (d, $J = 4.1$ Hz ,6 H), 5.29 (t, $J = 4.1$ Hz, 3 H), 6.75 (dd, $J = 8.1$ Hz/1.5 Hz, 3 H), 6.86 (d, $J = 7.8$ Hz, 3 H), 7.01 (s, 3 H), 7.12 (m, 3 H), 11.00 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.7, 15.4, 42.6, 109.2, 112.6,113.7, 128.7, 133.2, 136.2, 137.6, 148.9, 153.4. HRMS: calcd for $C_{36}H_{42}N_6O_3$ 606.3313, found 606.3312. $R_f = 0.83$.

1,3,5-Tris[(3-acetylphenyl)aminomethyl]-2,4,6-triethylbenzene Trioxime (2b). Yield: 80%. Mp: 133−134 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19 (t, $J = 7.3$ Hz, 9 H), 2.11 (s, 9 H), 2.72 (m, 6 H), 4.17 (d, $J = 3.6$ Hz, 6 H), 5.24 (t, $J = 3.6$ Hz, 3 H), 6.75 (dd, $J = 8.1$ Hz/1.5 Hz, 3 H), 6.87 (d, $J = 7.8$ Hz, 3 H), 7.01 (s, 3 H), 7.13 (m, 3 H), 11.02 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.7, 16.5, 22.6, 40.1, 109.0, 112.7, 113.9, 128.8, 132.7, 137.7, 142.9, 148.7, 153.4. HRMS: calcd for $C_{39}H_{48}N_6O_3$ 648.3782, found 648.3777. $R_f = 0.80$.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1a**,**b** and **2a**,**b** (Figures S1−S10). Representative mole ratio plot (Figure S11). Description of titration experiments with dodecyl β-D-maltoside (**3**) and octyl β-D-glucopyranoside. This material is available free of charge via the Internet at http://pubs.acs.org.

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