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# Recognition Properties of an Acyclic Biphenyl-Based Receptor toward Carbohydrates

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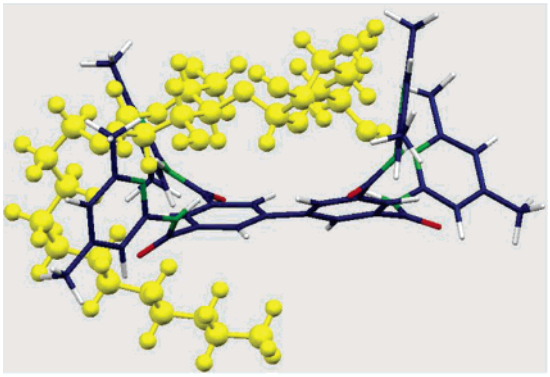

Biphenyl-based receptor **1**, incorporating four heterocyclic recognition units, was synthesized, and its binding properties toward neutral sugars were determined. Receptor **1** is a representative of a new series of acyclic carbohydrate-binding receptors, which were designed to recognize disaccharides. The compound **1** has been established as a highly effective receptor for dodecyl $\beta$-D-maltoside, showing successive 1:1 and 2:1 receptor/substrate complexation behavior toward the disaccharide. Both hydrogen bonding and interactions of the sugar CH's with the aromatic units of the receptor contribute to the stabilization of the receptor−maltoside complexes.

The selective recognition of carbohydrates by synthetic receptors operating through noncovalent interactions still represents a significant challenge (for reviews on carbohydrate recognition with artificial receptors, see ref 1). As pointed out by Davis and Wareham[1b] "synthetic carbohydrate receptors could be used as drugs (e.g., anti-infective agents), to target cell types (acting as synthetic antibodies), to transport saccharides or related pharmaceuticals across cell membranes, or in carbohydrate sensors". Recently, we have shown that acyclic benzene-spaced receptors (for example, amino- and amidopyridine receptors based on a 2,4,6-trimethyl- or 2,4,6-triethylbenzene frame and a 1,3,5-benzenetricarbonyl unit) perform effective recognition of carbohydrates through multiple interactions.[2] The binding modes were discussed in detail on the basis of chemical shift changes in $^1$H NMR spectra, X-ray analyses, and molecular modeling calculations. It is worth noting that the binding motifs found in the crystal structures of the complexes formed between the acyclic receptors and monosaccharides[2c] show remarkable similarity to the motifs observed in the protein−carbohydrate complexes.[3] The molecular structures of the synthetic complexes provide valuable model systems to study the basic molecular features of carbohydrate recognition. The acyclic scaffold provides simplicity in the synthetic plan for many modifications of the receptor structure, supplying a base for systematic studies toward recognition motifs for carbohydrates.

Molecular modeling calculations indicated that a 3,3′,5,5′-tetrasubstituted biphenyl scaffold provides a cavity of the correct shape and size for disaccharide encapsulation. In this paper, we describe the synthesis and binding properties of a representative of the new series of acyclic carbohydrate-binding receptors, which were expected to prefer disaccharides.

In the area of sugar recognition, the biphenyl unit has mostly been used as a building block for macrocyclic receptors.[1,4,5] Particularly interesting biphenyl-based macrocyclic architecture was designed by Davis and co-workers.[4] The tricyclic octaamide receptor system was constructed to provide both apolar and polar contacts to a monosaccharide, such as glucose. The recognition properties of a series of tricyclic oligoamides have been explored in organic solvents,[4d] in two-phase systems,[4b,c] and in water.[4a] A related macrotricyclic receptor featuring two 1,1′-biphenyl platforms linked by amide bridges was designed by molecular modeling by Diederich and co-workers.[5] The authors described synthetic routes to 3,3′,5,5′-tetraarylbiphenyls, suitably functionalized for the targeted construction of the macrocyclic system. Suzuki cross-coupling starting from 3,3′,5,5′-tetrabromo-1,1′-biphenyl provided access to a series of extended aromatic platforms for cleft-type and macrocyclic receptors.[5,6]

As a starting point for the design of the acyclic biphenyl-based receptors, we examined the binding properties of the receptor **1**, incorporating four heterocyclic recognition groups based on the 2-aminopyridine unit[7] (our previous binding studies toward monosaccharides showed that aminopyridines and ami-

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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) For a review on boronic acid based receptors, using covalent interactions for sugar binding, see: James, T. D.; Shinkai, S. *Top. Curr. Chem.* **2002**, *218*, 159−200.

(2) (a) Mazik, M.; Cavga, H. *J. Org. Chem.* **2006**, *71*, 2957−2963. (b) Mazik, M.; Kuschel, M.; Sicking, W. *Org. Lett.* **2006**, *8*, 855−858. (c) Mazik, M.; Cavga, H.; Jones, P. G. *J. Am. Chem. Soc.* **2005**, *127*, 9045−9052. (d) Mazik, M.; Radunz, W.; Boese, R. *J. Org. Chem.* **2004**, *69*, 7448−7462. (e) Mazik, M.; Sicking, W. *Tetrahedron Lett.* **2004**, *45*, 3117−3121. (f) Mazik, M.; Bandmann, H.; Sicking, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 551−554. (g) Mazik, M.; Sicking, W. *Chem.—Eur. J.* **2001**, *7*, 664−670. (h) Mazik, M.; Radunz, W.; Sicking, W. *Org. Lett.* **2002**, *4*, 4579−4582.

(3) For examples of the crystal structures of protein−carbohydrate complexes, see: (a) Lis, H.; Sharon, N. *Lectins*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2003. (b) Quiocho, F. A. *Pure Appl. Chem.* **1989**, *61*, 1293−1306. (c) Quiocho, F. A.; Wilson, D. K. *Nature* **1989**, *340*, 404−408. (d) Vyas, N. K.; Vyas, M. N.; Quiocho, F. A. *Science* **1988**, *242*, 1290−1295. (e) Weiss, W. I.; Drickamer, K. *Annu. Rev. Biochem.* **1996**, *65*, 441−473. (f) Lemieux, R. U. *Chem. Soc. Rev.* **1989**, *18*, 347−374. (g) Lis, H.; Sharon, N. *Chem. Rev.* **1998**, *98*, 637−674. (h) Ravishankar, R.; Ravindran, N.; Suguna, A.; Surolia, A.; Vijayan, M. *Curr. Sci.* **1997**, *72*, 855. (i) Spurlino, S. P.; Lu, G.-Y.; Quiocho, F. A. *J. Biol. Chem.* **1991**, *266*, 5202−5219.

(4) (a) Klein, E.; Crump, M. P.; Davis, A. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 298−302. (b) Velasco, T.; Lecollinet, G.; Ryan, T.; Davis, A. P. *Org. Biomol. Chem.* **2004**, *2*, 645−647. (c) Ryan, T. J.; Lecollinet, G.; Velasco, T.; Davis, A. P. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4863−4866. (d) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 2270−2273.

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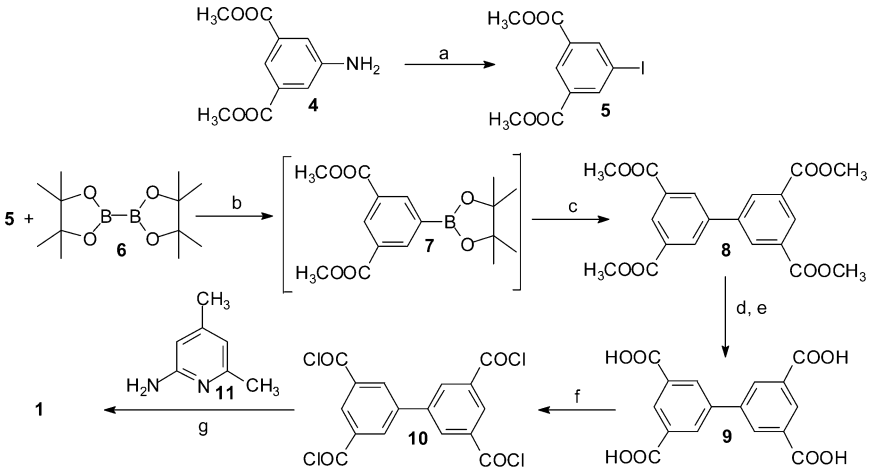
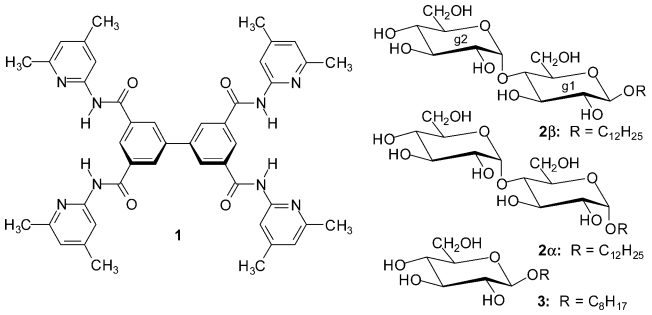
**SCHEME 1. Synthesis of Receptor 1**[a]



[a] Key: (a) $NaNO_2$, 20% HCl, KI, yield = 49%;[6] (b) $PdCl_2$(dppf), KOAc/DMF, 80 °C, 2 h;[10] (c) 2 equiv of **5**, $PdCl_2$(dppf), CsF, 80 °C, 12 h, yield = 82%; (d) 10% NaOH; (e) 50% $H_2SO_4$, yield = 89%; (f) $SOCl_2$, THF; (g) $NEt_3$, THF, yield = 76%.

dopyridines provide an excellent structural motif for binding carbohydrates, associated with the ability to form cooperative and bidentate hydrogen bonds with the sugar OH groups[2]). The biphenyl spacer of **1** provides additional apolar contacts to a saccharide, similar to sugar-binding proteins, which commonly place aromatic surfaces against patches of sugar CH groups.[3]



To evaluate the recognition capabilities of receptor **1** in aprotic solvents,[8,9] such as chloroform (or water-containing chloroform), and compare the binding properties with the properties of the previously published receptors, the dodecyl $\beta$-D-maltoside (**2**$\beta$), dodecyl $\alpha$-D-maltoside (**2**$\alpha$), and octyl $\beta$-D-glucopyranoside (**3**) were selected as substrates.

The crystal structure of the maltose-binding protein (MBP) with bound maltose shows one of the best examples of the extensive use of polar and aromatic residues in binding oligosaccharides.[3i] The bound maltose is buried in the groove and is almost completely inaccessible to the bulk solvent. The groove is heavily populated by polar and aromatic groups many of which are involved in extensive hydrogen-bonding and van der Waals interactions with the maltose. Quiocho et al.[3i] 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".

The artificial receptor **1** has been established as a highly effective receptor for $\beta$-D-maltoside **2**$\beta$. The synthesis of **1** is shown in Scheme 1 (see also refs 6 and 10). Interactions of this receptor with saccharides were investigated by $^1$H NMR spectroscopy.[11]

Contrary to $\beta$-glucopyranoside **3**, the $\beta$-maltoside **2**$\beta$ is poorly soluble in chloroform, but could be solubilized in this solvent in the presence of receptor **1**, indicating favorable interactions between **1** and **2**$\beta$. Thus, the receptor in $CDCl_3$ was titrated with a solution of maltoside dissolved in the same receptor solution. The shifts of the receptor amide NH, aromatic CH's, and $CH_3$ protons were monitored as a function of sugar concentra-

(6) For examples of other tetrafunctionalized biphenyl building blocks, see: Boomgaarden, W.; Vögtle, F.; Nieger, M.; Hupfer, H. *Chem.—Eur. J.* **1999**, *5*, 345−355.

(7) The 2-aminopyridine unit can be regarded as a heterocyclic analogue of the asparagine/glutamine primary amide side chain. See: Huang, C.-Y.; Cabell, L. A.; Anslyn, E. V. *J. Am. Chem. Soc.* **1994**, *116*, 2778−2792.

(8) Although molecular recognition of carbohydrates is relevant in water, the complexation studies in organic media are also of high importance. Quiocho et al. have 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 (see refs 3b,c,d,i). Thus, the recognition of sugars in lipophilic solvents provides important information about the factors which contribute to the affinity between receptors and saccharides. Such model studies are very useful in the development of both effective and selective receptor architectures.

(9) The importance of the model studies in organic media has been pointed out by Gokel et al. in *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."

(10) For one-pot biaryl synthesis via in situ boronate formation, see: Giroux, A.; Han, Y. X.; Prasit, P. *Tetrahedron Lett.* **1997**, *38*, 3841−3844.

(11) (a) 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 11e). The stoichiometry of receptor−sugar complexes was determined by mole ratio plots and by the curve-fitting analysis of the titration data. Dilution experiments show that receptor **1** does not self-aggregate in the used concentration range. For each system at least three titrations were carried out (for each titration, 12−20 samples were prepared). $CDCl_3$ was deacidified with $Al_2O_3$. (b) Error in a single $K_a$ estimation was <10%. (c) $K_a$ was estimated on the base of a 2:1 receptor/sugar binding model incorporated in the Hostest 5.6 program. (d) $K_{a1}$ corresponds to the 1:1 association constant. $K_{a2}$ corresponds to the 1:2 receptor/sugar association constant. (e) Wilcox, C. S.; Glagovich, N. M. *HOSTEST 5.6*; University of Pittsburgh: Pittsburgh, PA, 1994.

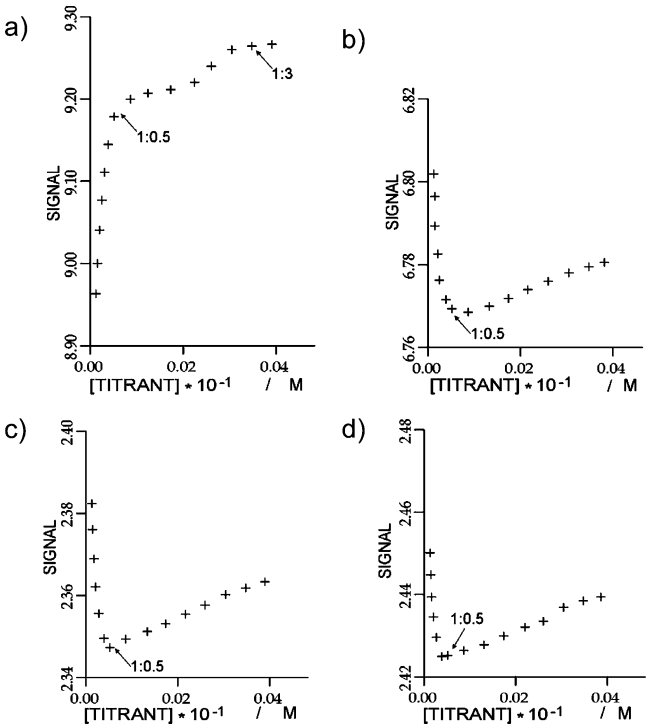



**FIGURE 1.** Plot of the observed chemical shifts of the NH (a), pyridine CH (b), and $CH_3$ (c, d) resonances of **1** as a function of added $\beta$-maltoside **2**$\beta$. The [receptor]:[sugar] ratio is marked.

tion. Interestingly, all of the CH and $CH_3$ signals first shifted upfield until the maltoside/receptor ratio reached 0.5, and then they moved in the opposite direction (Figures 1b−d and Figure S1).[12] The amide NH signal shifted downfield with broadening, as shown in Figure S1a. The plot of the observed chemical shifts of the NH resonances as a function of added $\beta$-maltoside (see Figure 1a) clearly shows two complexation steps.

Analysis of the first part of the titration curve[11e] (see also Figure S13a) indicated the formation of a very strong 2:1 receptor/maltoside complex.[13] The binding constant was estimated to be $K_a > 10^6$ $M^{-1}$.[11c] The titration results clearly indicate that the addition of maltoside to the solution of receptor **1** leads to the predominant formation of a 2:1 receptor/maltoside complex at the initial stages of titration up to a maltoside/receptor ratio of 0.5, which is then gradually replaced by the 1:1 complex (see Figure 2b) with increasing maltoside/receptor ratio. Similar complexation behavior and very strong binding of the maltoside **2**$\beta$ ($K_a > 10^6$ $M^{-1}$) could be also observed in water-containing chloroform solutions ([receptor]:[water] = 1:10, 1:20).[14] Dodecyl α-D-maltoside (**2**α) is poorly soluble in chloroform and could not be solubilized in this solvent in the presence of receptor **1** in the concentration range required for binding studies (contrary to the $\beta$-anomer, which is soluble in the presence of **1**), indicating weaker binding between **1** and the α-anomer. Thus, receptor **1** shows α/$\beta$-anomer selectivity in the recognition of maltosides.

According to molecular modeling calculations, the disaccharide **2**$\beta$ is encapsulated in the cavity between the two receptor

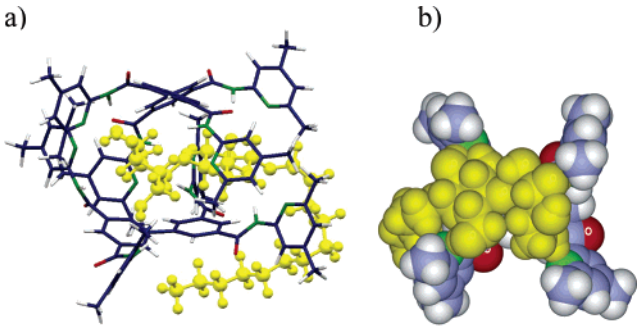



**FIGURE 2.** Energy-minimized structure of the 2:1 and 1:1 complexes formed between receptor **1** and $\beta$-D-maltoside **2**$\beta$ (MacroModel V.6.5, Amber* force field, Monte Carlo conformational searches, 50 000 steps): (a) 2:1 Receptor/sugar complex. (b) Space-filling representation of the 1:1 complex. Color code: receptor C, blue; O, red; N, green; the sugar molecule is highlighted in yellow.

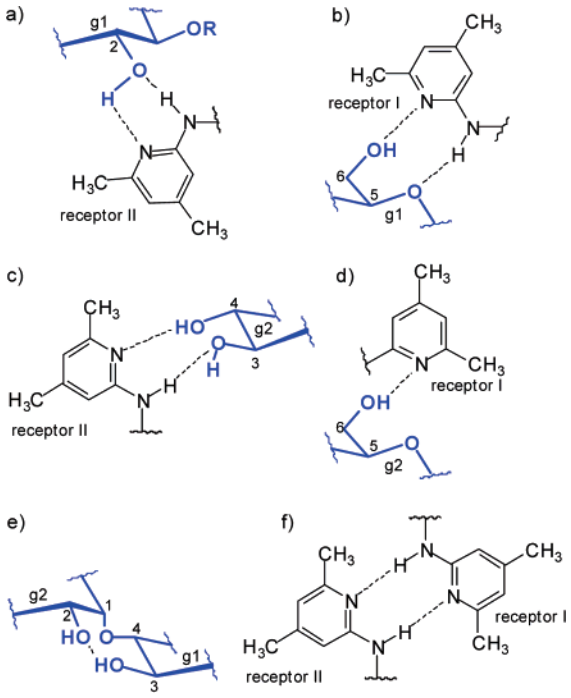



**FIGURE 3.** Examples of hydrogen-bonding motifs found by molecular modeling studies in the 2:1 complex between receptor **1** and maltoside **2**$\beta$ (MacroModel V.6.5, Amber* force field, Monte Carlo conformational searches, 50 000 steps).

molecules (see Figure 2a) in a similar way as in the protein−sugar complexes.

The 3- and 4-OH groups of the glucosyl unit g2 (for labeling see formula **2**$\beta$), the 6-OH group, and the ring oxygen atom of the g1 unit all participate in bidentate hydrogen bonds with the amidopyridine subunits of the receptor (see Figure 3c and 3b, respectively). The 2-OH of the g1 unit is involved in cooperative hydrogen bonds, which results from the simultaneous participation of the OH as acceptor for the NH group of the receptor and as donor for the pyridine nitrogen atom (Figure 3a). The 3- and 2-OH groups of the g1 and g2 unit, respectively, are involved in the formation of an intramolecular hydrogen bond (Figure 3e). Furthermore, hydrogen bonds between the two

(12) Similar 1:1 and 2:1 receptor/substrate complexation behavior was observed for a guanidinium-based receptor and sulfate anion. See: Kobiro, K.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 421−427.

(13) The linearity of the shift changes shows that the association constant is very large and could not be precisely determined from the NMR titrations data. For a review discussing the limitations of the NMR method, see: Fielding, L. *Tetrahedron* **2000**, *56*, 6151−6170.

(14) The presence of water may lead to the formation of water-mediated hydrogen bonds, in line with the observation in protein−carbohydrate complexes.

receptor molecules stabilize the 2:1 receptor/sugar complex (Figure 3f). In addition, the biphenyl units of both receptors stack on the sugar rings. Both sides of the pyranose rings are involved in the CH−$\pi$ interactions.[15] Interestingly, in the crystal structure of the MBP−maltose complex, the 3- and 4-OH groups of the glucosyl unit g2 participate in bidentate hydrogen bonds, the 2-OH group of the g1 unit is involved in cooperative hydrogen bonds, and the 3-OH(g1) and 2-OH(g2) form an intramolecular hydrogen bond, in line with observations in the synthetic complex.

The $^1$H NMR titration experiments with $\beta$-glucopyranoside **3** were carried out by adding increasing amounts of the sugar to a solution of receptor **1**. During titration, the signal due to the amide NH of **1** moved downfield by about 0.66 ppm (after the addition of 5 equiv of sugar; see Figure S2). Furthermore, the $^1$H NMR spectra showed changes in the chemical shifts of the biphenyl/pyridine CH's and the $CH_3$ protons (upfield shifts, in the range of 0.04−0.15 ppm), as illustrated in Figure S2. Typical titration curves are shown in Figure S3. Both the curve fitting of the titration data[11e] and the mole ratio plots (see Figure S13b) suggest the existence of 1:1 and 1:2 receptor/sugar complexes in chloroform. The binding constants for **1•3** were found to be 8800 ($K_{a1}$) and 300 ($K_{a2}$) $M^{-1}$ [in water-containing chloroform solutions ([receptor]:[water] = 1:10), the binding constants amount to 11 400 ($K_{a1}$) and 480 ($K_{a2}$) $M^{-1}$].[11b,d] Thus, the binding affinity of **1** for the monosaccharide **3** is expectedly significantly lower than that observed for the disaccharide **2**$\beta$.[16a]

In conclusion, the biphenyl-based receptor **1** has been established as a highly effective receptor for dodecyl $\beta$-D-maltoside (**2**$\beta$) in chloroform and water-containing chloroform solutions, showing successive 1:1 and 2:1 receptor/sugar binding behavior toward the disaccharide ($K_a > 10^6$ $M^{-1}$). This receptor provides both hydrogen bonding sites and aromatic units for facilitating stacking interactions with the sugar rings. This receptor type is able to bind both $\beta$-glucopyranoside **3** and $\beta$-maltoside **2**$\beta$, with a preference for the disaccharide.[16a] Furthermore, receptor **1** shows $\beta$ versus $\alpha$ binding selectivity in the recognition of maltosides **2**$\beta$ and **2**$\alpha$.[16b] The simple acyclic structure offers the possibility of an easy variation of the receptor structure. The results obtained with receptor **1** serve as a basis for the construction of new biphenyl-based receptors, incorporating both neutral and ionic hydrogen-bonding sites, for the recognition of saccharides in organic and aqueous media. Binding studies with this type of receptor and different oligosaccharides are now in progress.

## Experimental Section

**Dimethyl 5-Iodobenzene-1,3-dicarboxylate (5).[6]** A solution of sodium nitrite (8.63 g, 0.125 mol) in water (150 mL) was added to a suspension of 5-aminobenzene-1,3-dicarboxylate (**4**) (26.16 g, 0.125 mol) in 20% HCl (75 mL) at −5 °C. Toluene (200 mL) and then a solution of potassium iodide (42.00 g, 0.50 mol) in water (100 mL) were slowly added to the suspension. After the addition, the reaction mixture was stirred for 12 h and afterward refluxed for 1 h. The organic layer was separated and washed three times with water, dried with $MgSO_4$, filtered, and concentrated in vacuum. The crude product was recrystallized three times from methanol, giving **5** as light-brown crystals. Yield 49%. Mp 103−104 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.95 (s, 6H), 8.53 (d, 2H, $J$ = 1.5 Hz), 8.61 (t, 1H, $J$ = 1.5 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 52.6, 93.4, 129.8, 132.3, 142.4, 164.7. MS-EI, *m*/*z* (%): 320 (88) [$M^+$], 289 (100), 261 (25). $R_f$ = 0.54 (silica gel, ethyl acetate/hexane 3:7 v/v).

**3,3′,5,5′-Tetrakis(methoxycarbonyl)biphenyl (8).** A mixture of dimethyl 5-iodobenzene-1,3-dicarboxylate (**5**) (320 mg, 1.00 mmol), bis(pinacolato)diborane (**6**) (279 mg, 1.10 mmol), potassium acetate (294 mg, 3.00 mmol), $PdCl_2$(dppf) (24 mg, 0.03 mmol), and dried DMF (6 mL) was stirred at 80 °C for 2 h. The reaction mixture was cooled to room temperature. Then, dimethyl 5-iodobenzene-1,3-dicarboxylate (**5**) (640 mg, 2.00 mmol), $PdCl_2$(dppf) (24 mg, 0.03), and CsF (456 mg, 3.0 mmol; dissolved in 2.5 mL of water) were added. The mixture was stirred at 80 °C overnight and afterward extracted four times with diethyl ether (4 × 25 mL). The organic layer was dried with $MgSO_4$, and the solvent was removed in vacuum. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexane, 3:7 v/v). Yield 82%. Mp 214−215 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.00 (s, 12H), 8.51 (d, 4H, $J$ = 1.5 Hz), 8.72 (d, 2H, $J$ = 1.5 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 52.5, 130.2, 131.5, 132.3, 139.9, 165.9. $R_f$ = 0.50 (silica gel, ethyl acetate/hexane, 3:7 v/v). MS-EI, *m*/*z* (%): 386 (75) [$M^+$], 355 (100), 327 (15), 194 (10).

**Biphenyl-3,3′,5,5′-tetracarboxylic acid (9).** A mixture of 3,3′,5,5′-tetrakis(methoxycarbonyl)biphenyl (**8**) (0.96 g, 2.5 mmol), THF (40 mL), and NaOH (1.6 g, 40 mmol) dissolved in water (40 mL) was refluxed for 1 h. Then, the organic solvent was removed under reduced pressure, and the aqueous solution was refluxed again for 4 h. The reaction mixture was cooled and acidified with 50% $H_2SO_4$. The precipitate was filtered and dried to obtain **9** as a white powder. Yield 89%. Mp > 350 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 8.44 (d, 4H, $J$ = 1.5 Hz), 8.53 (t, 2H, $J$ = 1.5 Hz), 13.48 (br s, 4 H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ = 129.5, 131.4, 132.3, 139.2, 166.3. MS-EI, *m*/*z* (%): 330 (100) [$M^+$], 313 (40), 285 (15) 240 (5).

***N,N′,N″,N‴*-Tetrakis-[(4,6-dimethylpyridin-2-yl)biphenyl-3,3′,5,5′-tetracarboxamide (1).** (a) Synthesis of **10**. A mixture of biphenyl-3,3′,5,5′- tetracarboxylic acid (**9**) (0.30 g, 0.90 mmol) and thionyl chloride (0.53 mL, 7.20 mmol) in THF (20 mL) was heated under reflux for 3 h. The solvent was removed in vacuum. Then, THF (4 × 20 mL) was added, and again the solvent was removed in vacuum. The crude product was used directly for further reaction. (b) Synthesis of **1**. A solution of **10** in THF (20 mL) was added dropwise to a solution of 2-amino-4,6-dimethylpyridine (**11**) (0.47 g, 3.81 mmol) and triethylamine (0.76 mL) in THF (20 mL). After complete addition, the mixture was stirred at room temperature for 48 h. The reaction mixture was treated with water (100 mL), stirred for 15 min, and THF was removed in vacuum. The resulting precipitate was filtered, washed with water, dried, and recrystallized from THF/hexane or chloroform. Yield 76%. Mp 181−182 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 2.31 (s, 12 H), 2.37 (s, 12 H), 6.72 (s, 4H), 8.01 (s, 4H,), 8.47 (d, 4H, $J$ = 1.8 Hz), 8.53 (t, 2H, $J$ = 1.8 Hz), 8.91 (br s, 4H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 20.9, 23.2, 111.9, 120.4, 127.2, 129.8, 135.1, 139.1, 149.6, 151.4, 156.1, 165.3. HR-MS calcd for $C_{44}H_{42}N_8O_4$ 746.3329; found 746.3334. $R_f$ = 0.94 (silica gel, methanol/chloroform 1:7 v/v).

**Acknowledgment.** This work was supported by the Deutsche Forschungsgemeinschaft.

**Supporting Information Available:** $^1$H NMR titration data (Figures S1−S3). Copies of the $^1$H and $^{13}$C NMR spectra of all compounds (Figures S4−S12). Representative mole ratio plots (Figure S13). Description of a titration experiment with dodecyl $\beta$-D-maltoside (**2**$\beta$). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) For examples of CH−$\pi$ interactions in the crystal structures of the complexes formed between artificial receptors and carbohydrates, see ref 2c. (b) For a recent discussion on the importance of carbohydrate−aromatic interactions, see: Chávez, M. I.; Andreu, C.; Vidal, P.; Aboitiz, N.; Freire, F.; Groves, P.; Asensio, J. L.; Asensio, G.; Muraki, M.; Caòada, F. J.; Jiménez-Barbero, J. *Chem.—Eur. J.* **2005**, *11*, 7060−7074.

(16) (a) For an example of a macrocyclic receptor, which is able to distinguish between the octyl $\beta$-D-maltoside ($K_a$ = 11 000 $M^{-1}$) and octyl $\beta$-D-glucopyranoside (no binding) 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 1a.