Recognition properties of receptors based on dimesitylmethane-derived core: Di- *vs.* monosaccharide preference†

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Dimesitylmethane-derived receptors **12** and **13**, incorporating four heterocyclic recognition groups capable of serving as hydrogen bonding sites, were designed to recognize disaccharides. It has been shown by ^{1}H NMR and fluorescence spectroscopic titrations that compounds **12** and **13** display high binding affinities toward α- and β-maltoside, as well as strong di- *vs* monosaccharide preference in organic media. Both hydrogen-bonding and interactions of the sugar CH's with the phenyl rings of the receptor contribute to the stabilisation of the receptor–sugar complexes, as indicated by experimental data and molecular modeling calculations.

Introduction

The selective recognition of carbohydrates with artificial receptors employing noncovalent interactions remains a challenging goal of artificial receptor chemistry.[1–4] Subtle variations in the sugar structures and the three-dimensional arrangement of their functionality make carbohydrates complicated targets for such recognition; particularly, the neutral carbohydrates are especially challenging substrates to recognize.[1–3] The design of carbohydrate receptors is often inspired by the binding motifs found in the crystal structures of protein–carbohydrate complexes[5] (for example, see Fig. 1). In particular, many representatives of hydrogen bonding receptors have been prepared and studied. Most of the described binding studies involve the complexation of monosaccharides, whereas the oligosaccharides have received far less attention.[6–8] Although some receptors show interesting oligo- *vs.* monosaccharides preference, the selective recognition of oligosaccharides by receptors using noncovalent interactions is still rare.[6]

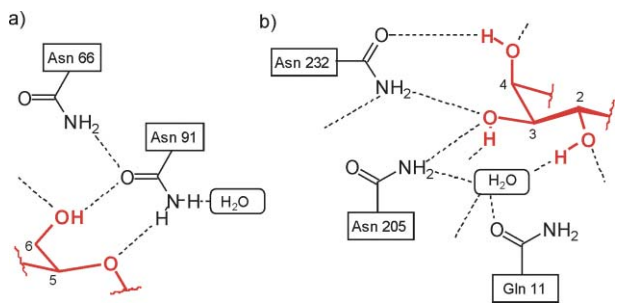

Fig. 1 Examples of hydrogen bonds in the complexes of (a) D-galactose-binding protein with D-glucose, and (b) L-arabinose-binding protein with L-arabinose.[5b]

Diederich *et al.* had shown that optically active, 1,1′-binaphthyl-derived cyclophane receptor with a preorganized central cavity lined with four anionic phosphodiester groups (see Fig. 2a, R = H) was able to form 1 : 1 complexes with disaccharides, such as octyl β-maltoside **1a** (K_{11} = 11000 M^{-1} in CD_3CN/CD_3OD, 88 : 12 v/v), whereas the smaller monosaccharides were not significantly bound.[6a,b] The four phosphodiester groups of the receptor converge towards the binding cavity, which is complementary in size to one disaccharide, and provide efficient bidentate ionic hydrogen bond acceptor sites. The incorporation of two methyl carboxylate groups into the receptor structure (Fig. 2a, R = CO_2CH_3) further enhanced the disaccharide binding affinity by additional hydrogen bonding interactions.[6b]

The potential of biphenyl- and terphenyl-based macrocyclic receptors for the recognition of mono- and oligosaccharides has been explored by Davis *et al.* (see, for example Fig. 2b).[3g,3h,6c] The receptors were designed to provide both apolar and polar contacts to a sugar molecule. A terphenyl-based macrotricycle was shown to be an effective receptor for the all-equatorial octyl β-cellobioside **2a** (see Fig. 3).[6c] In contrast, the biphenyl-based macrotetracyclic receptor, shown in Fig. 2b, complexed the dodecyl β-maltoside **1b** more strongly (K_{11} = 780 M^{-1} in $CHCl_3/CH_3OH$, 75 : 25) than the octyl β-cellobioside **2a** (K_{11} = 310 M^{-1}).[3g] More recently, a water-soluble *meta*-terphenyl-based tetracyclic receptor was developed to target all-equatorial disaccharides such as cellobiose.[3h] The receptor showed good affinities (for example, methyl β-cellobioside **2b** was bound with K_{11} ~ 900 M^{-1}) and remarkable selectivities for its chosen substrate in aqueous solutions.

Cyclic porphyrin–cryptand conjugates were investigated as receptors for mono-, di- and trisaccharides by Schmidtchen *et al.* The cyclic receptors showed selective binding of saccharides in water solution, revealing a trend increasing from mono- to trisaccharide.[6d]

Our studies showed that acyclic receptors **6–9**[3i,3q,9b] based on a trimethyl- or triethylbenzene scaffold[10] (see Fig. 4) are able to recognise both mono- and disaccharides, with a strong preference for the disaccharides. In contrast, the symmetrical receptor **10**, incorporating three heterocyclic groups capable of serving as hydrogen bonding sites, was shown to be able to form strong complexes with both mono- and disaccharides[3q,9b] (see Table 1). Comparison of the binding properties of **10** with those of the receptors **6–9** reveals that the replacement of heterocyclic groups by phenyl-based recognition units results in a substantial drop in

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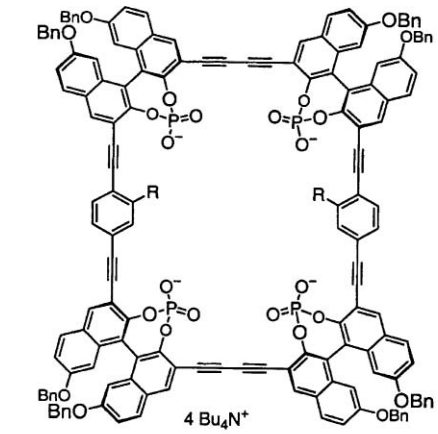
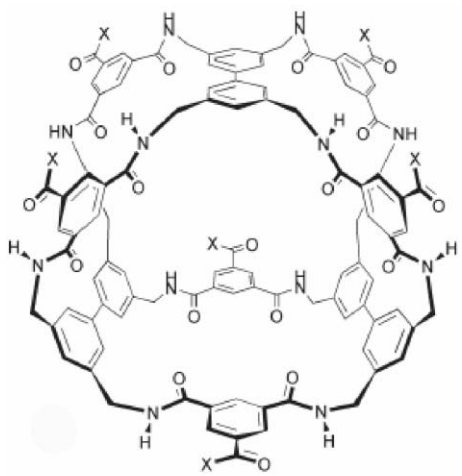


(a)



(b) X = NHC(CH2OCH2CH2CO2tBu)3

Fig. 2 Structure of (a) the 1,1′-binaphthyl-derived cyclophane receptor of Diederich *et al.* (R = H or CO_2CH_3, OBn = Benzyloxy group)[6a,b] and (b) the biphenyl-based macrotetracyclic receptor of Davis *et al.*[3h]

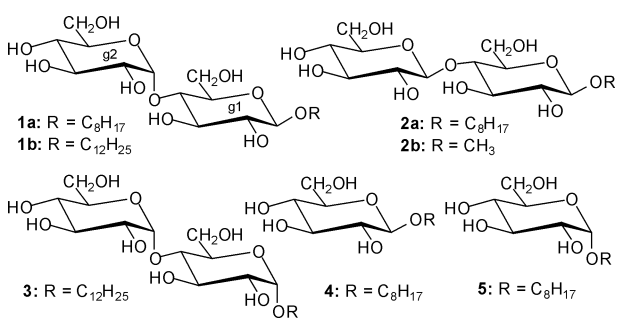


Fig. 3 Structures of sugar molecules.

the binding affinity towards monosaccharides (the binding affinity for monosaccharides, such as **4** and **5**, decreases with decreasing the number of the heterocyclic recognition groups attached to the central phenyl ring). In contrast, the incorporation of suitable substituted phenyl groups into the 2,4,6-trialkylbenzene scaffold provides receptors capable of forming strong complexes with disaccharides. The symmetrical oxime-based receptor **7**,[3i,11] for example, is able to form strong 1 : 1 complexes with dodecyl β-D- and α-D-maltoside, **1b** and **3**, in chloroform solutions (K_{11} ~1×10^5 M^{-1}). In the case of receptor **7**, both glucose units of the disaccharide **1b** or **3** have the possibility to interact with four phenyl rings of the receptor (three oxime-substituted phenyl rings and the central phenyl ring); these interactions seem to be responsible for the 1 : 1 binding stoichiometry, similar to the complex between maltose binding protein (MBP) and maltose. 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".[5f] In the case of MBP the aromatic residues involve three indol rings (from Trp 62, Trp 230, and Trp 340) and hydroxyphenyl ring (from Tyr 155).[5f]

Di- *vs.* monosaccharide preference in the recognition of carbohydrates was also observed for the acyclic biphenyl-based receptor **11**, which was designed to recognise disaccharides.[3b] Molecular modeling calculations indicated that a 3,3′,5,5′-tetrasubstituted-biphenyl scaffold[12] should provide a cavity of the correct shape and size for disaccharide encapsulation.

The aim of this work was to explore the potential of dimesitylmethane-based receptors **12** and **13** (see Fig. 5), incorporating four 2-aminopyridine units capable of serving as hydrogen bonding sites, in the recognition of neutral sugar molecules. It should be noted that 2-aminopyridine group provides an excellent structural motif for binding carbohydrates, associated with the ability to form cooperative and bidentate hydrogen bonds with the sugar OH groups, as shown by our previously binding studies with different receptor molecules.[9] 2-aminopyridine units can be regarded as analogues of natural recognition groups, namely as heterocyclic analogues of the asparagine/glutamine primary amide side chains (see Fig. 1; see also ref. 13).

To compare the binding properties of receptors **12** and **13**[14] with the properties of previously published receptors, the dodecyl β-D-maltoside (**1b**), dodecyl α-D-maltoside (**3**), and octyl β-D-glucopyranoside (**4**) were selected as substrates. The interactions of the receptors and carbohydrates were investigated by ^{1}H NMR and fluorescence spectroscopy in organic media. The ^{1}H NMR binding titration data were analyzed using the Hostest 5.6 program.[15] The fluorescence binding titration data were analyzed using the Hyperquad 2006 program.[16] Stoichiometry of the receptor–sugar complexes was determined by mole ratio plots[17] and by the curve-fitting analysis of the titration data.

Results and discussion

Synthesis of the receptors

The synthetic route for **12** and **13** is shown in Scheme 1. Four bromomethyl groups were appended to dimesithylmethane (**14**) over two steps leading to 3,3′,5,5′-tetrabromomethyl-2,2′,4,4′,6,6′-hexamethyldiphenylmethane (**16**).[18] The reaction of **16** with 2-amino-6-methylpyridine (**17**) or 2-amino-4,6-dimethylpyridine (**18**) provided the compounds **12** and **13**, respectively (see Scheme 1).

Binding studies

Dodecyl β-D-maltoside (**1b**) and dodecyl α-D-maltoside (**3**) are poorly soluble in $CDCl_3$, but could be solubilized in this solvent in

Table 1 Association constants[a,b] for receptors **12** and **13** and sugars **1b**, **3** and **4** as well as for the previously studied receptors **7–11** and sugars **1b** and **4**[c]

Receptor–sugar complex	Solvent	K_{11}/M^{-1}	K_{21}[d] or K_{12}[e]/M^{-1}	β_{21} or β_{12}[f]/M^{-2}	Method[g]
12·1b	$CDCl_3$		>100 000 (K_{21})[h]		NMR
	$CHCl_3$		5.76×10^7 (K_{21})		Fluorescence
	1% DMSO/$CHCl_3$	14 600			Fluorescence
12·3	$CHCl_3$		1.61×10^7 (K_{21})		Fluorescence
	1% DMSO/$CHCl_3$	10 300			Fluorescence
12·4	$CDCl_3$	260	630 (K_{12})	1.63×10^5	NMR
	$CHCl_3$	350	840 (K_{12})	2.94×10^5	Fluorescence
13·1b	$CDCl_3$		>100 000 (K_{21})[h]		NMR
	1% DMSO-d_6/$CDCl_3$	19 800			NMR
13·3	$CDCl_3$		>100 000 (K_{21})[h]		NMR
13·4	$CDCl_3$	270	560 (K_{12})	1.51×10^5	NMR
7·1b	$CDCl_3$	100 500			NMR
	$CHCl_3$	98 900			Fluorescence
7·4	$CDCl_3$	170	1730 (K_{12})	2.94×10^5	NMR
8·1b	$CHCl_3$	371 200	7950 (K_{21})	2.95×10^9	Fluorescence
8·4	$CDCl_3$	2050	720 (K_{12})	1.48×10^6	NMR
9·1b	$CDCl_3$		>100 000 (K_{21})[h]		NMR
9·4	$CDCl_3$	1830	180 (K_{12})	3.29×10^5	NMR
10·1b	$CHCl_3$	130 700	42 300 (K_{21})	5.52×10^9	Fluorescence
10·4	$CDCl_3$	48 630	1320 (K_{12})	6.42×10^7	NMR
	$CHCl_3$	54 920	1470 (K_{12})	8.07×10^7	Fluorescence
11·1b	$CDCl_3$		>100 000 (K_{21})[h]		NMR
11·4	$CDCl_3$	8800	300 (K_{12})	2.64×10^6	NMR

[a] Average K_a values from multiple titrations. [b] Errors in K_a are less than 10%. [c] According to the references 3*b*,3*i*,3*q*, and 9*b*. [d] K_{21} corresponds to 2 : 1 receptor–sugar association constant. [e] K_{12} corresponds to 1 : 2 receptor–sugar association constant. [f] $\beta_{21} = K_{11}K_{21}$, $\beta_{12} = K_{11}K_{12}$. [g] ^{1}H NMR spectroscopic titrations ($CDCl_3$ and DMSO-d_6/$CDCl_3$, 1 : 99 v/v) or fluorescence titrations ($CHCl_3$ and DMSO/$CHCl_3$, 1 : 99 v/v. [h] The best fit of the titration data was obtained with the "pure" 2 : 1 receptor–substrate binding model (see ref. 15*b*).

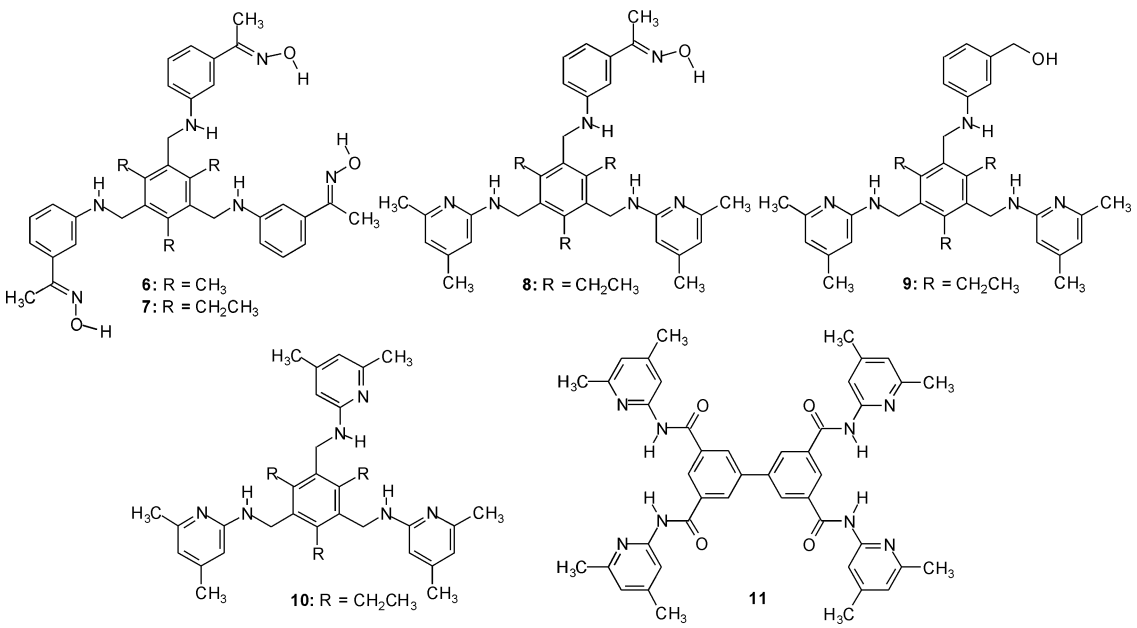
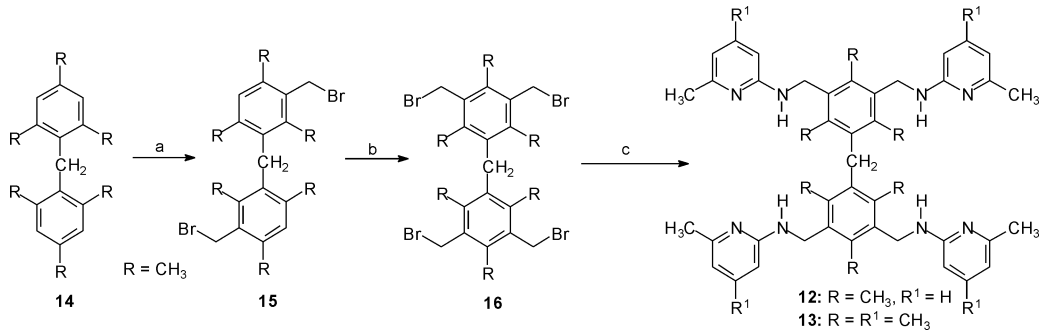


Fig. 4 Structures of the previously studied receptors **6–11**.[3b,3i,3q,9b]

the presence of the receptor **12** or **13**, indicating favourable interactions between the binding partners (similar solubility behaviour of the disaccharides **1b** and **3** was observed in the presence of the previously described receptors **6–9**). Thus, the receptor in $CDCl_3$ was titrated with a solution of maltoside dissolved in the same receptor solution. In addition, ^{1}H NMR titration experiments with the disaccharides were performed in DMSO-d_6/$CDCl_3$ mixtures. The ^{1}H NMR titrations with β-glucopyranoside **4** were carried out by adding increasing amounts of the sugar to a $CDCl_3$ solution of the receptor **12** or **13**. The complexation between **12** or **13** and the saccharides **1b**, **3** and **4** was evidenced by several changes in the NMR spectra (for examples, see Fig. 6 and 7).

During the titrations of both of the receptors with the disaccharide **1b** or **3** in $CDCl_3$ the signal due to the amine NH of **12** and **13** moved downfield by about 0.25–0.30 ppm indicating the participation of the NH groups in the formation of intermolecular hydrogen bonds. It should be noted that the addition of only 0.5 equivalent of sugar **1b** or **3** led to practically



Scheme 1 Reaction conditions: (a) CH_2O, HBr, CH_3COOH, (b) CH_2O, HBr, $ZnCl_2$, CH_3COOH, (c) 4.4 equiv of 2-amino-6-methylpyridine (**17**) or 2-amino-4,6-dimethylpyridne (**18**), CH_3CN/THF, K_2CO_3.

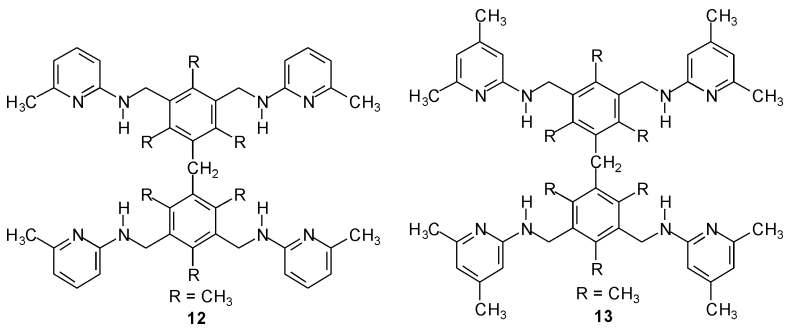


Fig. 5 Structures of receptors investigated in this study.

complete complexation of the receptors **12** and **13** (see Fig. 6a and 7a). Furthermore, the ^{1}H NMR spectra showed changes in the chemical shifts of the CH_3, CH_2 and CH resonances of the receptors (up- and downfield shifts in the range of 0.03–0.05 ppm). The best fit of the titration data for **12**·**1b**, **12**·**3**, **13**·**1b**, and **13**·**3** was obtained with the 2 : 1 receptor–sugar binding model[15b] (typical titration plot is shown in Fig. 7a); however, the binding constants were too large to be accurately determined by ^{1}H NMR titrations in $CDCl_3$ ($K_{21} > 100\,000$ M^{-1}, see Table 1).[19,20] The formation of complexes with 2 : 1 receptor–maltoside binding stoichiometry was further supported by the mole ratio plots.

According to molecular modeling calculations the 2 : 1 receptor-maltoside complexes are stabilized by several hydrogen bonds as well as interactions of sugar CHs with the phenyl groups of both of the receptor molecules. The two receptor molecules almost completely enclose the sugar (for example, see Fig. 8a), leading to involvement of sugar OH groups and the ring-O in interactions with the two receptor molecules (OH $\cdots$ N-pyr, HO $\cdots$ HN, and ring-O $\cdots$ HN hydrogen bonds, see Table 2). The sugar OH groups are engaged in the formation of cooperative hydrogen bonds resulting from the simultaneous participation of a sugar OH as donor and acceptor of hydrogen bonds (similar to interactions in protein–carbohydrate complexes[5]). Examples of noncovalent interactions indicated by molecular modeling calculations for the complex formed between receptor **13** and the disaccharide **1b** are given in Fig. 9 and Table 2.

Studies performed with the receptor **13** and β-maltoside **1b** in DMSO-d_6/$CDCl_3$ mixture (1 : 99 v/v) revealed that the affinity of **13** for the disaccharide **1b** significantly decreases as solvent polarity increases. The motions of the signals observed during the titrations of **13** with **1b** in the presence of DMSO-d_6 were consistent with 1 : 1 receptor–sugar binding; the binding constant for **13**·**1b** was determined to be 19 800 M^{-1}.

The interactions between the receptor **12** and the disaccharide **1b** or **3** could also be analysed on the base of fluorescence titrations (the binding properties of the receptor **13** could not be analysed on the base of fluorescence spectroscopy).[21] The fluorescence titration experiments were carried out by adding increasing amounts of the sugar **1b** or **3** (both disaccharides are soluble in $CHCl_3$ in the concentration range required for fluorescence titrations) to a $CHCl_3$ solution of the receptor **12** (for example, see Fig. 10a). The best fit of the titration data at 360 nm was obtained with the 2 : 1 receptor–sugar binding model, in agreement with the ^{1}H NMR binding studies; the binding constant for **12**·**1b** was found to be 5.76×10^7 M^{-1}, whereas that for **12**·**3** amounted to 1.61×10^7 M^{-1}. The spectral changes observed during the titrations of **12** with **1b** or **3** in the presence of DMSO (DMSO/$CHCl_3$, 1 : 99 v/v) were less substantial than those observed during the titrations in pure chloroform and were consistent with 1 : 1 receptor–sugar binding; the binding constant for **12**·**1b** was determined to be 14 600 M^{-1}, that for **12**·**3** amounted to 10 300 M^{-1}. Thus, the addition of dimethyl sulfoxide caused both the change of the binding model and a substantial drop in the binding affinity, as indicated by ^{1}H NMR titrations.

^{1}H NMR titrations of **12** or **13** with the glucopyranoside **4** in $CDCl_3$ indicated much weaker interactions of the both receptors with the monosaccharide than those with the disaccharides. Whereas after the addition of about 0.5 equivalent of the disaccharide **1b** or **3** almost no more change was observed in the chemical shift of the receptor signals, the addition of more than 5 equivalents of monosaccharide **4** was necessary to achieve the saturation. During the titrations of **12** and **13** with

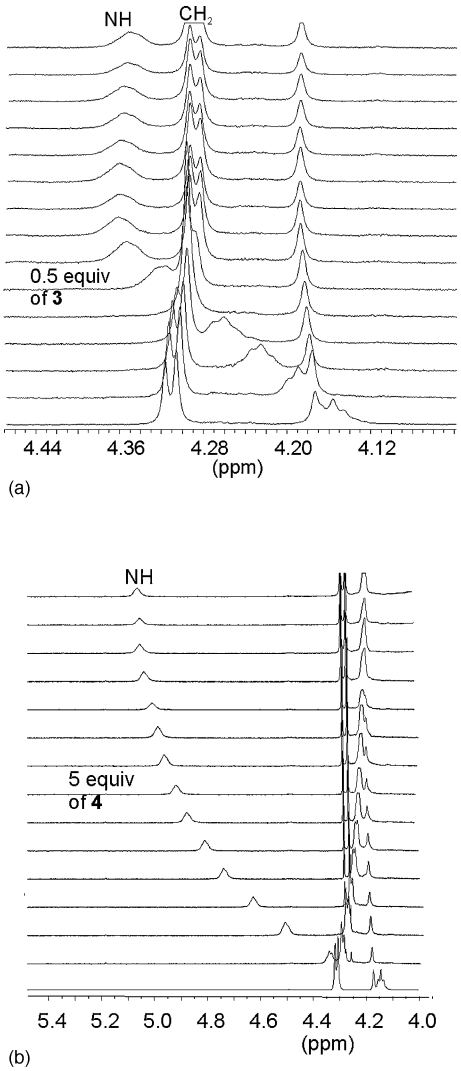


Fig. 6 (a) Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$) of **13** after addition of (from bottom to top) 0.00–2.28 equiv of α-maltoside **3** ([**13**] = 1.02 mM). (b) Partial ^{1}H NMR spectra of **13** after addition of (from bottom to top) 0.00–13.16 equiv of β-glucoside **4** ([**13**] = 0.93 mM).

the monosaccharide **4** the signal due to the amine NH of **12** and **13** moved downfield by about 0.9 ppm (after the addition of ~9 equivalents of sugar, as illustrated in Fig. 6b), whereas the signals of the CH_3, CH_2, and CH protons shifted up- or downfield in the range of 0.02–0.10 ppm. 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 Fig. 7b). A calculated structure of the 1 : 2 receptor–sugar complex formed between receptor **13** and β-glucopyranoside **4** is shown in Fig. 8b (MacroModel V.8.5, OPLS-AA force field, MCMM, 50 000 steps). The binding constants for **12**·**4** were found to be 260 (K_{11}) and 630 (K_{12}) M^{-1}, whereas those for **13**·**4** amounted to 270 (K_{11}) and 560 (K_{12}) M^{-1}.[19c]

Interactions between receptor **12** and β-glucopyranoside **4** could also be detected by fluorescence (fluorescence intensity increased with increasing monosaccharide concentration); however, the spectral changes observed during the fluorescence titrations with glucopyranoside **4** were less substantial than those observed during the titrations with disaccharides **1b** and **3** (for example, see Fig. 10b). The analysis of the titration data (at 360 nm) 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 in $CDCl_3$ (see Table 1).

Comparison of the binding properties of **12** and **13** with those of the receptors **6–9** and **11** (see Table 1) reveals similar tendency to the formation of relative weak 1 : 1 and 1 : 2 receptor–sugar complexes with the monosaccharide **4** (in contrast to the symmetrical aminopyridine-based receptor **10**, which has been established as a powerful receptor for β-glucopyranoside **4**; see Table 1).

Conclusion

As part of our program aimed at the development of selective carbohydrate receptors using noncovalent interactions, we have prepared dimesitylmethane-based receptors **12** and **13**, which were expected to prefer disaccharides. The compounds **12** and **13** consist of four heterocyclic recognition groups capable of serving as hydrogen bonding sites. According to molecular modeling calculations, the hydrogen bonding interactions are complemented by CH-π interactions between the sugar CH's and the phenyl rings of the receptor **12** or **13** (see Table 2).[22,23] The phenyl rings provide additional apolar contacts to a saccharide, similar to sugar-binding proteins,[5] which commonly place aromatic surfaces against patches of sugar CH groups.

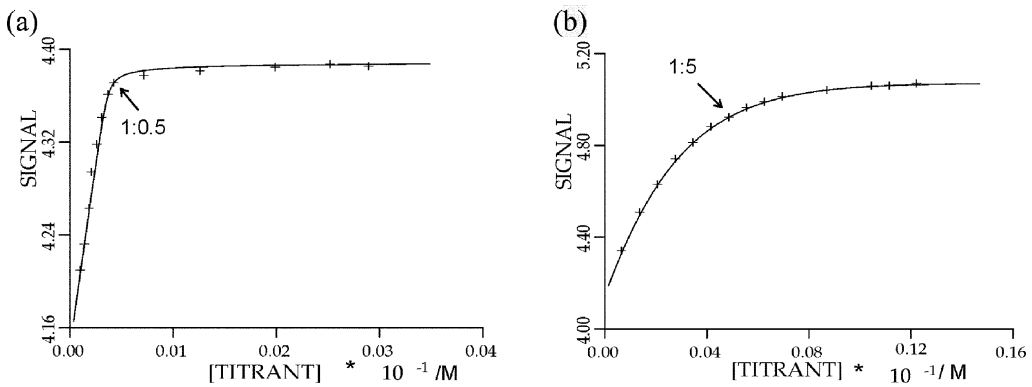


Fig. 7 Plot of the observed (+) and calculated (–) chemical shifts of the NH resonances of **13** (1.02 mM) as a function of added β-maltoside **1b** (a) or β-glucopyranoside **4** (b) The [receptor] : [sugar] ratio is marked.

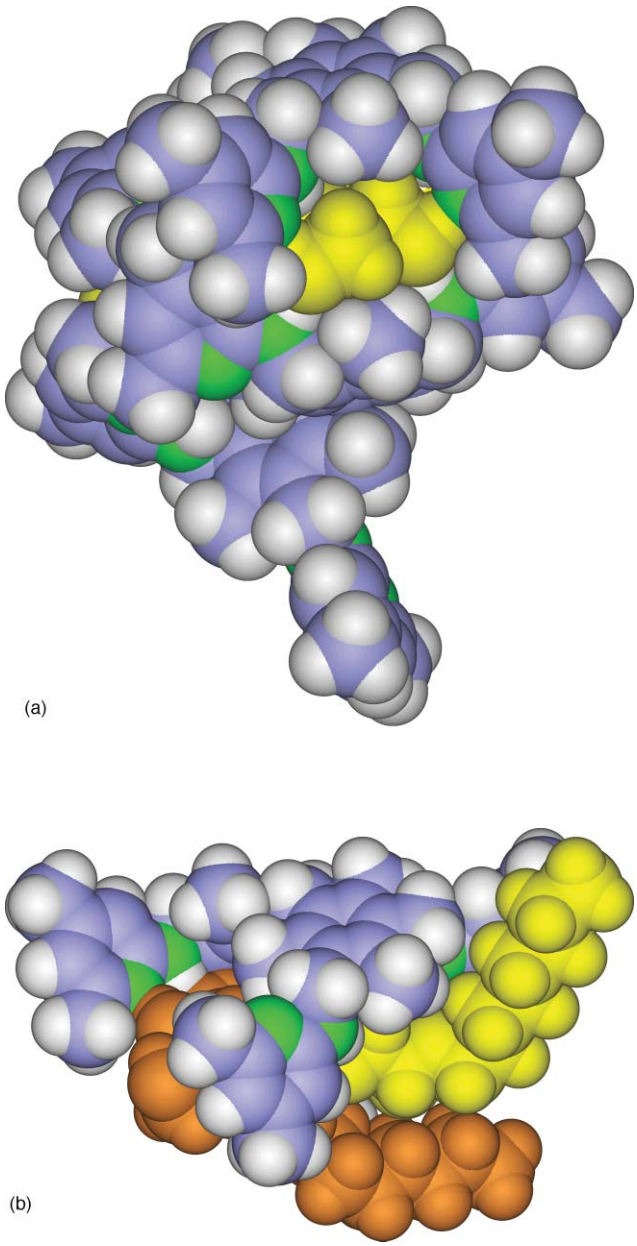


Fig. 8 Energy-minimized structure of the 2 : 1 receptor–sugar complex formed between receptor **13** and β-maltoside **1b** (a) and 1 : 2 receptor–sugar complex between receptor **13** and β-glucoside **4** (b). MacroModel V.8.5, OPLS-AA force field, MCMM, 50 000 steps. Color code: receptor C, blue; receptor N, green; sugar molecule, yellow or orange.

It has been shown by ^{1}H NMR and fluorescence spectroscopic titrations that compounds **12** and **13** display high binding affinity toward β- and α-maltoside, **1b** and **3**, as well as strong di-*vs* monosaccharide preference in organic media (similar to the previously described receptors **6–9** and **11**). The curve fitting of all titration data suggested the existence of very strong 2 : 1 receptor–disaccharide complexes in chloroform solutions ($K_{21} > 10^5$ M^{-1}, see Table 1).[15b,19c] The addition of dimethyl sulfoxide caused both the change of the binding model and a substantial drop in the binding affinity. The curve fitting of the titration data obtained in the presence of DMSO or DMSO-d_6 indicated the formation of complexes with 1 : 1 receptor–disaccharide stoichiometry with K_{11} of 10^4 M^{-1} (see Table 1).

As expected, relative low binding constants were obtained on titrating the compounds **12** or **13** with β-glucopyranoside **4**. The binding studies indicated the formation of complexes with 1 : 1 and 1 : 2 receptor–monosaccharide stoichiometry with K_{11} and K_{12} in the range of 10^2 M^{-1} in chloroform (see Table 1). Both ^{1}H NMR and fluorescence titrations clearly showed that the receptor–monosaccharide complexes are much less stable than those formed with the disaccharides **1b** and **3**.

Receptors **12** and **13** are thus representatives of a new series of acyclic carbohydrate-binding receptors displaying an interesting di- *vs.* monosaccharide preference. The acyclic architecture is notably easy to prepare and especially suitable for systematic variations; such synthetic receptors provide valuable model systems to study the basic molecular features of carbohydrate recognition. Syntheses of new receptors based on dimesitylmethane-derived core and incorporating different recognition groups are in progress.

Experimental section

Analytical TLC was carried out on silica gel 60 F_{254} plates. Melting points are uncorrected. Dimesitylmethane (**14**), dodecyl β-D-maltoside (**1b**), dodecyl α-D-maltoside (**3**), and octyl β-D-glucopyranoside (**4**) are commercially available. ^{1}H NMR and fluorescence titration experiments were carried out similar to those described in the supplementary information of ref. 3*q*.

3,3′-Bisbromomethyl-2,2′,4,4′,6,6′-hexamethyldiphenylmethane (15)

Dimesitylmethane (**14**) (2 g, 0.008 mmol) was combined with glacial acetic acid (30 mL) and paraformaldehyde (1.44 g, 0.048 mol). This mixture was heated to ~80 °C, at which time

Table 2 Examples of noncovalent interactions indicated by molecular modeling calculations[a] for the 2 : 1 receptor–sugar complex formed between receptor **13** and sugar **1b**

Receptor–substrate complex	Noncovalent interactions[b,c]
13·**1b** 2 : 1 receptor–sugar complex[b]	(I) pyridine-N ··· HO-4 (g2); (I) NH ··· OH-3 (g2); (I) pyridine-N ··· HO-6 (g2); (I) NH ··· O-ring (g2); (I) NH ··· OH-3 (g1); (I) pyridine-N ··· HO-6 (g1); (I) NH ··· OH-6 (g1); (II) pyridine-N ··· HO-3 (g2); (II) NH ··· OH-4 (g2); (II) NH ··· OH-6 (g2); (g2) 2-OH ··· OH-3 (g1); (I) phenyl ··· HO-2 (g2); (I) phenyl ··· HC-2 (g1); (II) phenyl ··· HC-3 (g1); (I) pyridine-CH_3 ··· O-ring (g1)

[a] MacroModel V.8.5, OPLS-AA force field, MCMM, 50 000 steps. [b] I and II: two receptors in the 2 : 1 receptor–sugar complex; [c] g1 and g2: the glucose units of **1b** (for labeling see Fig. 3).

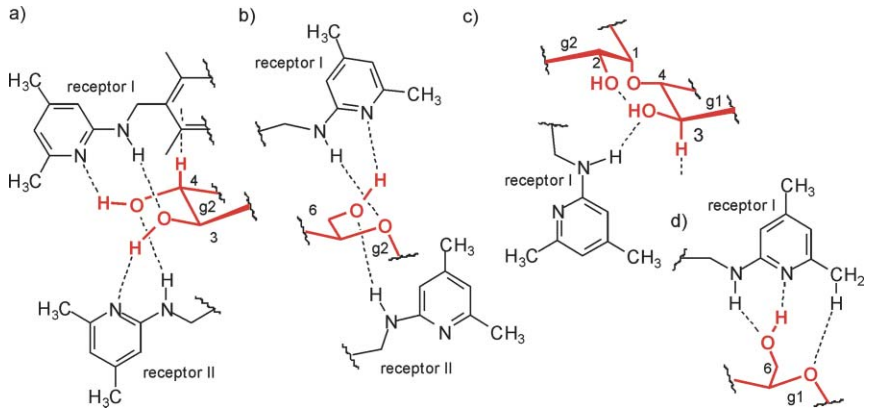


Fig. 9 Examples of hydrogen-bonding motifs found by molecular modeling studies in the 2 : 1 complex between receptor **13** and maltoside **1b** (MacroModel V.8.5, OPLS-AA force field, MCMM, 50 000 steps).

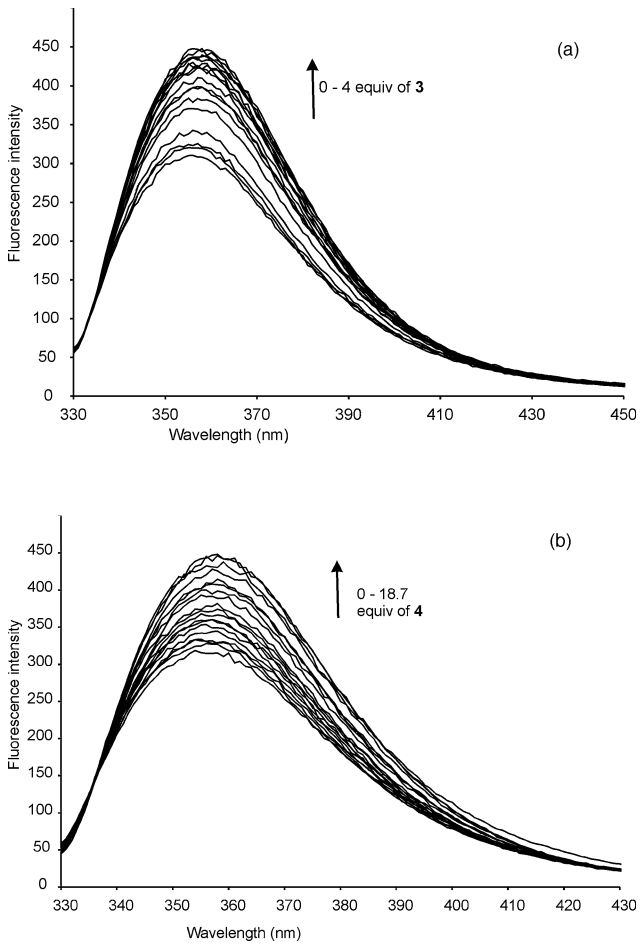


Fig. 10 Fluorescence titration of receptor **12** with α-maltoside **3** (a) and β-glucopyranoside **4** (b) in $CHCl_3$; [**12**] = 8.51×10^{-5} and 9.57×10^{-5} M; Equiv of **3** = 0.00–4.03; Equiv of **4** = 0.00–18.69. Excitation wavelength 324 nm. Fluorescence intensity increased with increasing sugar concentration.

30 mL of a 33% hydrobromic acid–acetic acid solution was added. The mixture was heated until a clear solution was formed. Afterwards the reaction mixture was stirred allowing the mixture to cool to room temperature. The solid precipitating from the solution was filtered, washed with water, potassium carbonate solution, and again with water. Yield 96% (3.36 g, 0.078 mol). Mp 132–133 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.09 (s, 6H), 2.10 (s, 6H), 2.36 (s, 6H), 4.05 (s, 2H), 4.55 (s, 4H), 6.82 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 15.83, 19.21, 21.22, 30.87, 32.22, 130.90, 132.21, 134.86, 136.44, 136.60, 137.46. HR-MS calcd for $C_{21}H_{26}Br_2$ 438.03764; found: 438.03748. R_f = 0.83 (toluene/ethyl acetate, 1 : 1 v/v).

3,3′,5,5′-Tetrabromomethyl-2,2′,4,4′,6,6′-hexamethyl-diphenylmethane (16)

Paraform-aldehyde (0.86 g, 0.0288 mol) was combined with 40 mL of glacial acetic acid, and then zinc(II) bromide (0.60 g, 0.0026 mol) and 3 mL of a 33% hydrobromic acid–acetic acid solution were added. This suspension was heated to 100 °C for 0.5 h (at this time a clear solution was formed), and then 3,3′-bisbromomethyl-2,2′,4,4′,6,6′-hexamethylbiphenylmethane (**15**) (1.05 g, 0.0024 mol) was added (in portions). This solution was heated to 100 °C for 8 h. Afterwards the mixture was cooled to the room temperature, and the resulting precipitate was filtrated. The solid was washed with water, potassium carbonate solution, and again with water. Yield 79% (1.19 g, 1.90 mmol). Mp 171–172 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.14 (s, 12H), 2.45 (s, 6H), 4.17 (s, 2H), 4.55 (s, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 15.19, 16.65, 30.88, 33.11, 132.95, 134.94, 137.16, 137.76. HR-MS calcd for $C_{23}H_{28}Br_4$ 619.89190; found: 619.89232. R_f = 0.95 (toluene/ethyl acetate, 1 : 1 v/v).

3,3′,5,5′-Tetrakis[(6-methylpyridin-2-yl)aminomethyl]-2,2′,4,4′,6,6′-hexamethyl-biphenylmethane (12)

A mixture of 3,3′,5,5′-tetrabromomethyl-2,2′,4,4′,6,6′-hexamethylbiphenylmethane (**16**) (0.50 g, 0.80 mmol), 2-amino-6-methyl-pyridine (0.45 g, 4.16 mmol) and K_2CO_3 (1.50 g, 10.86 mmol) in CH_3CN/THF (1 : 1 v/v; 40 mL) was stirred at room temperature for 72 h (the solution was monitored by TLC). After filtration and evaporation of solvents, the crude product was purified by column chromatography (aluminium oxide, chloroform/diethyl ether, 2 : 3 v/v). Yield 56% (0.33 g, 0.45 mmol). Mp 115–116 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.13 (s, 12H), 2.38 (s, 18H), 4.18 (s, 2H), 4.22 (t, 4H, J = 4.28 Hz), 4.33 (d, 8H, J = 4.3 Hz), 6.26 (d, 4H, J = 8.3 Hz), 6.46 (d, 4H,

$J = 7.3$ Hz), 7.36 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) $\delta = 15.84$, 16.83, 24.36, 33.41, 42.04, 102.77, 112.28, 133.41, 134.61, 135.98, 137.56, 137.87, 157.06, 158.17. HR-MS (ESI) calcd for $C_{47}H_{57}N_8$ 733.47007; found: 733.46974. $R_f = 0.60$ (chloroform/diethyl ether, 2 : 3 v/v).

3,3′,5,5′-Tetrakis[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,2′,4,4′,6,6′-hexamethyl-biphenylmethane (13)

A mixture of 3,3′,5,5′-tetrabromomethyl-2,2′,4,4′,6,6′-hexamethylbiphenylmethane (**16**) (0.50 g, 0.80 mmol), 2-amino-4,6-dimethyl-pyridine (0.47 g, 3.85 mmol) and K_2CO_3 (1.50 g, 10.86 mmol) in CH_3CN/THF (1 : 1 v/v; 60 mL) was stirred at room temperature for 72 h (the solution was monitored by TLC). After filtration and evaporation of solvents, the crude product was purified by column chromatography (aluminium oxide, chloroform/diethyl ether, 2 : 3 v/v). Yield 50% (0.32 g, 0.40 mmol). Mp 145–146 °C. ^{1}H-NMR (400 MHz, THF-d_8): $\delta =$ 2.11 (s, 12H), 2.16 (s, 12H), 2.25 (s, 12H), 2.51 (s, 6H), 4.22 (s, 2H), 4.40 (d, J = 4.3 Hz, 8 H), 5.06 (t, J = 4.3 Hz, 4H), 6.05 (s, 4H), 6.20 (s, 4H). ^{13}C-NMR (100 MHz, THF-d_8): $\delta = 15.90$, 16.88, 20.90, 24.34. 34.17, 42.10, 105.09, 113.07, 135.01, 135.31, 136.33, 138.01, 147.93, 156.81, 159.63. HR-MS calcd for $C_{51}H_{64}N_8$ 788.52242; found: 788.52249. $R_f = 0.57$ (chloroform/diethyl ether, 2 : 3 v/v).

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