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Artificial Carbohydrate Receptors

Complexes Formed between Artificial Receptors and β-Glucopyranoside in the Crystalline State

Linda Köhler,[a] Wilhelm Seichter,[a] and Monika Mazik*[a]

Abstract: In contrast to numerous known crystal structures of protein-carbohydrate complexes, which act as a source of structural information about carbohydrate-mediated recognition processes, there are only individual literature reports on crystal structures of complexes formed between artificial receptors and sugars. In this context, the new crystalline complexes of acyclic receptors and β-D-glucopyranoside described in this article provide particularly valuable model systems to study the basic molecular features of carbohydrate recognition. The detailed analyses of the binding modes observed in these complexes have shown their remarkable similarity to those used by carbohydrate-binding proteins. It is noteworthy that many of the basic molecular features of protein-carbohydrate interactions, that have been summarized years ago in some literature reports, apply to interactions observed in complexes formed by the artificial receptors.

Introduction

Interactions of proteins with carbohydrates play a key role in numerous natural processes[1–3] and therefore the knowledge of the molecular details of these recognition events is of great importance. The crystalline protein-carbohydrate complexes represent an especially valuable source of structural information about carbohydrate recognition. A large number of X-ray crystal structures of proteins bound to various sugar substrates have been described in the literature[2,3] and provide detailed information about the noncovalent interactions that contribute to the selective and effective binding of carbohydrates by proteins. In contrast, only individual reports on crystal structures of complexes formed between artificial receptors and sugars can be found in the literature. In this context, the crystalline complexes of acyclic receptors that were reported in 2005[4] as well as the complexes of foldamers[5a–5c] and a macrocyclic receptor[5d] that were reported between 2015 and 2018, provide valuable model systems to study the basic molecular features of carbohydrate recognition. It should be mentioned that artificial carbohydrate receptors not only act as valuable model systems,[6] but have also the potential to be a basis for the development of new therapeutics, such as anti-infective or anticancer agents.[7]

In this paper, we describe new crystal structures of complexes formed between acyclic receptor molecules (compounds **1**–**3**) and methyl β-D-glucopyranoside (**MeβGlc**), which are schematically illustrated in Figure 1. Receptors **1**–**3** belong to the class of compounds consisting of a 1,3,5-trisubstituted 2,4,6-trialkylbenzene scaffold,[8] the representatives of which we have systematically examined for their ability to bind carbohydrates.[9–11]

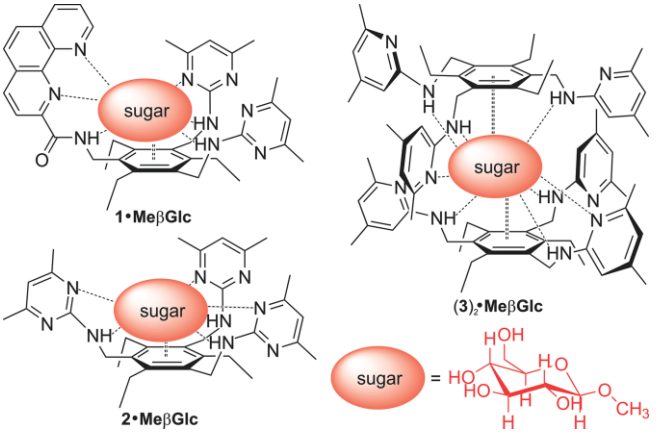

Figure 1. Schematic illustration of the 1:1 and 2:1 receptor-sugar complexes, the crystal structures of which are discussed in this paper.

Remarkably, each of the three crystal structures discussed in this paper is characterized by the presence of two types of receptor-sugar complexes (assigned as complex I and II), as shown in Figure 2. The detailed analyses of the noncovalent interactions responsible for the stabilization of these complexes and the detailed consideration of the differences between the complexes are subject of this work. In addition, the binding modes observed in these new receptor-sugar complexes are compared with those recognized in the crystalline complexes reported by us previously.

[a] L. Köhler, Dr. W. Seichter, Prof. Dr. M. Mazik
Institut für Organische Chemie, Technische Universität Bergakademie Freiberg,
Leipziger Strasse 29, 09599 Freiberg, Germany
E-mail: monika.mazik@chemie.tu-freiberg.de
http://tu-freiberg.de/fakultaet2/orgch

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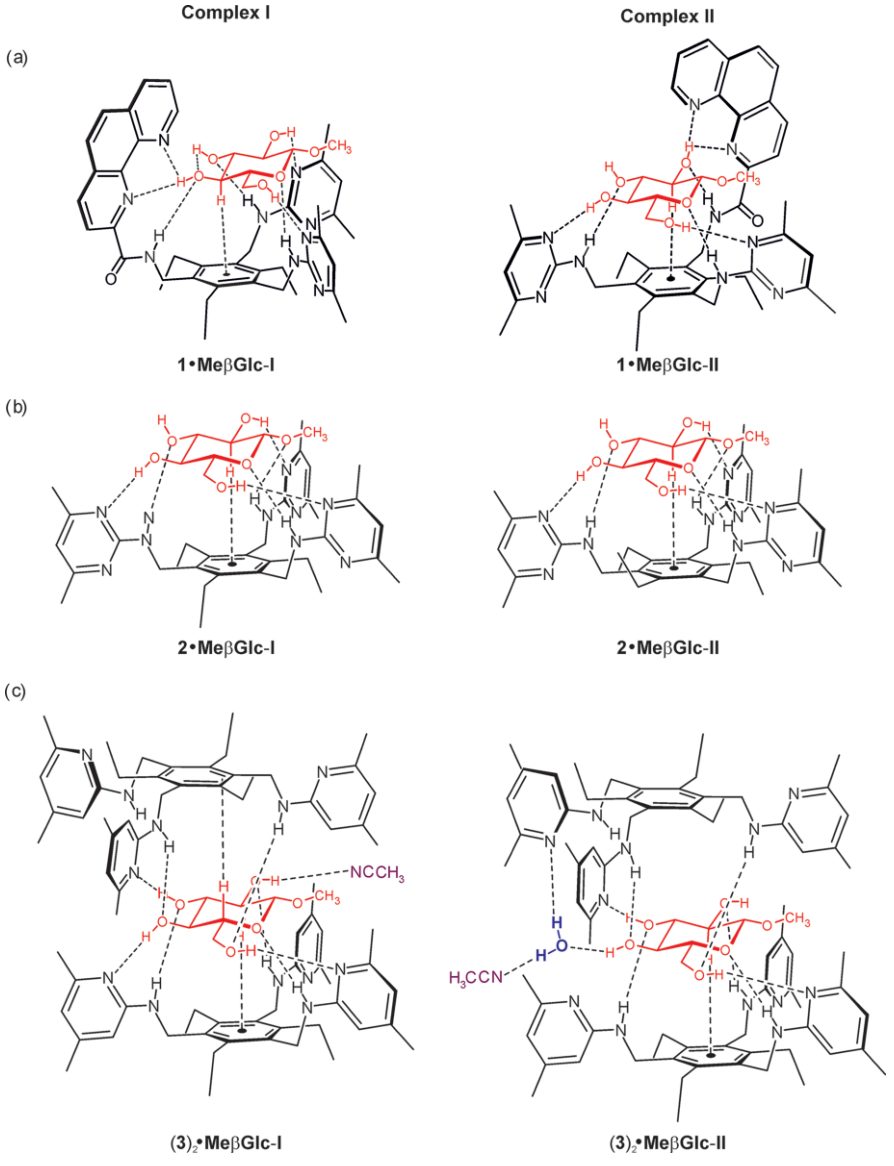

Figure 2. Receptor-sugar complexes observed in the crystal structures **1·MeβGlc**, **2·MeβGlc** and **3·MeβGlc**.

Results and Discussion

Crystal Structure 1·MeβGlc: 1:1 Receptor-Sugar Complexes 1·MeβGlc-I and 1·MeβGlc-II

1,3,5-Trisubstituted 2,4,6-triethylbenzenes consisting of phenanthroline- and aminopyridine-based recognition units have been identified by us as powerful carbohydrate receptors with interesting binding preferences.[11] The new compound **1**, containing one 1,10-phenanthrolin-2-yl group, is an analog of one of the previously investigated compounds and has two sidearms that carry pyrimidinyl instead of pyridinyl groups. The crystalline complexes formed between **1** and methyl β-D-glucopyranoside (**MeβGlc**) provide particularly interesting insights into the principles of carbohydrate recognition (for information on crystallization conditions, see Experimental Section).

The crystal structure **1·MeβGlc** contains two receptor molecules and two molecules of methyl β-D-glucopyranoside (**MeβGlc**) in the asymmetric unit of the cell (monoclinic space group $P2_1$). These molecules are combined to two 1:1 receptor-sugar complexes (**1·MeβGlc-I** and **1·βMeGlc-II**), the structures of which are shown in Figure 2a and Figure 3.

In both complexes the substituents of their receptor molecules are arranged in an alternating order above and below the plane of the central benzene ring and the glucopyranoside molecule is accommodated in the cavity created by the sidearms bearing the heterocyclic units. Nevertheless, the complexes display fundamental differences, which are obvious from Figure 3b and the molecular structures illustrated in Figure 4 and Figure 5 as well as from geometrical parameters listed in Tables S2 and S3 (see Supporting Information). These differences are also reflected by the interplanar angles between the heterocyclic units of the receptors which are 8.5, 63.9, 72.2° for complex I and 51.0, 8.3, 59.2° for complex II; the twist angle between the NHC=O group and the phenanthroline moiety is

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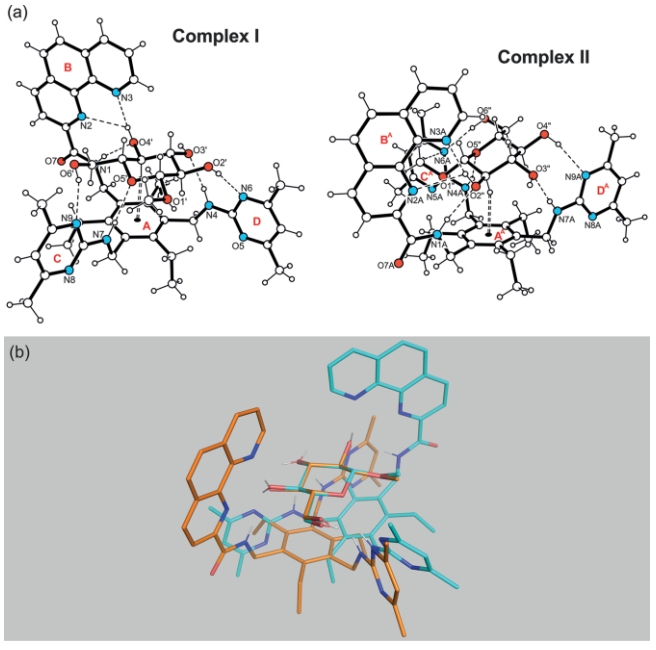

Figure 3. (a) Perspective views of the molecular structures of **1·MeβGlc-I** and **1·MeβGlc-II** including the numbering of N- and O-atoms. Broken lines represent hydrogen bonds, broken double lines C–H···π interactions. (b) A view of superposition of **1·MeβGlc-I** (orange lines) and **1·MeβGlc-II** (light blue lines) fitting on the carbohydrate atoms C1–C5 and O5 (N atoms are colored blue and O atoms red; all non-polar hydrogens are omitted for clarity).

7.0 and 11.5°, respectively. When looking at the superposition of the two complexes, the difference becomes particularly evident (see Figure 3b).

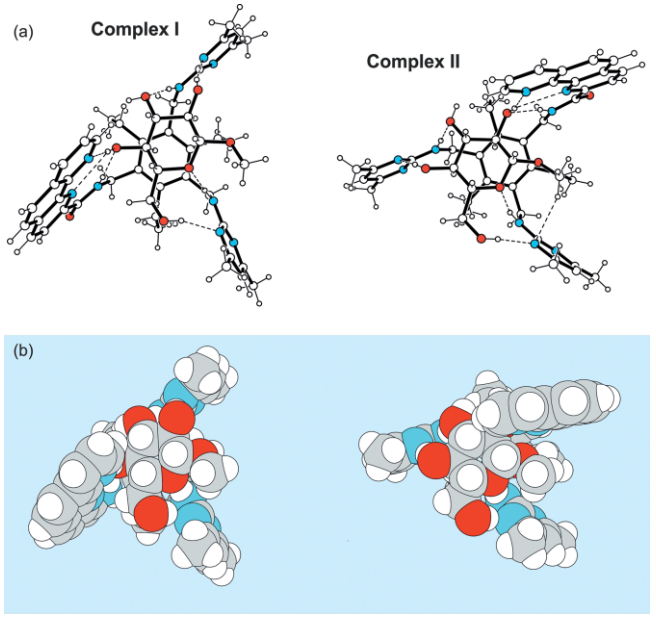

Figure 4. Top views of the complexes **1·MeβGlc-I** and **1·MeβGlc-II** as ball-and-stick representations (a) and space-filling models (b). In order to emphasize the structural differences of the complexes, a uniform orientation of the methyl β-D-glucopyranoside facing the viewer is used.

An essential difference between the complexes concerns the position and orientation of the carbohydrate inside the cavity

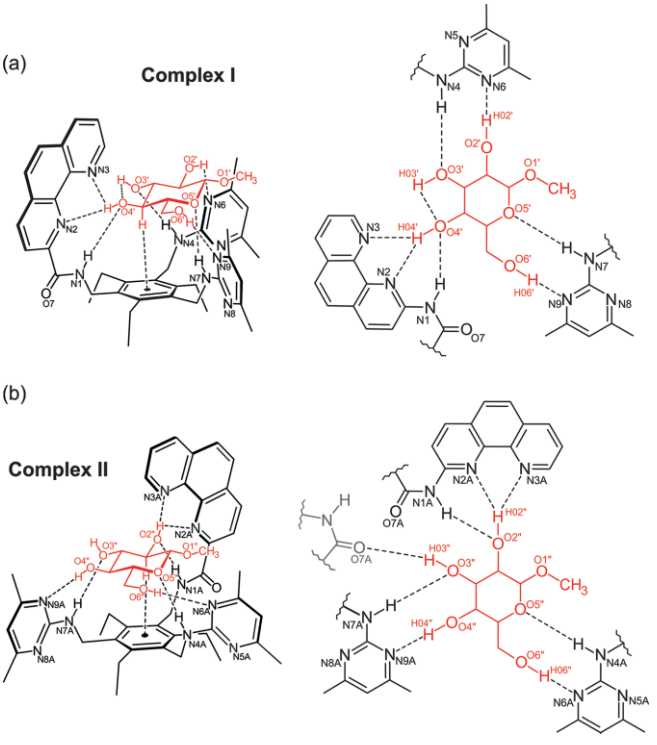

Figure 5. Schematic representation of hydrogen bonds and C–H···π interactions between receptor **1** and methyl β-D-glucopyranoside in the complexes **1·MeβGlc-I** and **1·MeβGlc-II**; the amide unit of the adjacent complex, which participates in 3-OH···O=C hydrogen bond, is marked in gray.

of the respective receptor. Consequently, in each of the two complexes, the hydroxy groups of the sugar molecule interact in a different way with the binding site of the receptor molecule. This is obvious from Figure 5, showing the patterns of hydrogen bond interactions between the complex components. As given in this Figure and Figure 3, the atoms of the sugar molecule in the complex I are labeled differently as in the complex II; for example, OH-2′ for **1·MeβGlc-I** and OH-2″ for **1·MeβGlc-II**. In order to simplify the discussion given below, this additional marking is not taken into account when describing the two complexes.

Both complexes are characterized by two cyclic supramolecular motifs of the graph set[12] $R_2^2(9)$ which however involve different donor and acceptor positions of the carbohydrate molecules. In complex I, the 2-, 3- and 6-OH groups as well as the ring oxygen of **MeβGlc** participate in bidentate hydrogen bonds[13a] with the aminopyrimidine subunits of the receptor. These bidentate hydrogen bonds include 2-OH···$N_{pyrimidine}$/N–H···OH-3 and 6-OH···$N_{pyrimidine}$/N–H···O_{ring} interactions (see Figure 5a). The hydrogen atom of the 4-OH group acts as a bifurcated donor for hydrogen bonding with the two nitrogen atoms of the phenanthroline moiety, whereas the oxygen atom takes part in an intermolecular N–H_{amide}···OH-4 and an intramolecular 3-OH···OH-4 hydrogen bond, the latter involving the neighbored 3-OH-group of the sugar.

In the second complex, the hydroxyl groups at positions 3, 4, and 6 as well as the ring oxygen of the glucopyranoside participate in bidentate hydrogen bonds with the aminopyrimidine subunits of the receptor. In this case, the bidentate

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Table 1. Selected XH···Y distances and angles for complexes **1·MeβGlc-I**, **1·MeβGlc-II**, **2·MeβGlc-I**, and **2·MeβGlc-II**.

XH···Y interactions **Complex I**	XH···Y [Å]	X···Y [Å]	XH···Y angle [deg]	XH···Y interactions **Complex II**	XH···Y [Å]	X···Y [Å]	XH···Y angle [deg]
1·MeβGlc-I				**1·MeβGlc-II**			
NH···OH-4	2.04	2.92	164	NH···OH-2	2.06	2.94	170
NH···OH-3	1.97	2.87	175	NH···O-5	2.15	3.01	162
NH···O-5	2.18	3.06	165	NH···OH-3	2.02	2.91	174
2-OH···N(6)[a]	2.03	2.85	163	2-OH···N(3A)[c]	2.04	2.88	171
4-OH···N(2)[b]	2.63	3.03	111	2-OH···N(2A)[c]	2.65	3.09	114
4-OH···N(3)[b]	1.95	2.79	177	3-OH···O(7A)[d]	2.71	3.09	110
6-OH···N(9)[a]	2.05	2.90	177	4-OH···N(9A)[e]	2.11	2.93	164
4-CH···π[f]	2.53	3.51	166	6-OH···N(6A)[e]	2.08	2.91	170
				2-CH···π[f]	2.52	3.50	165
2·MeβGlc-I				**2·MeβGlc-II**			
NH···OCH_3	2.14	3.01	179	NH···OCH_3	2.10	2.99	173
NH···O-5	2.31	3.19	177	NH···O-5	2.38	3.25	170
NH···OH-3	2.08	2.96	168	NH···OH-3	2.10	2.96	174
2-OH···N(3)[g]	2.12	2.93	160	2-OH···N(3A)[i]	2.07	2.88	161
3-OH···N(9)[g]	2.31	3.11	158	3-OH···N(9A)[i]	2.34	3.13	156
4-OH···N(9)[g]	2.17	2.98	161	4-OH···N(9A)[i]	2.16	2.96	159
6-OH···N(5)[g]	2.02	2.85	168	6-OH···N(5A)[i]	2.07	2.89	166
2-CH···π[h]	2.69	3.68	171	2-CH···π[h]	2.74	3.73	170
5-CH···π[f]	2.94	3.92	165	5-CH···π[f]	2.77	3.73	161

[a] N(6), N(9): pyrimidine nitrogen atoms. [b] N(2), N(3): phenanthroline nitrogen atoms (see Figure 5a). [c] N(2A), N(3A): phenanthroline nitrogen atoms. [d] O(7A): amide oxygen. [e] N(6A), N(9A): pyrimidine nitrogen atoms; (see Figure 5b). [f] Centroid (center of gravity) of the central benzene ring. [g] N(3), N(5), N(9): pyrimidine nitrogen atoms (see Figure 7). [h] An individual ring atom instead of the ring center was chosen as an acceptor site. [i] N(3A), N(5A), N(9A): pyrimidine nitrogen atoms.

hydrogen bonds include 4-OH···$N_{pyrimidine}$/N–H···OH-3 and 6-OH···$N_{pyrimidine}$/N–H···O_{ring} interactions. The 2-OH hydrogen of the sugar acts as a bifurcated donor for hydrogen bonding with the nitrogen atoms of the phenanthroline moiety, whereas the 3-OH hydrogen makes a weak hydrogen bond with the amide oxygen atom of an adjacent receptor molecule (see Figure 5b).

For complex I, the distances of the OH···N/N–H···O hydrogen bonds are in the range of 1.95–2.63 Å with angles at the H-atom of 111–177°; for complex II, these values are 2.02–2.65 Å and 110–174° (see Table 1 and Table S3 in Supporting Information). Moreover, each of the complexes is stabilized by a C–H···π interaction[14–16] between a sugar CH and the central arene ring of the receptor. In the case of complex I the 4-CH···*Cg* (ring A) distance amounts to 2.53 Å, whereas for complex II a distance of 2.52 Å for 2-CH···*Cg* (ring A^A) is observed. Although the two complexes are stabilized by seven hydrogen bonds, the conformation of the sugar molecules is close to an ideal $^4C_1$ chair conformation.

Cross-linking of the complexes is accomplished by a variety of C–H···O[17] and C–H···N[18] type hydrogen bonds to form a close three-dimensional supramolecular network which includes receptor-sugar [*d*(H···O) 2.48–2.59 Å, *d*(H···N) 2.54 Å] and sugar–sugar interactions [*d*(H···O) 2.43, 2.51 Å]. In the latter, the intermolecular C–H···O hydrogen bonds involving a methoxy hydrogen atom and the 6-OH oxygen atom connect the carbohydrate molecules of the neighboring complexes in a strand-like fashion as shown in Figure S1.

Moreover, the heterocyclic units of the receptor molecules interact via π···π[19] (face-to-face) stacking with distances of 3.81–3.86 Å between the centroids of the aromatic rings. An excerpt of the packing structure is presented in Figure S2 in Supporting Information.

Crystal Structure 2·MeβGlc: 1:1 Receptor-Sugar Complexes 2·MeβGlc-I and 2·MeβGlc-II

Compound **2**[9d] differs from **1** by the presence of a third aminopyrimidine-based recognition unit in place of the phenanthroline moiety. In the case of the crystal structure **2·MeβGlc** (monoclinic space group *C*2) the asymmetric part of the unit cell contains two independent but geometrically different receptor molecules and two molecules of the carbohydrate which are connected to form two 1:1 receptor-sugar complexes (see Figure 2b and Figure 6). A space-filling model of complex I is shown in Figure S3.

In each of the complexes the ring oxygen, the methoxy O atom, and all of the OH groups of **MeβGlc** are involved in bidentate hydrogen bonds which include the interactions 2-OH···$N_{pyrimidine}$/NH···$O_{methoxy}$, 4-OH···$N_{pyrimidine}$/NH···OH-3, and 6-OH···$N_{pyrimidine}$/NH···O_{ring} (see Figure 7a and 7b). In addition, the hydroxy groups at positions 2 and 3 of **MeβGlc** are engaged in hydrogen bonding interactions with the pyrimidinyl group of a symmetry-related complex molecule, as shown in Figure 7a and 7b; the 3-OH donates a hydrogen bond to the pyrimidine nitrogen, whereas the oxygen atom of the 2-OH group acts as an acceptor for a weak CH···O bond.

Moreover, in each of the two complexes the 2-CH of the carbohydrate molecule participates in C–H···π interaction with the central benzene ring of the receptor [see Figure 7b and 7c;

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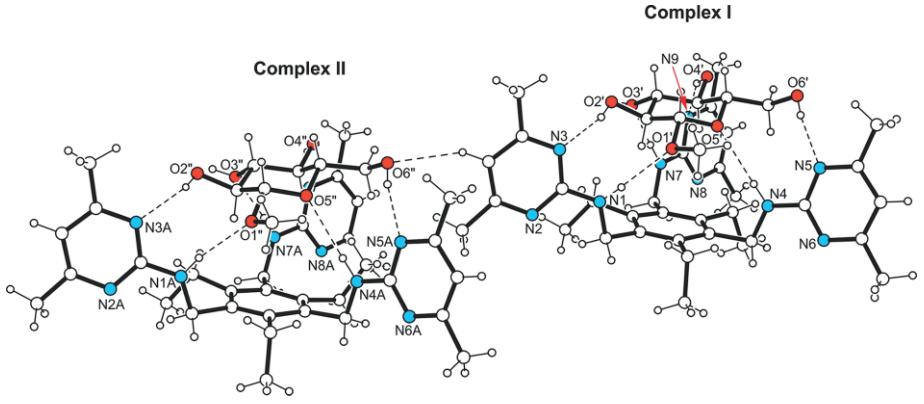

Figure 6. Crystal structure **2·MeβGlc** (2:2): Perspective view of the molecular structures of the 1:1 receptor-sugar complexes **2·MeβGlc-I** and **2·MeβGlc-II** including the labeling of relevant atoms (hydrogen bonds are displayed as broken lines).

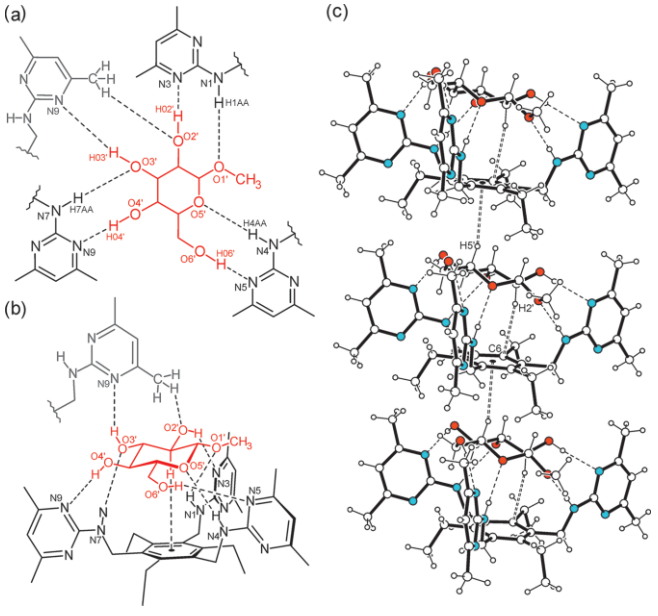

Figure 7. (a,b) Schematic representation of the pattern of hydrogen bonds (broken lines) in complex I in the crystal structure **2·MeβGlc**; the pyridinyl unit from an adjacent complex, which participates in C–H···O/N···HO hydrogen bonds, is marked in gray. (c) Packing excerpt of **2·MeβGlc** showing the C–H···π interactions between the 1:1 receptor-sugar complexes.

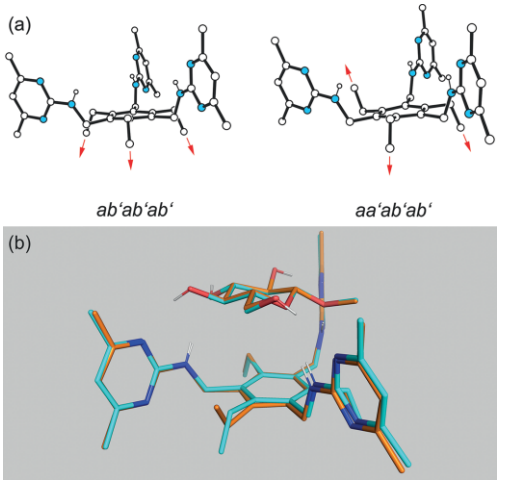

Figure 8. (a) Conformations of the receptor molecules in the complexes **2·MeβGlc-I** and **2·MeβGlc-II** [*a* = above, *b* = below (*a'*/*b'* = Et above/below[20])]. (b) A view of superposition of **2·MeβGlc-I** (light blue lines) and **2·MeβGlc-II** (orange lines) fitting on the carbohydrate atoms C1–C5 and O5 (N atoms are colored blue and O atoms red; all non-polar hydrogens are omitted for clarity).

d(H···π) 2.69/2.74 Å, ∠(C–H···π) 171/170°], whereas the sugar 5-CH is engaged in C–H···π interaction with the neighboring complex, as shown in Figure 7c and S4.

A closer inspection of the 1:1 complexes reveals different conformations of their receptor molecules (see Figure 8). In one of the receptors the substituents are arranged in an alternating order above and below the plane of the central arene ring (*ab'ab'ab'* pattern), whereas in the case of the second complex, the substituents of the receptor adopt an *aa'ab'ab'* arrangement [see Figure 8a; *a* = above, *b* = below (*a'*/*b'* = Et above/below); for a discussion on the conformations of triethylbenzene-based compounds, see ref.[20]].

As shown in Figures S5 and S6, the crystal structure **2·MeβGlc** is composed of rotation symmetric dimers of 1:1 complexes held together by O-H···N and N-H···O hydrogen bonds that create a 12-membered ring motif of the graph set $R_4^4(12)$. These dimers, that propagate along the crystallographic *c*-axis, are poorly connected via C_{arene}–H···O bonds [*d*(H···O) 2.45 Å].

Crystal Structure 3·MeβGlc: 2:1 Receptor-Sugar Complexes $(3)_2$·MeβGlc-I and $(3)_2$·MeβGlc-II

In contrast to compound **2**, each of the three functionalized side-arms of compound **3**[10i] bears a pyridinyl instead of a pyrimidinyl group. The crystal structure **3·MeβGlc** was solved in the space group *P*1 with the unit cell containing four independent receptor molecules, two molecules of the carbohydrate, four molecules of acetonitrile, and one molecule of water. These components are combined into two structurally different 2:1 receptor-sugar complexes which include different contents of hydrogen-bonded solvent molecules. In each of the complexes (designated as complex I and II in Figure 9), the sugar molecule is located in a cavity created by the aminopyridine-bearing side-arms of a pair of receptor molecules. The complex forma-

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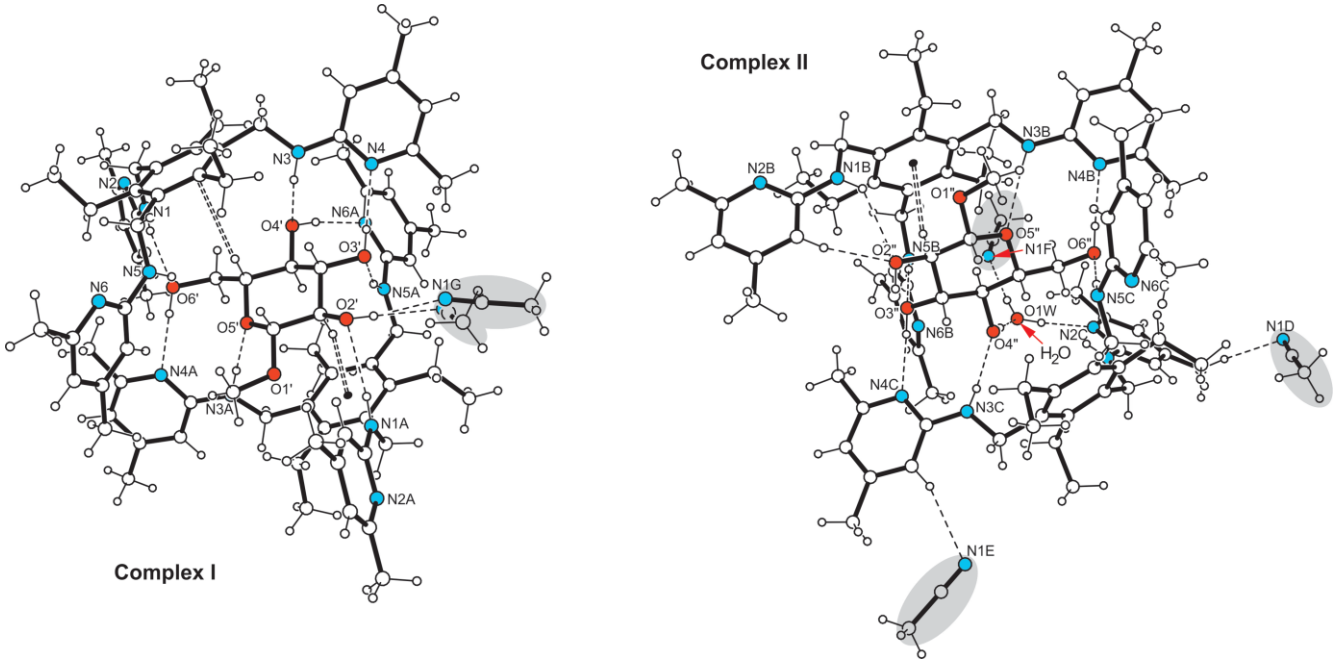

Figure 9. Perspective view of the structures of complexes I and II in the crystal structure **3·MeβGlc** including the labeling of relevant atoms [complexes (**3**)$_2$·**MeβGlc-I** and (**3**)$_2$·**MeβGlc-II**]. Hydrogen bond type interactions are displayed as broken lines, C–H···π interactions as broken double lines. Areas marked by shading represent the positions of the solvent molecules.

tion requires a receptor conformation, in which the heterocyclic moieties are arranged on one side of the benzene ring and the ethyl groups oriented to the opposite side of the ring plane. Within a 2:1 complex no interactions are observed between the receptor molecules so that each of the complexes is stabilized by multiple hydrogen bonds between the receptors and the sugar molecule. Despite this high extent of hydrogen bonding, the ring of the glucopyranoside molecules deviates slightly from an ideal chair conformation.

A comparative analysis of the complexes reveals differences regarding the receptor conformation and the pattern of hydrogen bonding, thus justifying a separate description of their structures.

Complex I. The structure of the complex (**3**)$_2$·**MeβGlc-I** is displayed in Figure 10a (composition of complex I: **3**/**MeβGlc**/CH_3CN = 2:1:1). The pyridine rings of the receptor molecules are inclined at angles of 73.3, 89.0, 67.5° and 89.9, 80.0, 76.2° with reference to the plane of the respective benzene ring (for further details, see Table S2 in Supporting Information). These conformational differences can be ascribed to the asymmetric nature of the included sugar molecule. The hydroxy groups at the positions 3, 4, and 6 as well as the ring oxygen participate in bidentate hydrogen bonds with the aminopyridine moieties of the receptor molecules [d(H···$N_{pyridine}$) 2.01–2.06 Å, ∠(O–H···$N_{pyridine}$) 159–172°; d(H···O) 2.05–2.29 Å, ∠(N–H···O) 146–171°], thus creating three structurally similar ring motifs of the graph set $R_2^2(9)$. The 2-OH group participates in O–H···N bonding with the N atom of the disordered solvent molecule. All OH groups are involved in cooperative[13b] hydrogen bonds, which result from the simultaneous participation of the OHs as

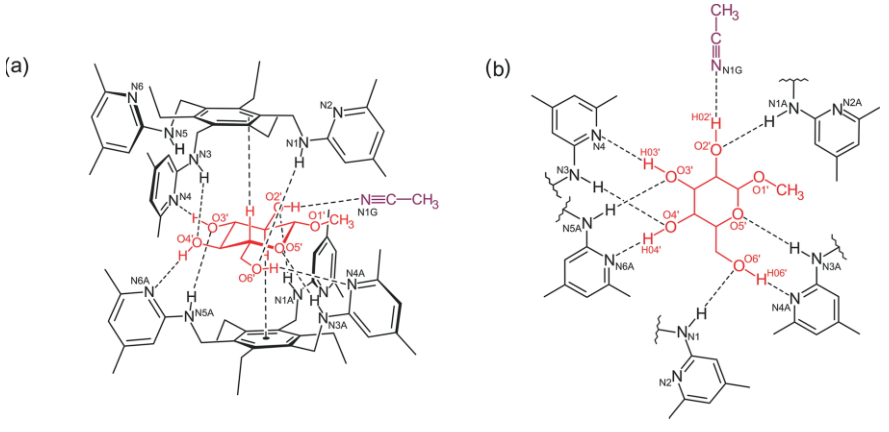

Figure 10. Schematic representation of the pattern of hydrogen bonds (shown as dashed lines) formed between the receptor **3** and methyl β-D-glucopyranoside in complex I [(**3**)$_2$·**MeβGlc-I**]. The carbohydrate molecule is displayed in red, the solvent molecule in violet. Only one disordered position of the solvent molecule is shown.

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Table 2. Selected XH···Y distances and angles for complexes **3·MeβGlc-I** and **3·MeβGlc-II**.

XH···Y interactions **Complex I**	XH···Y [Å]	X···Y [Å]	XH···Y angle [deg]	XH···Y interactions **Complex II**	XH···Y [Å]	X···Y [Å]	XH···Y angle [deg]
3·MeβGlc-I				**3·MeβGlc-II**			
NH···OH-6	2.29	3.15	171	NH···OH-2	2.45	3.11	132
NH···OH-4	2.15	2.92	146	NH···O-5	2.15	3.01	166
2-OH···N(1G)	2.18	2.91	146	NH···OH-3	2.21	3.08	170
3-OH···N(4)[a]	2.01	2.84	172	CH···OH-2[e]	2.56	3.20	125
4-OH···N(6A)[a]	2.06	2.88	166	CH···OH-6[f]	2.64	3.19	115
6-OH···N(4A)[a]	2.06	2.86	159	3-OH···N(4C)[b]	1.96	2.80	174
NH···OH-2	2.37	3.24	174	4-OH···O(1W)	1.85	2.69	177
NH···O-5	2.19	3.03	158	6-OH···N(4B)[b]	1.93	2.77	176
NH···OH-3	2.05	2.90	161	NH···OH-4	2.05	2.93	172
2-CH···π[c]	2.62	3.60	166	NH···OH-6	2.08	2.97	174
5-CH···π[d]	3.02	3.97	161	2-CH···π[c]	2.66	3.64	165

[a] N(4), N(6A), N(4A): pyridine nitrogen atoms (see Figure 10). [b] N(4C), N(4B): pyridine nitrogen atoms (see Figure 12). [c] Centroid (center of gravity) of the central benzene ring. [d] An individual ring atom instead of the ring center was chosen as an acceptor site. [e] Pyridine CH. [f] CH of the pyridine methyl group.

an acceptor for NH groups of the receptor molecules and as a donor for pyridine and solvent nitrogen atoms, respectively, as shown in Figure 10b.

Moreover, the close distance of the sugar 2-CH to the center of the adjacent benzene ring of a receptor molecule [*d*(H···*centroid*) 2.62 Å] and the well-defined bond geometry [∠(C–H···*centroid*) 166°] indicate the presence of a C–H···π contact (see Figure 10a). In addition, the sugar 5-CH participate in a C–H···π contact with the central benzene ring of the second receptor molecule within the 2:1 receptor-sugar complex (see Table 2).

The pyridine nitrogen atoms N2 and N2A are excluded from the complex formation (see Figure 10), while N6 is involved in C–H···N hydrogen bonding with the methyl hydrogen of a solvent molecule allocated to complex II. All in all, the 2:1 receptor-sugar complex is stabilized by eight classical hydrogen bonds.

Due to the given mode of non-covalent bonding the complex I is composed of two conformationally different receptor molecules. In one of them the three atomic sequences $N_{pyridine}$–C–N–H represent *anti-anti-syn* conformation, whereas a *syn-syn-anti* conformation is observed in the second receptor molecule (see Figure 11).

Complex II. The structure of the complex $(\mathbf{3})_2$**·MeβGlc-II** is displayed in Figure 9 and Figure 12 (composition of complex II: **3**/**MeβGlc**/CH_3CN/H_2O = 2:1:3:1). The content of solvent molecules and the presence of a strong donor/acceptor species (H_2O) induce a complex structure that considerably differs from that of complex I. In the present complex, the water molecule reduces the extent of hydrogen bonding between the glucopyranoside and the receptor molecules. In a similar way as in complex I, the 3-, 4- and 6-OH groups as well as the ring oxygen atom participate in bidentate hydrogen bonding with aminopyridine subunits of the receptor molecules [*d*(H···$N_{pyridine}$) 1.93–1.96 Å, ∠(O–H···$N_{pyridine}$) 174–176°; *d*(H···O) 2.05–2.21 Å, ∠(N–H···O) 166–174°]. In addition, the 4-OH group of the sugar molecule is associated with the water molecule via O–H···O bonding [*d*(H···O) 1.85 Å, ∠(O–H···O) 177°], while the hydrogen atoms of the water molecule are connected to the pyridine nitrogen of a receptor and the nitrogen of one solvent molecule

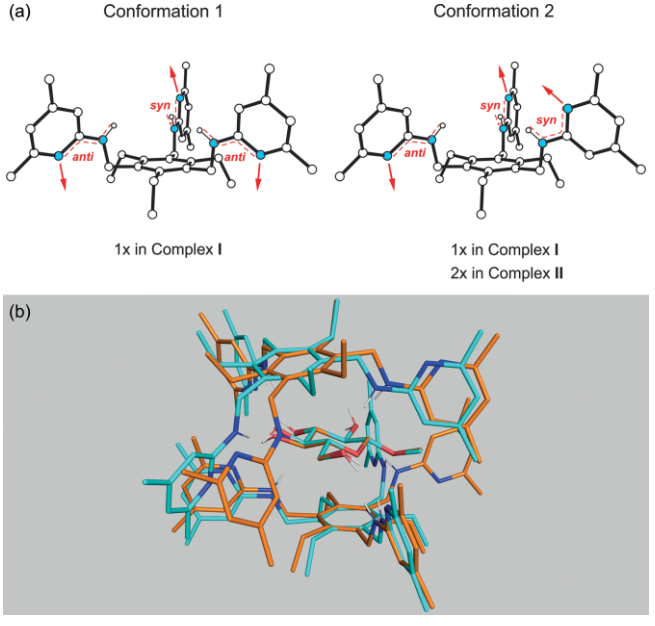

Figure 11. (a) Conformations of the receptor molecules in the crystal structure **3·MeβGlc**. (b) A view of superposition of $(\mathbf{3})_2$**·MeβGlc-I** (orange lines) and $(\mathbf{3})_2$**·MeβGlc-II** (light blue lines) fitting on the carbohydrate atoms C1–C5 and O5 (N atoms are colored blue and O atoms red; all non-polar hydrogens omitted for clarity).

(see Figure 12). Since neither the sugar 2-OH donates a hydrogen bond to a receptor subunit nor one of the amino hydrogens of the receptor is involved in molecular association (see Figure 12b), only seven directly hydrogen bonds contribute to the stabilization of the 2:1 receptor-sugar complex; two additional hydrogen bonds are water-mediated (in the complexes of carbohydrate-binding proteins water-mediated hydrogen bonds are often observed). The nitrogen atoms of two acetonitrile molecules take part in C–H···N bonding with arene and methyl hydrogen atoms of the same receptor molecule, as shown in Figure 12. Owing to the given pattern of receptor-sugar interactions in complex II, one pyridine N atom of each receptor molecule is excluded from molecular association.

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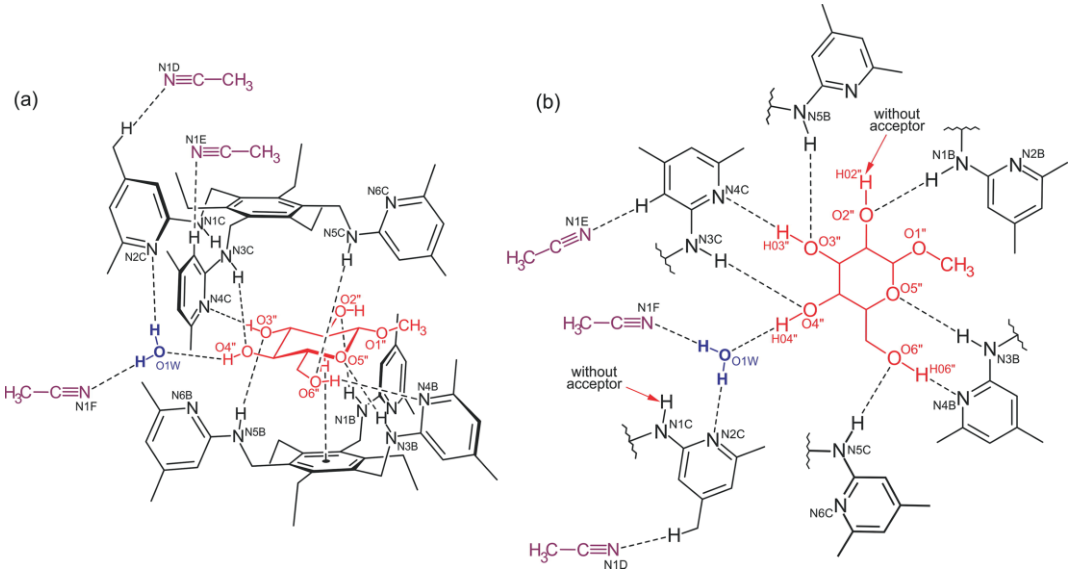

Figure 12. Schematic representation of the pattern of hydrogen bonds (broken lines) in complex II [(**3**)$_2$·**MeβGlc-II**; composition of complex II: **3**/**MeβGlc**/CH_3CN/H_2O = 2:1:3:1].

Hence, the complex is constructed of conformationally similar receptor molecules with an *anti-syn-syn* combination of their atomic sequences $N_{pyridine}$–C–N–H.

Comparative Discussion

In order to gain deeper insight in the recognition behavior of a receptor molecule towards β-D-glucopyranoside a comparative examination of the crystal structures **1·MeβGlc**, **2·MeβGlc** and **3·MeβGlc** as well as of the previously examined structures **4·MeβGlc** and **5·OctβGlc**[4] follows.

The crystal structure **1·MeβGlc** is composed of two different 1:1 receptor-sugar complexes (**1·MeβGlc-I** and **1·MeβGlc-II**). Although the patterns of hydrogen bond interactions in the complexes appear similar, the OH groups of the sugar molecule are connected in a different way to the receptor in each of the complexes. For example, in one of the complexes, the 4-OH hydrogen of the glucopyranoside acts as a bifurcated donor for O–H···N bonding to the phenanthroline nitrogen atoms, while in the second complex the 2-OH hydrogen of the sugar molecule participates in this kind of interaction. This finding suggests functional equivalence of the structurally dissimilar recognition elements of the receptor molecule.

Comparing the crystal structures **1·MeβGlc** and **2·MeβGlc** reveals some interesting features. In the latter case, the crystal is constructed of two structurally similar 1:1 receptor-sugar complexes (**2·MeβGlc-I** and **2·MeβGlc-II**). The presence of three aminopyrimidine-based recognition elements hardly affects the overall geometry of the complexes showing for one of the receptors a fully alternating orientation of substituents (*ab′ab′ab′*) around the central benzene ring and an *aa′ab′ab′* arrangement of substituents for the second complex. The complexes **2·MeβGlc-I** and **2·MeβGlc-II** reveal identical modes of non-covalent interactions, the distances of which differ only slightly from one another in the two complexes (see Table 1). The OH groups, the ring oxygen, and the methoxy oxygen atom of **MeβGlc** contribute to bidentate hydrogen bonds to form three cyclic supramolecular motifs of graph set $R_2^2(9)$ so that each of the complexes is stabilized by seven conventional hydrogen bonds (see Table 1). Another structural feature virtually common to all crystalline receptor-sugar complexes is the presence of a C–H···π bond formed between the CH-2 of **MeβGlc** and the center of the benzene ring of **2**.

Compared to **2·MeβGlc**, the enhanced steric demand of the phenanthroline moiety in **1·MeβGlc** has a fundamental influence on the pattern of molecular crosslinking and the packing behavior of the molecules in the crystal. This is also reflected in the different space group symmetries (*C*2 vs. $P2_1$) and cell parameters. While the crystal structure **2·MeβGlc** is characterized by the presence of C–H_{sugar}···π interactions between the complexes, significant π···π arene interactions contribute to the stability of the packing structure of **1·MeβGlc**.

The crystal structure **3·MeβGlc** consists of two different "sandwich-like" 2:1 receptor-sugar complexes each stabilized by multiple O–H···N and N–H···O interactions. The complexes include hydrogen-bonded solvent (CH_3CN) to a different degree. The presence of an additional H_2O molecule in one of the complexes reduces the number of hydrogen bonds within the 2:1 receptor-sugar unit which obviously has no influence on the stability of the complex in the crystalline state. In contrast to **2·MeβGlc**, the methoxy oxygen atom of the bound sugar in **3·MeβGlc** is not involved in the formation of hydrogen bonds stabilizing the 2:1 receptor-sugar complexes.

Another structural feature is the presence of C–H···π interactions formed between the sugar CHs and the aromatic ring of the receptor. In the case of the complex (**3**)$_2$·**MeβGlc-I** these interactions are formed with the participation of the CH units in the positions 2 and 5 of **MeβGlc**, so that both sides of the sugar molecule are involved in this kind of interactions with the central benzene ring of each of the two receptor molecules. In

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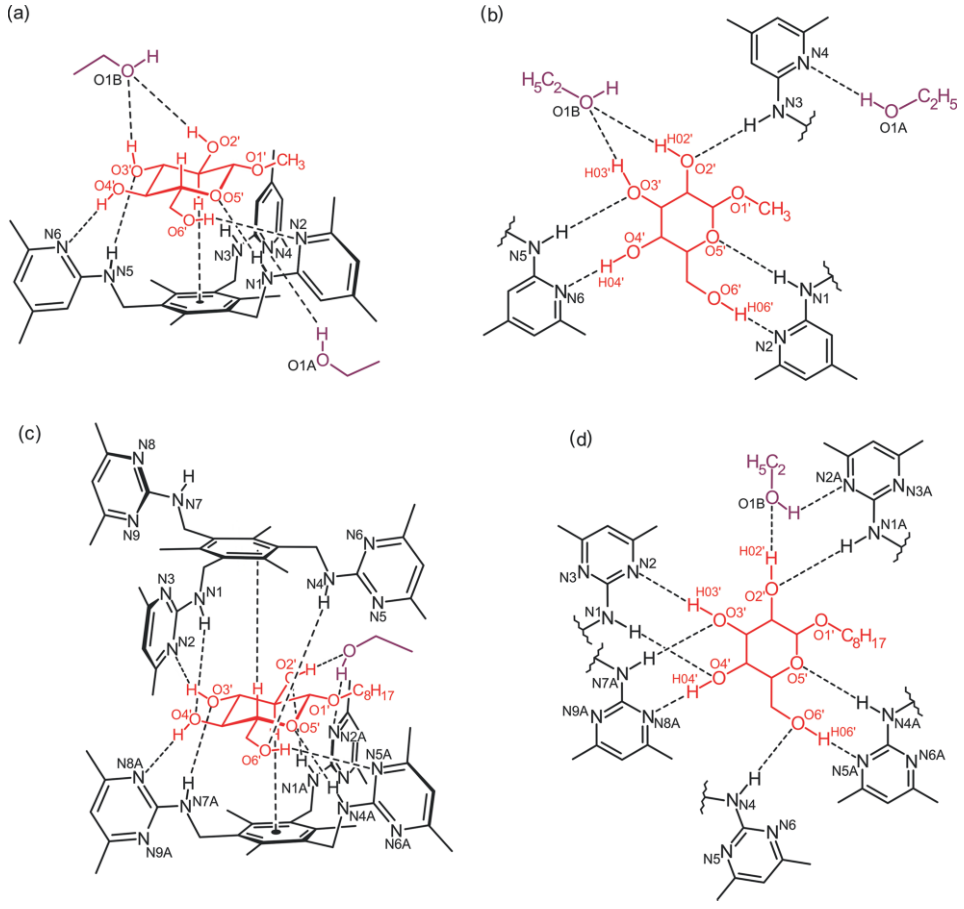

Figure 13. (a,b) Schematic representation of the pattern of hydrogen bonds (broken lines) in the complex **4·MeβGlc**[4] (**4**/**MeβGlc**/EtOH = 1:1:2). (c,d) Schematic representation of the pattern of hydrogen bonds (broken lines) and C–H···π interactions in the reported complex **5·OctβGlc**[4] (**5**/**OctβGlc**/EtOH = 2:1:1).

contrast, complex $(\mathbf{3})_2$**·MeβGlc-II** is characterized by the presence of only one C–H···π interaction formed between the CH-2 of **MeβGlc** and the benzene ring of one receptor molecule.

A comparative inspection of the carbohydrate complexes **3·MeβGlc** and **2·MeβGlc** and previously described complexes of this type[4] reveal some interesting features. In the 1:1 complex formed between compound **4**, which represent the trimethylbenzene-based analog of **3**, and methyl β-D-glucopyranoside (**4·MeβGlc**) the strongly interacting solvent markedly affects the pattern of non-covalent bonds within the complex unit (composition of the complex: **4**/**MeβGlc**/EtOH = 1:1:2). In this complex, only the 3-, 4- and 6-OH groups, as well as the ring oxygen of the pyranoside, participate in bidentate hydrogen bonds with aminopyridine subunits of the receptor ($4\text{-OH}\cdots N_{pyridine}/N\text{–H}\cdots\text{OH-3}$ and $6\text{-OH}\cdots N_{pyridine}/N\text{–H}\cdots O_{ring}$), and the sugar CH-2 participates in a C–H···π interaction with the benzene ring of **4**. The hydroxy hydrogens H3 and H2 of the sugar are involved in O–H···O bonding with the oxygen atom of the ethanol molecule. The second ethanol molecule is connected via O–H···N bonding to a pyridine N atom of the receptor, as illustrated in Figure 13a and 13b.

Quite remarkably, a structural situation similar to that of **3·MeβGlc** is found in the reported crystal structure of the 2:1 receptor-sugar complex formed between compound **5**, a trimethylbenzene-based analog of **2**, and octyl β-D-glucopyranoside. A comparative analysis of complex **5·OctβGlc** (**5**/**OctβGlc**/EtOH = 2:1:1), the schematic structure of which is presented in Figure 13c and 13d, and complex I of **3·MeβGlc** reveals nearly identical patterns of non-covalent bonds between the complex components. A slight structural difference between the complexes is caused by the coordinating solvent molecule. In this particular case neither the structure of the recognition elements of the receptor (pyridine vs. pyrimidine) nor the nature of the used solvent and the modification of the alkoxy group of the sugar component affect the structure of the complexes.

For a better comparison between the new and previously described complexes, the overlays of **2·MeβGlc-I**, **2·MeβGlc-II**, and **4·MeβGlc** as well as of $(\mathbf{3})_2$**·MeβGlc-I**, $(\mathbf{3})_2$**·MeβGlc-II** and **5·OctβGlc** are given in Figure S7 and Figure S8, respectively.

Conclusion

As mentioned above, crystalline complexes formed between artificial receptors and carbohydrates are very rarely reported in the literature and the presence of two complexes in one crystal structure is particularly remarkable. Even more noteworthy is that each of the three crystal structures described here is characterized by the presence of two different receptor-sugar complexes. Such a situation was not observed in the case of the

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crystal structures reported by us earlier, in which only one receptor-sugar complex was present.

Particularly interesting is that the binding modes found in the crystalline complexes formed between the artificial receptors **1**–**5** and glucopyranoside show remarkable similarity to those used by the carbohydrate-binding proteins.[2] It is noteworthy that many of the basic molecular features of protein-carbohydrate interactions, that have been summarized years ago by Quiocho,[2e,2f] apply to interactions observed in complexes formed by the artificial receptors. Both in the natural complexes and in the complexes of the artificial receptors **1**–**5**, the ring oxygen and the OH groups of the bound sugar are involved in the formation of hydrogen bonds, including bidentate and cooperative hydrogen bonds (see Figure 14a and 14b) as well as water-mediated (see Figure 14c) hydrogen bonding. The crystal structure of protein-carbohydrate complexes revealed that bidentate hydrogen bonds can not only be formed by participation of two adjacent hydroxy groups (when both are equatorial or one is equatorial and the other axial), but also by the contribution of the ring oxygen, when paired, for example, with the OH-6 of D-glucose or the axial OH-4 of L-arabinose. Such bidentate hydrogen bonds can also be observed in the receptor-sugar complexes described here, as exemplarily shown in Figure 14a and 14b.

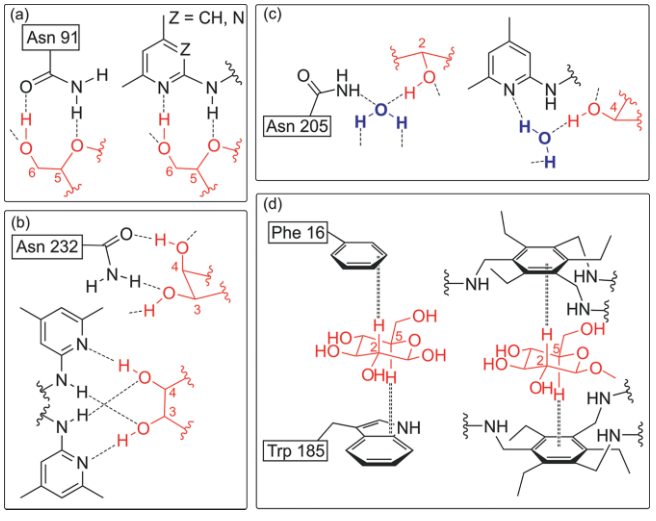

Figure 14. Examples of hydrogen bonds and C–H···π interactions in complexes formed by carbohydrate-binding proteins [complex of D-galactose- and L-arabinose-binding proteins with D-glucose (a, d) and L-arabinose (b, c),[2e] respectively] and by artificial receptors described in this work.

The 2-aminopyridine/-pyrimidine units are able to participate in the formation of similar hydrogen bonding motifs as these observed in the natural complexes for the amide group (see Figure 14a) and can be regarded as heterocyclic analogs[22] of the asparagine/glutamine primary amide side chain. Cooperative hydrogen bonds, which result from the simultaneous participation of a sugar hydroxy group as donor and acceptor of hydrogen bonds, are typical for both the natural and artificial complexes and examples of such interactions are also given in Figure 14. The above-mentioned hydrogen bonds are supplemented by weaker interactions, such as CH···O/N hydrogen bonds and van der Waals contacts. Many of the first-mentioned interactions are characterized by short H···O/N contacts and favorable bond geometry [for example, *d*(H···O/N) 2.43/2.48 Å, ∠(C–H···O/N) 153/172°, as given in Table S4], which indicate their important contribution[23] to the overall stabilization[24] of the complexes. As in natural complexes, one or two aromatic groups of the artificial receptors stack on the sugar ring, where the sandwich-like complexation is only observed in the 2:1 receptor-sugar complexes (Figure 14d).

Crystal structures of artificial receptors with a bound sugar provide deeper insights into the phenomena of molecular recognition of carbohydrates and act as a source of ideas for the development of new carbohydrate-binding agents with more predictable binding properties.

Experimental Section

Syntheses of Compounds 1–3: Compounds **2** and **3** were prepared by the reaction of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene with 2-amino-4,6-dimethylpyrimidine or 2-amino-4,6-dimethylpyridine, respectively, as reported by us previously.[9d,10i]The synthesis of compound **1** is given below.

1-[(1,10-Phenanthrolin-2-yl-carbonyl)aminomethyl]-3,5-bis[(4,6-dimethylpyrimidin-2-yl)aminomethyl]-2,4,6-triethylbenzene (1)

Synthesis of 1,10-phenanthroline-2-carbonyl chloride: A mixture of 1,10-phenanthroline-2-carboxylic acid (0.183 g, 0.82 mmol) and thionyl chloride (20 mL) was refluxed for 6 h and afterwards thionyl chloride was removed in vacuo. To completely remove thionyl chloride, dry THF (20 mL) was added and the solvent (together with residues of thionyl chloride) was removed under reduced pressure. This procedure was repeated three times and then the crude product was used directly for further reaction.

Synthesis of 1: A solution of 1-(aminomethyl)-3,5-bis[(4,6-dimethylpyrimidin-2-yl)amino-methyl]-2,4,6-triethylbenzene[21] (0.35 g, 0.75 mmol) and triethylamine (0.11 mL) in THF/CH_2Cl_2 (1:1, v/v; 50 mL) was added dropwise to a solution of 1,10-phenanthroline-2-carbonyl chloride in THF/CH_2Cl_2 (1:1, v/v; 40 mL). After complete addition, the mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvents were removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 10:1) and recrystallized from THF/*n*-hexane. Yield 51 % (255 mg, 0.38 mmol). R_f = 0.48 ($CHCl_3$/MeOH, 10:1). M.p. 235–236 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.26 (t, *J* = 4.7 Hz, 1H), 9.15 (dd, *J* = 4.4, 1.7 Hz, 1H), 8.62 (d, *J* = 8.3 Hz, 1H), 8.41 (d, *J* = 8.3 Hz, 1H), 8.28 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.85 (s, 2H), 7.66 (dd, *J* = 8.1, 4.4 Hz, 1H), 6.32 (s, 2H), 5.01 (t, *J* = 3.9 Hz, 2H), 4.85 (d, *J* = 4.7 Hz, 2H), 4.62 (d, *J* = 4.3 Hz, 4H), 2.90 (q, *J* = 7.5 Hz, 4H), 2.79 (q, *J* = 7.5 Hz, 2H), 2.30 (s, 12H), 1.29 (t, *J* = 7.6 Hz, 6H), 1.25 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 167.4, 164.5, 161.9, 150.1, 150.0, 145.7, 144.4, 144.2, 143.8, 137.4, 136.5, 133.0, 131.9, 130.1, 129.0, 127.8, 126.5, 123.3, 121.6, 109.7, 40.0, 38.4, 24.0, 23.3, 23.1, 16.7, 16.6. HRMS-ESI: $C_{40}H_{45}N_9O$ *calcd*. for $[M + H]^+$: 668.38198, found 668.38193.

Crystallographic Data

The crystals were grown by isothermal evaporation of the solvent from a solution of the receptor in the presence of glucopyranoside. The sugar/receptor stoichiometry was varied between 1:1 to 1:10 and as solvents were used dry and water-containing methanol, eth-

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anol, acetonitrile, and chloroform as well as different mixtures of these solvents. The experiments revealed that the determination of the crystallization conditions that predictably lead to 1:1 or 2:1 receptor-sugar complexes is currently not possible. For example, in the case of compound **1**, the use of 1:1, 2:1, and 4:1 receptor/sugar stoichiometry always led to the formation of the same 1:1 receptor-sugar complexes. In contrast, crystals of compound **2** with the bound sugar were only obtained from 1:1 receptor/sugar solutions. In the case of compound **3** the use of 1:1, 2:1 and 10:1 receptor/sugar stoichiometry always provided 2:1 receptor/sugar complexes. We are currently conducting systematic studies of the crystallization conditions that should enable the above-mentioned predictability.

Crystal data for **2·MeβGlc** and **3·MeβGlc** were collected on a Bruker X8 APEX CCD diffractometer using φ- and ω-scans. Preliminary structure models were derived by application of direct methods[25a] and were refined by full-matrix least-squares calculation based on F^2 for all reflections.[25b] In the case of **1·MeβGlc** the crystal data were collected on a STOE IPDS-2T Diffraktometer (Stoe & Cie, 2002) with Mo-K_α-radiation (λ = 0.71073 Å). Software for data collection and cell refinement: STOE X-AREA;[26a] data reduction: X-RED.[26b] Reflections were corrected for background, Lorentz, and polarization effects. Preliminary structure models were derived by application of direct methods[27a] and were refined by full-matrix least-squares calculation based on F^2 for all reflections.[27b] The chosen experimental conditions (T = 153 K) of data collection yielded a data set of moderate quality ($\theta \approx 26°$) resulting in a data/parameter ratio of ca. 8.0. All non-hydrogen atoms were refined anisotropically. The positions of the OH hydrogen atoms of the carbohydrate molecules were identified in the differential electron density maps. All other hydrogen atoms were included in the models in calculated positions and were refined as constrained to bonding atoms.

Deposition Numbers 2022053 (**1·MeβGlc**), CCDC 2022052 (**2·MeβGlc**), and CCDC 2022054 (**3·MeβGlc**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Supporting Information (see footnote on the first page of this article): Packing excerpts of **1·MeβGlc** and **2·MeβGlc** (Figures S1, S2, S4–S6). Space-filling representation of complex I in the crystal structure **2·MeβGlc** (Figure S3). A view of superposition of **2·MeβGlc-I**, **2·MeβGlc-II**, and **4·MeβGlc** (Figure S7). As well as of $(\mathbf{3})_2$**·MeβGlc-I**, $(\mathbf{3})_2$**·MeβGlc-II**, and **5·OctβGlc** (Figure S8). Crystallographic and structure refinement data of **1·MeβGlc**, **2·MeβGlc**, and **3·MeβGlc** (Table S1). Selected geometric parameters of **1·MeβGlc**, **2·MeβGlc**, and **3·MeβGlc** (Table S2). Geometrical parameters of hydrogen bonds and arene interactions in the crystal structures **1·MeβGlc**, **2·MeβGlc**, and **3·MeβGlc** (Table S3 and S4). ^{1}H and ^{13}C NMR spectra of compound **1** (Figures S9 and S10).

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Keywords: Molecular recognition · Receptor-sugar complexes · Carbohydrates · Hydrogen bonds · CH-π Interactions

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