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Binding modes of methyl α -D-glucopyranoside to an artificial receptor in crystalline complexes[†]

 Linda Köhler, Conrad Hübler, Wilhelm Seichter and Monika Mazik *

Compared to the numerous X-ray crystal structures of protein-carbohydrate complexes, the successful elucidation of the crystal structures of complexes between artificial receptors and carbohydrates has been very rarely reported in the literature. In this work, we describe the binding modes of two complexes formed between methyl α -D-glucopyranoside and an artificial receptor belonging to the class of compounds consisting of a 1,3,5-trisubstituted 2,4,6-trialkylbenzene scaffold. It is particularly noteworthy that these two complexes are present in one crystal structure, as was observed by us for the first time in the case of the recently reported three crystal structures of the complexes with methyl β -D-glucopyranoside, each containing two different receptor-carbohydrate complexes. The noncovalent interactions stabilizing the new complexes are compared with those observed in the aforementioned crystalline complexes with methyl β -D-glucopyranoside.

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1 Introduction

Recently we have reported the crystal structures of complexes formed between methyl β -D-glucopyranoside (**Me β Glc**) and artificial receptors¹ belonging to the class of compounds consisting of a 1,3,5-trisubstituted 2,4,6-trialkylbenzene scaffold² (compounds **1–3**, as given in Fig. 1 and 2), the representatives of which we have systematically examined for their ability to bind carbohydrates over the past few years.^{3–5} Especially noteworthy is that each of the described crystal structures is characterized by the presence of two different receptor-sugar complexes, as illustrated in Fig. 1. In contrast to these results, the presence of only one type of receptor-sugar complex could be observed in the crystal structures reported by us earlier.⁶ It should be emphasized that the crystal structures of complexes formed between artificial receptors and sugars have rarely been reported until now. Beside the above mentioned crystalline complexes of acyclic receptors,^{1,6} the crystal structures of foldamers^{7a–d} and of a macrocyclic receptor⁸ with a bound sugar molecule are described in the literature and contribute to a better

understanding of the basic molecular features of carbohydrate recognition (for recent examples of binding studies in solution, see ref. 9). In contrast, a large number of X-ray crystal structures of proteins bound to various sugar substrates has been described in the literature^{10,11} and represents an important source of information about the noncovalent interactions that contribute to the selective and effective binding of carbohydrates by proteins.

The above mentioned complexes of the artificial systems contain such bound carbohydrates as methyl^{1,6} and octyl β -D-glucosides,⁶ β -D/ β -L-glucopyranose,⁸ β -D/ α -L-mannopyranose, β -D/ β -L-fructopyranose, α -D/ α -L-xylopyranose,^{7a,c,d} and α -1,4-xylobiose.^{7b} To the best of our knowledge, no crystalline complexes with α -D-glucopyranosides have been reported in the literature so far.

In this paper we describe the binding modes of complexes formed between methyl α -D-glucopyranoside (**Me α Glc**) and the triethylbenzene derivative **2** bearing three aminopyrimidine-based recognition units. It is particularly remarkable that again two different complexes are present in the crystal structure **2**·**Me α Glc** (assigned as **2**·**Me α Glc-I** and **2**·**Me α Glc-II**), as previously observed by us for the crystal structures of the receptor-carbohydrate complexes containing methyl β -D-glucopyranoside.¹

In addition to the detailed analysis of the noncovalent interactions stabilizing the new complexes, their comparison with those observed in the aforementioned crystalline complexes with methyl β -D-glucopyranoside¹ is also the subject of this work.

2 Results and discussion

2.1 Crystal structure **2**·**Me α Glc**: 1 : 1 receptor-sugar complexes **2**·**Me α Glc-I** and **2**·**Me α Glc-II**

The crystal structure **2**·**Me α Glc** was solved in the space group *P1* with the asymmetric unit containing two receptor molecules,

Institut für Organische Chemie, Technische Universität Bergakademie Freiberg, Leipziger Strasse 29, 09599 Freiberg, Germany. E-mail: monika.mazik@chemie.tu-freiberg.de; Web: https://tu-freiberg.de/fakultaet2/orgch; Fax: +49 3731393170; Tel: +49 3731392389

[†] Electronic supplementary information (ESI) available: ORTEP-plot of the crystal structure **2**·**Me α Glc** (Fig. S1). Space filling representation of complex I in the crystal structure **2**·**Me α Glc** (Fig. S2). Views of the superimposed complex structures of **2**·**Me α Glc-I** and **2**·**Me α Glc-II** with **2**·**Me β Glc-I** fitted on the carbohydrate atoms C1–C5 and O5 (Fig. S3). Crystallographic and structure refinement data of **2**·**Me α Glc** (Table S1). Selected geometric parameters of **2**·**Me α Glc** (Table S2). Geometrical parameters of hydrogen bonds and arene interactions in the crystal structure **2**·**Me α Glc** (Table S3). Synthesis of compound **2**. CCDC 2072720. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra03390e



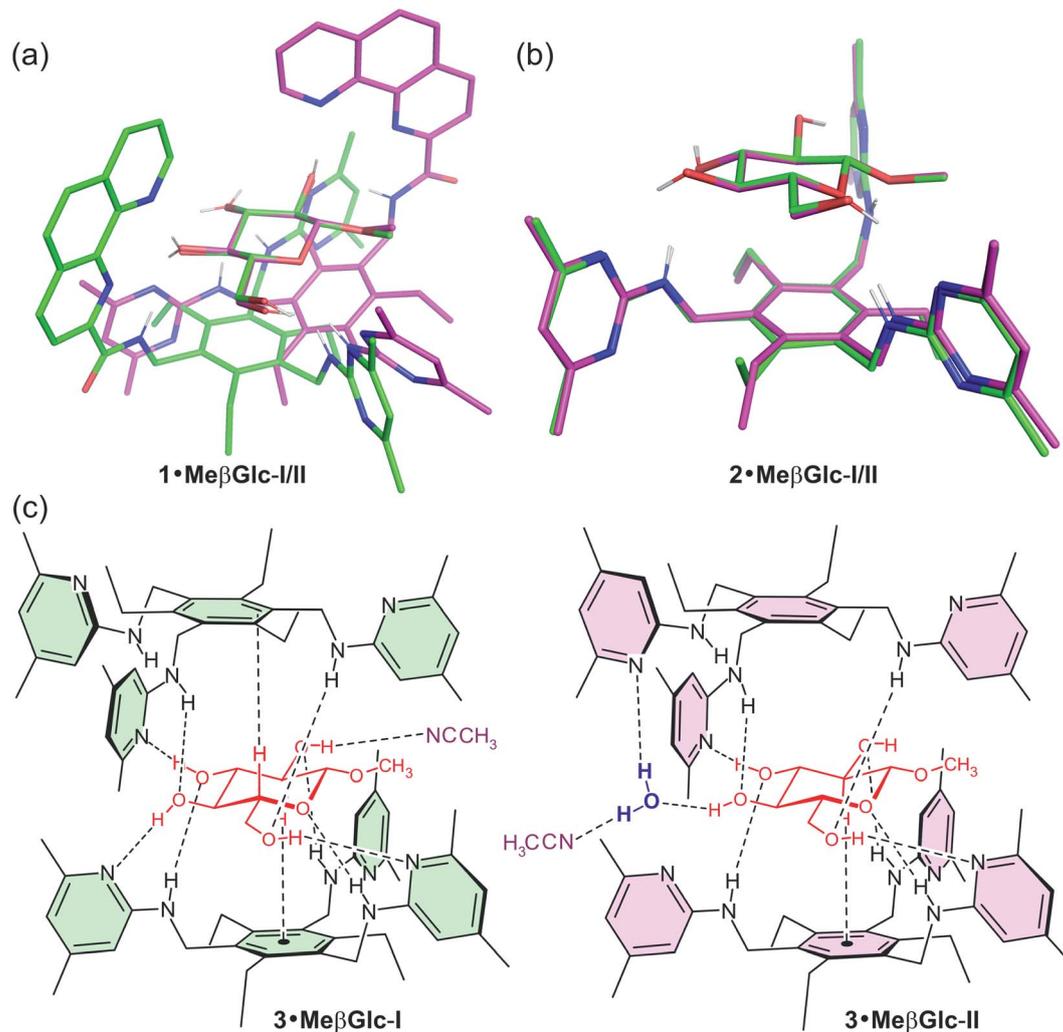


Fig. 1 A view of the superposition of complex I (green lines) and complex II (pink lines) observed in the crystal structure **1·MeβGlc** (a) and in the crystal structure **2·MeβGlc** (b) fitted on the carbohydrate atoms C1–C5 and O5 (N atoms are colored blue and O atoms red; all H atoms, which are not involved in hydrogen bonds or C–H... π interactions are omitted for clarity). (c) Schematic view of the crystalline 2 : 1 receptor–sugar complexes **3·MeβGlc-I** (green) and **3·MeβGlc-II** (pink).[†] For structures of compounds 1–3, see Fig. 2.

two molecules of the carbohydrate, one water and six methanol molecules. These components are connected to two 1 : 1 receptor–sugar complexes, designated as complex I and II, as shown in Fig. 3. Under the chosen experimental conditions the methanol molecules marked as F and G (see Fig. S1[†]) display large displacement parameters, so that their anisotropic refinement was dispensed with.

The two complexes display structural similarities which become particularly evident when looking at their superposition viewed in Fig. 3b. In both complexes the substituents of the

receptor molecule are arranged in an alternating order above and below the plane of the benzene ring [$ab'ab'$ arrangement, a = above, b = below (a'/b' = Et above/below)¹²]. The sugar molecule is located in the receptor cavity created by the three functionalized side-arms. The space-filling model of complex I showing the spatial fit of the sugar component towards the receptor molecule is presented in Fig. S2.[†]

The functionalized side-arms of the receptor molecules exist in an elongated conformation with torsion angles of 160.6–179.9° for the atomic sequences C_{benzene}–C–N–C_{pyrimidine}. The

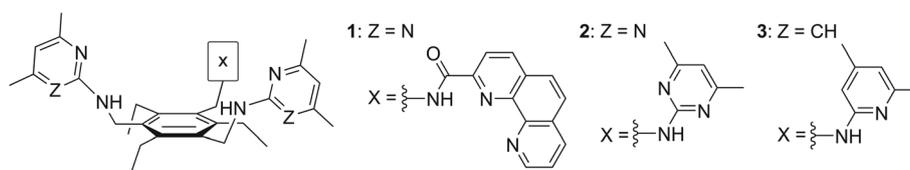


Fig. 2 Structures of the compounds 1–3.



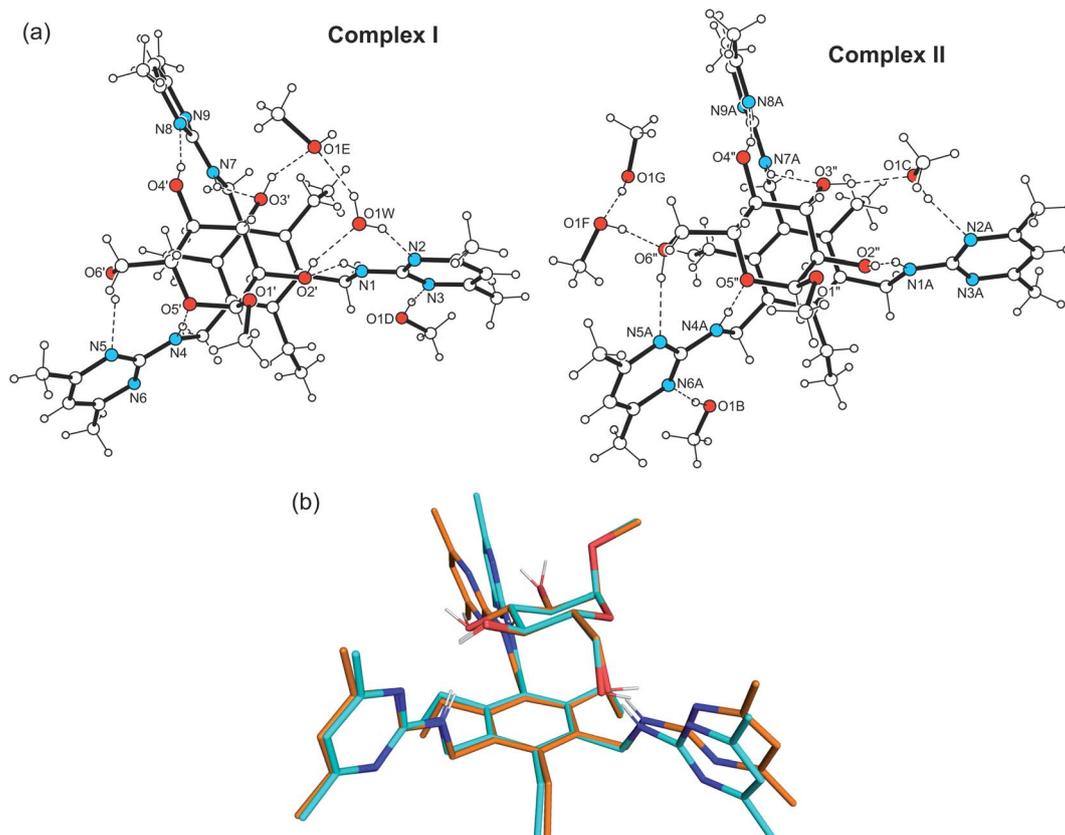


Fig. 3 (a) Top views of the complexes $2 \cdot \text{Me}\alpha\text{Glc-I}$ and $2 \cdot \text{Me}\alpha\text{Glc-II}$ as ball-and-stick representation. In order to emphasize the structural differences of the complexes, a uniform orientation of the methyl α -D-glucopyranoside facing the viewer is used. (b) A view of the superposition of the complex I ($2 \cdot \text{Me}\alpha\text{Glc-I}$; light blue lines) and the complex II ($2 \cdot \text{Me}\alpha\text{Glc-II}$; orange lines) fitted on the carbohydrate atoms C1–C5 and O5 (N atoms are colored blue and O atoms red; all H atoms, which are not involved in hydrogen bonds are omitted for clarity).

inclination angles of the heterocyclic units with reference to the benzene plane are 79.8, 72.1 and 87.5° for complex I, whereas for complex II they amount to 74.0, 88.1 and 76.7° (for further details, see Table S2†).

The structural differences between the complexes are essentially due to the coordination behavior of the solvent molecules, which result in different connection patterns between the complex components. These are shown schematically in Fig. 4.

In each of the complexes, the 3-, 4- and 6-OH groups as well as the ring O atom contribute to the formation of bidentate hydrogen bonds^{13a} with two pyrimidin-2-yl-amino units thus forming two cyclic synthons of the graph set¹⁴ $R_2^2(9)$. These bidentate hydrogen bonds include the interactions 4-OH...N_{pyrimidine}/N-H...OH-3 and 6-OH...N_{pyrimidine}/N-H...O_{ring}.

In complex I ($2 \cdot \text{Me}\alpha\text{Glc-I}$; see Fig. 4), the water molecule and one of the alcohol molecules (E) prevent the 3-OH group of the glucopyranoside to act as hydrogen bond donor to the receptor. Instead, two fused synthons of structures $R_3^3(8)$ and $R_2^3(9)$ emerge from the connection of these guest (solvent) molecules with the 2-OH and 3-OH groups of the sugar molecule and the remaining pyrimidin-2-yl-amino moiety of the receptor. The atom N(3) of this heterocyclic unit acts as an acceptor for an O-H...N bond with the second methanol molecule (D). The

hydrogen bond lengths in complex I are 1.96–2.09 Å for O-H...N, 1.94–2.65 Å for N-H...O, and 1.84–1.92 Å for O-H...O interactions (see Tables 1 and S3†).

In contrast to complex I, the complex II ($2 \cdot \text{Me}\alpha\text{Glc-II}$) does not contain a bound water molecule, but four methanol molecules. While three of the alcohol molecules are located in the peripheral region of the complex and therefore do not significantly affect the binding mode between the sugar and receptor, the remaining solvent molecule prevents the direct connection of the 3-OH group of $\text{Me}\alpha\text{Glc}$ with the pyrimidine atom N(2A) of the receptor thus forming a 11-membered synthon of the graph set $R_3^3(11)$.

A common structural feature of the binding mode in both complexes is the presence of a C-H... π contact¹⁵ between the sugar 2-CH and the central benzene ring of the receptor molecule with distances of 2.74 Å (complex I) and 2.75 Å (complex II). As a result of the axial arrangement of the methoxy group of $\text{Me}\alpha\text{Glc}$, the oxygen atom of this group is excluded from the interactions with the receptor molecule.

The excerpt of $2 \cdot \text{Me}\alpha\text{Glc}$ displayed in Fig. 5 reveals a strand-like linkage of sugar, alcohol and water molecules that creates an infinite pattern of O-H...O bonds in direction of the crystallographic *a*-axis. The hydroxymethyl group of the sugar molecule of complex II as well as the methanol molecules E, F



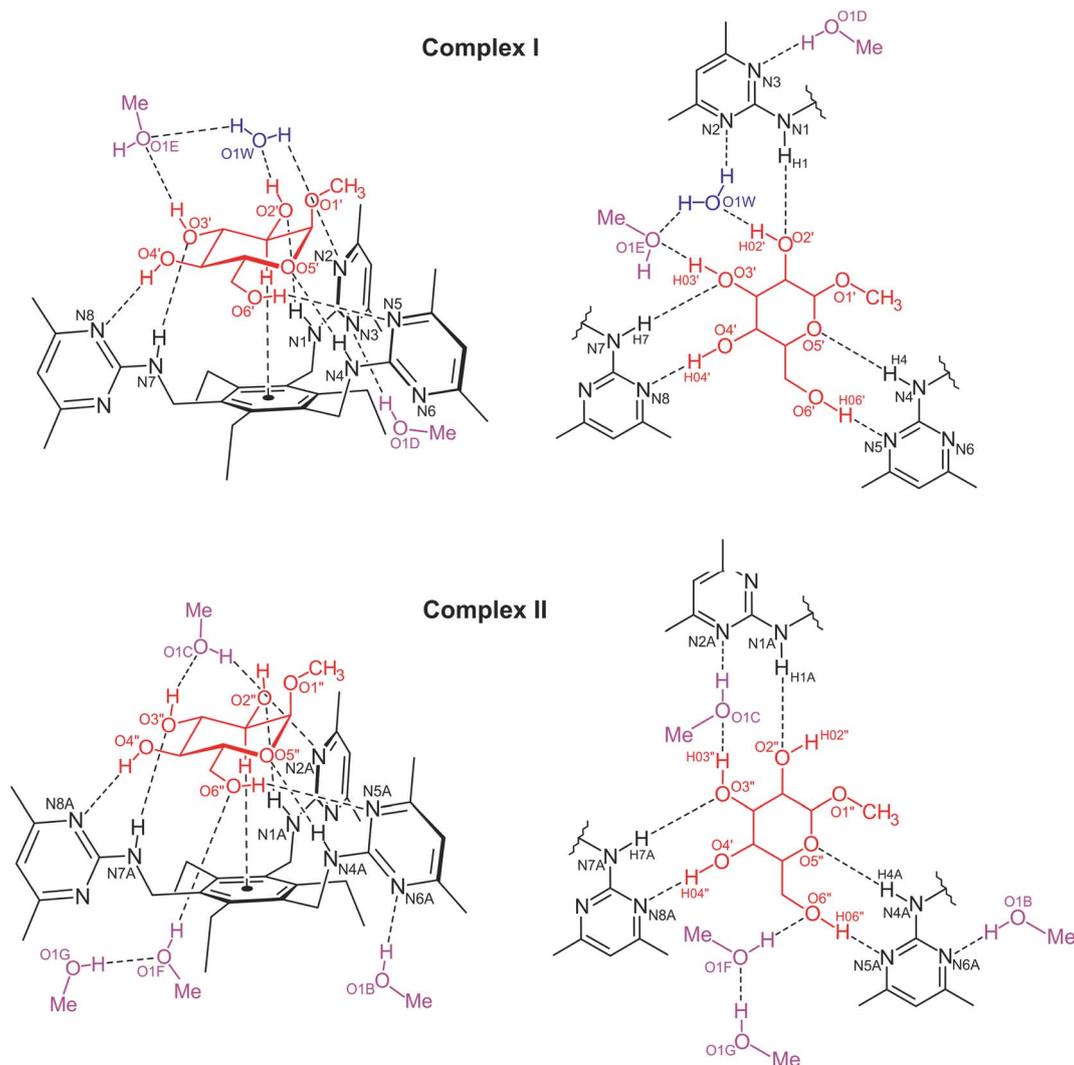


Fig. 4 Schematic representation of hydrogen bonds and C–H... π interactions (shown as dashed lines) between receptor **2** and methyl α -D-glucopyranoside in the complexes **2**·Me α Glc-I and **2**·Me α Glc-II. The carbohydrate molecule is displayed in red, the water molecule in blue and the methanol molecules in violet. Composition of complex I: **2**·Me α Glc/CH₃OH/H₂O = 1 : 1 : 2 : 1; composition of complex II: **2**·Me α Glc/CH₃OH = 1 : 1 : 4.

and G contribute in the formation of this supramolecular strand-like structure. Only one hydrogen atom of each water molecule is included in this hydrogen bond pattern. The

crystallographically independent receptor molecules interact *via* offset π ... π arene interactions¹⁶ with a *centroid*...*centroid* (C_g ... C_g) distance of 3.53 Å and a slippage of 0.56 Å between the

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

2 ·Me α Glc-I				2 ·Me α Glc-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)
NH...OH-2	1.94	2.82	172	NH...OH-2	2.06	2.91	158
NH...OH-3	1.99	2.88	173	NH...O5	2.53	3.34	152
NH...O5	2.65	3.45	151	NH...OH-3	2.05	2.93	169
2-OH...O(1W) ^a	1.92	2.73	165	3-OH...O(1C) ^b	1.96	2.77	158
3-OH...O(1E) ^b	1.84	2.64	158	4-OH...N(8A) ^e	2.14	2.97	173
4-OH...N(8) ^c	2.09	2.92	166	6-OH...N(5A) ^e	1.99	2.79	162
6-OH...N(5) ^c	1.96	2.79	168	2-CH... π ^d	2.75	3.70	158
2-CH... π ^d	2.74	3.66	154				

^a O(1W): water oxygen atom. ^b O(1C), O(1E): methanol oxygen atoms. ^c N(5), N(8): pyrimidine nitrogen atoms. ^d Centroid (centre of gravity) of the central benzene ring. ^e N(5A), N(8A): pyrimidine nitrogen atoms.



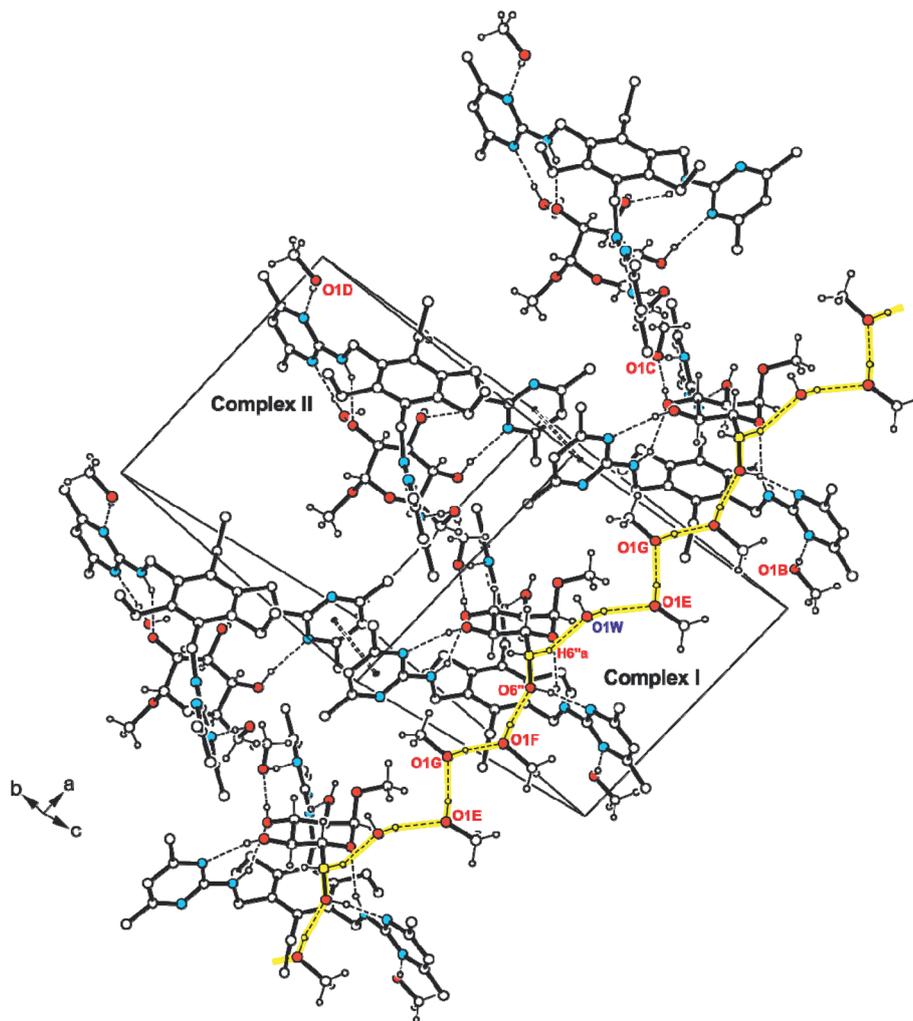


Fig. 5 Packing excerpt of $2 \cdot \text{Me}\alpha\text{Glc}$ [$2/\text{Me}\alpha\text{Glc}/\text{CH}_3\text{OH}/\text{H}_2\text{O} = 2 : 2 : 6 : 1$]. Dashed lines represent hydrogen bond interactions, dashed double lines $\pi \cdots \pi$ arene interactions. The strand-like hydrogen bond pattern, consisting of sugar CH_2OH group and solvent molecules, is highlighted in yellow.

pyrimidine rings involved in this interaction. Moreover, $\text{C-H} \cdots \text{O}$ interactions¹⁷ [$d(\text{H} \cdots \text{O})$ 2.47–2.50 Å] and $\text{C-H} \cdots \pi$ contacts [$d(\text{H} \cdots \text{C}_g)$ 2.80–2.95 Å; see Table S3†] connect the complexes to a three-dimensional supramolecular network.

It should also be noted that as in the case of the previously investigated crystalline complexes of the triethylbenzene-based receptors with β -D-glucosides,^{1,6} the binding motifs observed in the complexes with methyl α -D-glucoside show a similarity to those observed in protein–carbohydrate complexes. To mention is, for example, the use of bidentate hydrogen bonds (Fig. 6c), the presence of water-mediated (methanol-mediated) hydrogen bonds (Fig. 6a and b) and the additional stabilization of the complex by $\text{CH} \cdots \pi$ interactions, as shown for the 2-CH of α -D-glucose (natural complex) and methyl α -D-glucoside ($2 \cdot \text{Me}\alpha\text{Glc-I/II}$) in Fig. 6d. In the formation of the aforementioned bidentate hydrogen bonds in the complexes $2 \cdot \text{Me}\alpha\text{Glc-I-II}$ are not only involved two adjacent hydroxy groups ($4\text{-OH} \cdots \text{N}_{\text{pyrimidine}}/\text{N-H} \cdots \text{OH-3}$), but also the ring oxygen and the 6-OH of the methyl α -D-glucoside ($6\text{-OH} \cdots \text{N}_{\text{pyrimidine}}/\text{N-H} \cdots \text{O}_{\text{ring}}$). A similar

situation is observed in natural complexes, and is exemplarily illustrated in Fig. 6c for the case where ring oxygen and the 6-OH of D-glucose are involved in the formation of bidentate hydrogen bonds ($6\text{-OH} \cdots \text{O}=\text{C}/\text{N-H} \cdots \text{O}_{\text{ring}}$).

The importance of the above mentioned hydrogen bonds and $\text{CH} \cdots \pi$ interactions has also been demonstrated by binding studies in solution using both anomers of the glucopyranoside, in which, however, the compound 2 was shown to be a more powerful receptor for β -D-glucopyranoside than for the α -anomer.^{4d}

2.2 Comparison of the crystal structures $2 \cdot \text{Me}\alpha\text{Glc}$ and $2 \cdot \text{Me}\beta\text{Glc}$ (complexes $2 \cdot \text{Me}\alpha\text{Glc-I/II}$ and $2 \cdot \text{Me}\beta\text{Glc-I/II}$)

The pronounced donor/acceptor properties of the solvent species present in the crystal structure $2 \cdot \text{Me}\alpha\text{Glc}$ only permit a limited comparison with the recently reported solvent-free structure of the same receptor with β -glucopyranoside,¹ since in the latter case the binding behavior of the carbohydrate



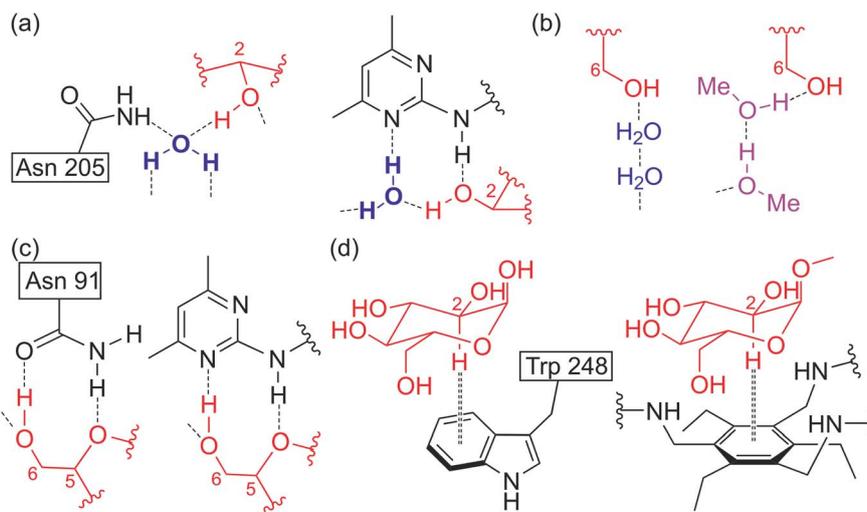


Fig. 6 Examples of hydrogen bonds (a–c) and C–H... π interactions (d) in the complexes formed by carbohydrate-binding proteins (left) and by the artificial receptor (right) described in this work (complexes $2 \cdot \text{Me}\alpha\text{Glc-I}$ and $2 \cdot \text{Me}\alpha\text{Glc-II}$). In the case of the protein–carbohydrate complexes, the binding motifs observed in the complexes of D-galactose-binding protein with D-glucose (a, c)^{30e} and α -D-glucose-binding protein with α -D-glucose (b, d)^{10h} are illustrated.

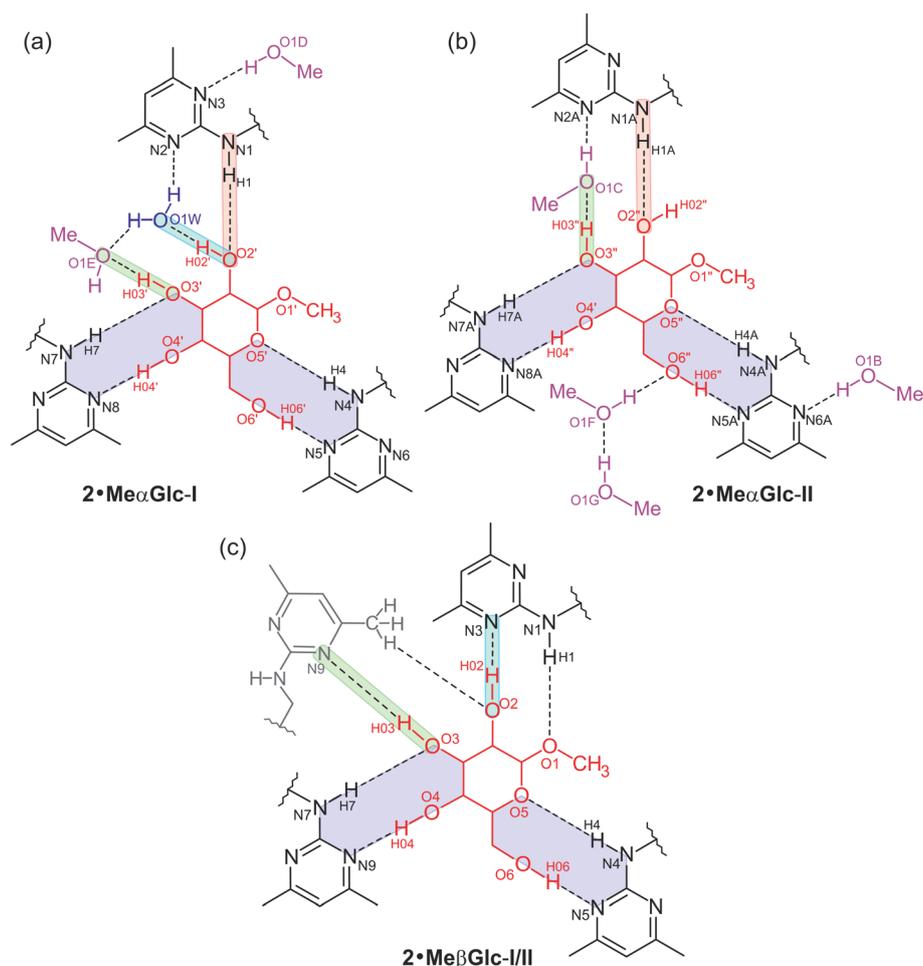


Fig. 7 Schematic representation of hydrogen bond interactions between receptor 2 and methyl α -D-glucopyranoside in the complexes $2 \cdot \text{Me}\alpha\text{Glc-I}$ (a) and $2 \cdot \text{Me}\alpha\text{Glc-II}$ (b) and methyl β -D-glucopyranoside (c). The carbohydrate molecule is displayed in red, the water molecule in blue and the methanol molecules in violet. Similar binding motifs are highlighted in the same color.



towards the receptor is unaffected by a strongly coordinating solvent. Therefore, the almost identical 1 : 1 receptor–sugar complexes (**2·MeβGlc-I** and **2·MeβGlc-II**, see Fig. 1b) of this crystal structure represent an ideal case in which the recognition process between the complex components proceeds undisturbed resulting in formation of an approximately symmetrical pattern of hydrogen bonds in which all OH groups and the ring O atom of the glucopyranoside are included. This gives rise to formation of three 9-membered cyclic hydrogen bond motifs of identical structures (Fig. 7).

The crystal structure **2·MeαGlc** also consists of two complexes in which, however, different numbers of solvent molecules are associated with the receptor–sugar unit. Analogous to the solvent-free structure **2·MeβGlc**, the 4-OH, 5-OH and 6-OH groups as well as the ring O atom of the sugar are involved in the interactions with two aminopyrimidine-based recognition units of the receptor. Thus the difference is restricted to the binding behavior of the sugar molecule with the third recognition unit of the respective receptor molecule, which is disrupted by solvent molecules. The water and one of the alcohol molecules present in complex I prevent the direct linkage of the 3-OH group of the sugar molecule with a pyrimidine N atom of this recognition unit by creating a complex H-bond pattern consisting of two ring synthons. Similarly, one of the methanol molecules present in complex II affects the binding behavior between receptor and sugar by inserting its OH group in the binding pattern thus creating an 11-membered supramolecular synthon.

The solvent molecules mediate hydrogen bonds between the sugar and the receptor molecule in a similar way, as it is realised by the water-mediated hydrogen bonds in protein-carbohydrate complexes.

The structural difference between the α - and β -anomer of the sugar molecule is limited to the spatial arrangement of the methoxy group at the anomeric center of the ring. The equatorial position of this group in the β -anomer enables the formation of a strong hydrogen bond between its O-atom and an amino H-atom of the receptor molecule and thus has a stabilizing influence on the complex formation. This applies to both complexes of the crystal structure **2·MeβGlc**. The axial arrangement of the methoxy group in the α -anomer of the glucopyranoside prevents this interaction with the receptor. Instead, in both complexes of the crystal structure **2·MeαGlc**, the spatial environment of the methoxy group is determined by solvent molecules. Moreover, the presence of solvent molecules prevents unfavorable steric interactions within the complexes, so that the six-membered ring of each sugar molecule adopts an almost ideal 4C_1 conformation.

3 Conclusion

Compared to numerous X-ray crystal structures of protein-sugar complexes, the crystalline complexes of artificial receptors have rarely been published so far, therefore the new complexes with methyl α -D-glucopyranoside described here make an important contribution to this field of research and to the understanding of the basic principles of the molecular recognition of

carbohydrates. It should be emphasized that the presence of two different complexes in one crystal structure represents an especially interesting result and, to the best of our knowledge, has been observed for the first time for artificial carbohydrate receptors in the crystal structures of the complexes with methyl β -D-glucopyranoside we have recently reported.¹⁸

The detailed analysis of the non-covalent interactions in the receptor–glucopyranoside complexes gives a deeper insight into the process of molecular recognition of carbohydrates and allows a comparison with the results obtained in solution. The crystallographic investigations confirmed the binding strategy, which was predicted from the receptor design and indicated by the binding studies in solution.

4 Experimental section

4.1 Synthesis of 1,3,5-tris[(4,6-dimethylpyrimidin-2-yl)aminomethyl]-2,4,6-triethylbenzene (2)

Compound **2** was prepared by the reaction of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene with 2-amino-4,6-dimethylpyrimidine, as reported by us previously^{4d} (see also ESI†).

4.2 Crystallographic investigations

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 solvent was used a mixture of water-containing methanol and acetonitrile.

Crystal data for **2·MeαGlc** were recorded at 113 K on a STOE diffractometer (MoK α radiation, $\lambda = 0.71073$ Å) equipped with an image plate detector (IPDS-2T). The software used for data collection and cell refinement was X-AREA.¹⁹ Absorption correction was carried out using X-AREA.¹⁹ Preliminary structural models were created using direct methods.²⁰ The structures were refined using a full-matrix least-squares calculation based on F^2 values for all reflexes.²¹ With the exception of two of the methanol molecules, all other non-hydrogen atoms were refined anisotropically. The positions of the OH hydrogen atoms of the carbohydrate molecules were identified in the difference Fourier maps. All other hydrogen atoms were included in the model in calculated positions and were refined as constrained to bonding atoms.

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 2072720.†

Conflicts of interest

There are no conflicts to declare.

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