Carbohydrate binding through first- and second-sphere coordination within aromatic oligoamide metallofoldamers

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Aromatic oligoamide capsules that fold upon metal binding recognize carbohydrate guests in solution as evidenced by CD and NMR titrations. Crystallographic data reveals that, besides their structural role, metal ions also contribute to guest recognition through either first- or second-sphere coordination.

The design of molecular receptors for the recognition of a given complex target guest remains a challenging task. Early approaches aimed at building macro(poly)cyclic architectures[1] or self-assembled capsules[2] designed to surround their substrates and establish multiple complementary interactions through pre-organized convergent functionalities. However, the design and synthesis of molecular receptors is frequently hampered by a lack of precise knowledge about the conformational features of both receptors and substrates and by hurdles associated with the synthesis of elaborate and relatively large structures that are difficult to further modify and optimize.

Nature has selected folding as the means to create well defined cavities with atomically precise arrays of chemical groups in space that achieve high binding affinity and selectivity. Taking this as inspiration, chemists have developed oligomeric sequences that also rely on folding to produce well defined architectures in solution – *i.e.* foldamers.[3] In particular, helical structures may possess a cavity suitable for the recognition of cations,[4] anions[5] or neutral molecules.[6] Furthermore, foldamer helices have been designed in such way that they possess a reduced diameter at each extremity and a wide diameter at the centre thereby forming capsules that enclose guest molecules and isolate them from the surrounding medium (Fig. 1a, right).[7] In aza-aromatic oligoamide capsules, numerous hydrogen bond donors and acceptors decorate the helix inner wall and promote tight, selective, and diastereoselective binding of polyhydroxylated guests such as organic hydroxy-acids[7c,g] and monosaccharides.[7f]

In an effort to extend the potential for tight and selective guest binding of aromatic oligoamide-based capsules, we have recently described aromatic oligoamide capsule oligomer **1** (Fig. 1b). In this sequence, the central pyz–pyr–pyz segment coordinates transition metal ions[8] Cu^{+}, Cu^{2+} and Ag^{+} as well as alkali metals Na^{+} and K^{+}.[9] In all cases the metal sits on the cavity wall leaving part of its coordination sphere occupied solely by solvent molecules, and thus available to bind a guest (Fig. 1a). Coordination bonds to the guest may indeed enhance binding affinity, while the capsule shell gives rise to shape and size selectivity. Here we show that the metal complexes of sequences **1** and **2** can be used for the binding of complex chiral guests such as carbohydrates by taking advantage of first- and/or second-sphere coordination.

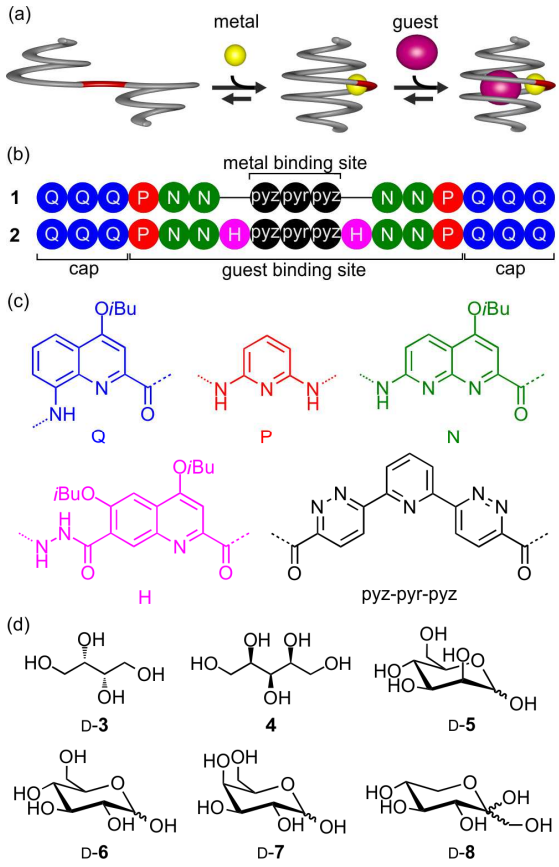

Fig. 1 (a) Principle of helical-capsule folding upon metal coordination followed by metal-assisted guest encapsulation. (b) Oligoamide sequences **1** and **2**. Note that amide orientation with respect to the sequence is inverted at each of the diamine and diacid sites. The two terminal Q units have an 8-nitro group instead of an 8-amino function. (c) Letter and colour codes of the amino acid, diamine, and diacid monomers. (d) Formulae of guest molecules: D-threitol, D-**3**; xylitol, **4**; D-mannopyranose, D-**5**; D-glucopyranose, D-**6**; D-galactopyranose, D-**7**; D-fructopyranose, D-**8**. The monosaccharides are depicted in their pyranose form although in solution they exist as mixtures of α/β-pyranoses and α/β-furanoses.

The inner volume of the helical capsule **1** is relatively modest and may be suitable for small carbohydrates. Titrations of **1**, **1-Na⁺** and **1-K⁺** with four-carbon carbohydrate D-threitol **3** at 298K in $CHCl_3$/DMSO (9:1 vol/vol) were monitored by circular dichroism (CD) spectroscopy. In the absence of metal ion, sequence **1** was found not to bind D-**3** (Fig. 2a). This was attributed to the fact that when no metal is present the pyz–pyr–pyz segment exists in an *anti–anti* conformation favoured by repulsion between endocyclic nitrogen atoms that confers the oligomer with an extended conformation instead of the capsular shape.[8] Coordination of Na^+ and K^+ induces folding of sequence **1** into a capsular shape by favouring a *syn–syn* conformation of the pyz–pyr–pyz monomer.[9]

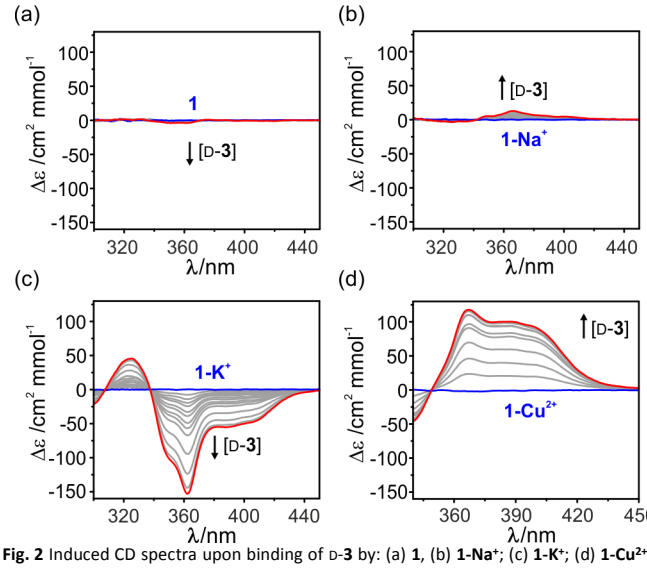

Fig. 2 Induced CD spectra upon binding of D-**3** by: (a) **1**, (b) **1-Na⁺**; (c) **1-K⁺**; (d) **1-Cu²⁺** at 298 K, [host] = 60 μM, 9:1 (vol/vol) $CHCl_3$/DMSO. Red-coloured spectra in (a-d) denotes the molar ellipticity of the hosts in the presence of D-**3** at the concentrations of 21, 19, 32 and 2 mM, respectively.

We then found that capsule **1-Na⁺** binds to D-**3**, although with a modest affinity (K_a = 145 M^{-1}) and with poor diastereoselectivity as evidenced by the small induced CD signal observed (Fig. 2b). In contrast, **1-K⁺** binds the same guest almost 3 times stronger (K_a = 400 M^{-1}) and shows much higher diastereoselectivity (Fig. 2c) with a negative band suggestive of a preferred *M* handedness.[10] A ^{1}H NMR titration of **1-K⁺** with D/L-**3** at 298K in $CDCl_3$/DMSO-d6 (9:1 vol/vol) gave consistent results (K_a = 370 M^{-1}). Only one set of host-guest complex signals were observed, which confirms the quantitative diastereoselectivity of the association (Fig. S8 in the ESI). For comparison, a ^{1}H NMR titration of **1-K⁺** with a slightly larger carbohydrate, xylitol (**4**), revealed a lower binding (K_a = 150 M^{-1}, see Fig. S9 in the ESI), presumably because **4** cannot properly fit inside the cavity. Binding studies using the Cu^{2+} complex of **1** showed that **1-Cu²⁺** binds D-**3** almost 14 times stronger than **1-K⁺** (K_a = 5500 M^{-1}) and adopts the opposite helix handedness (Fig. 2d).

Next, we sought to obtain structural information on the complexes. Single crystals suitable for X-ray diffraction analysis were grown by slow diffusion of hexane into solutions of **1-K⁺**⊃D/L-**3** and **1-Cu²⁺**⊃D/L-**3**.

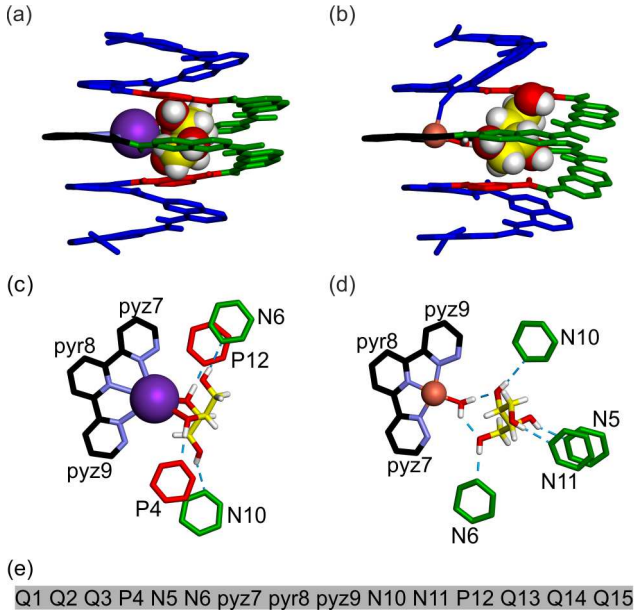

Fig. 3 Solid-state structures of the association between D-**3** and complexes ***M*-1-K⁺** (a) and ***P*-1-Cu²⁺** (b). Top views of ***M*-1-K⁺**⊃D-**3** (c) and ***P*-1-Cu²⁺**⊃D-**3** (d), showing the heterocycles that interact with the guest molecules. Dashed blue lines indicate hydrogen bonds. Details of these hydrogen bonds (distances, angles) can be found in the Supplementary Tables S3 and S6. (e) Numbering of the monomers of sequence **1** used in this figure. Isobutoxy side chains, cavity-excluded solvent molecules and counterions are omitted for clarity. The capsule backbone is represented in sticks. Potassium and copper atoms are represented in purple and bronze scaled balls, respectively.

The crystal structure of **1-K⁺**⊃D/L-**3** (Fig. 3a and 3c) validated (i) the complete encapsulation of the guest; (ii) the position of the metal ion on the cavity wall *via* tridendate coordination to pyz-pyr-pyz (see also Fig. S10 in the ESI); and (iii) the handedness preference indicated by CD (D-**3** is bound by the *M* helix). The structure also revealed bidentate coordination of the two central hydroxy groups of the guest. Furthermore, hydrogen bonds are established between the guest's peripheral hydroxy groups and endocyclic nitrogen atoms of the cavity walls. The volume fraction of the cavity occupied by the guest was calculated using SURFNET[11] and reaches 68% (Table 1), well above the common benchmark of 55%.[12] Interestingly, the volume of the cavity in the **1-K⁺**⊃D/L-**3** complex is slightly smaller than when the cavity of **1-K⁺** is occupied solely by water molecules[9] (139 versus 148 Å^3, see Table 1) which means that there is a contraction of the foldamer structure to better accommodate the guest.

The crystal structure of **1-Cu²⁺**⊃ D/L-**3** (Fig. 3b and 3c) also corroborated CD data and showed an opposite handedness preference (D-**3** is bound by the *P* helix). The Cu(II) centre displays a square-pyramidal stereochemistry with three nitrogen groups of the pyz-pyr-pyz monomer and an oxygen atom of a water molecule defining the basal plane. An oxygen atom of a carbonyl group of quinoline monomer occupies the apical position, which creates an angle between quinoline monomers that leads to a conformation in which the capsule is

slightly open in one of the extremities. This is reflected in the larger cavity volume found for **1-Cu^{2+}**⊃D/L-**3** (165 Å^3) compared with the cavity of **1-Cu^{2+}** (144 Å^3) only occupied by an acetonitrile molecule (Table 1).[8] It is not clear whether the coordination of the main chain amide carbonyl is the cause or the consequence of the distortion and volume enlargement of the capsule to accommodate the guest. The two events are likely to be synergistic.

Table 1 Calculated cavity volume.

Capsule	Volume (Å^3)[a]	P. C. (%)[b]
1-K$^+$ [c]	148	–
1-Cu^{2+} [d]	144	–
2-Cu^{2+} [e]	249	–
1-K$^+$⊃D-**3**	139	68
1-Cu^{2+}⊃D-**3**	165	57
2-Cu^{2+}⊃D-**5**	294	43

[a] Volume of capsule cavities determined using SURFNET v1.4 (see SI). [b] Packing coefficients defined here as the ratio of the guest volume to the host cavity volume. Volumes of guests D-**3** and D-**5** were found to be 94 and 128 Å^3, respectively. [c] From ref. 9. In this case the cavity of **1-K$^+$** is occupied by water molecules. [d] From ref. 8. In this case the cavity of **1-Cu^{2+}** is occupied by an acetonitrile molecule. [e] Predicted capsule structure obtained by molecular modelling (MMFFs force field) using Maestro v6.5.

Interestingly, the guest is not directly coordinated to the metal ion but instead is bound through second-sphere coordination in which a coordinated water molecule bridges the metal and the guest. This result was surprising, taking into account that **1-Cu^{2+}** binds D-**3** almost 14 times stronger than **1-K$^+$**, where direct coordination is in effect. This indicates that Cu^{2+} polarizes the water molecule in such way that it becomes a very strong hydrogen bond donor. Second-sphere interactions involve two hydroxyl groups in positions 1 and 3 of the threitol molecule. Consequently, the guest is not centrally located causing the deformation of the capsule cavity.

In order to target larger carbohydrates, new sequence **2** was prepared (Fig. 1b). It features two additional H monomers that almost double the binding cavity volume with respect to **1** (Table 1). These monomers present a hydrazide carbonyl group towards the binding cavity as a good hydrogen acceptor.[7f] CD titrations at 298K in $CHCl_3$/DMSO (8:2 vol/vol) showed that **2-Cu^{2+}** can bind various monosaccharide guests in solution (see Figs. S4-S7 in the ESI) and revealed a preference for D-mannose **5** (K_a = 450 M^{-1}) over D-glucose **6**, D-galactose **7** and D-fructose **8** (K_a of 270, 100 and 40 M^{-1}, respectively). An X-ray crystal structure of **2-Cu^{2+}**⊃D/L-**5** was eventually obtained (Fig. 4). The Cu(II) centre in **2-Cu^{2+}**⊃D/L-**5** again adopts a square pyramidal geometry, being bound by three nitrogen groups of the pyz-pyr-pyz monomer and by two oxygen atoms of two water molecules. The water molecule in the apical position is located outside the cavity and establishes a hydrogen bond with a carbonyl oxygen of a quinoline monomer, while the second water molecule is encapsulated and points towards the interior of the cavity. As in the case of **1-Cu^{2+}**⊃D/L-**3**, the metal ion does not bind directly to the guest, but instead solvent molecules (a water and a methanol molecules) bridge the metal and guest. Clearly the cavity is too large to efficiently bind D-**5**, which occupies only 43% of the total cavity volume (Table 1). This agrees with the moderate affinities found for the monosaccharide guests. Interestingly, although D-**5** exists predominantly (97%) in the α-pyranose form in $CHCl_3$/DMSO 8:2 (vol/vol) solution,[7f] it assumes the β-pyranose form in the **2-Cu^{2+}**⊃D/L-**5** complex.

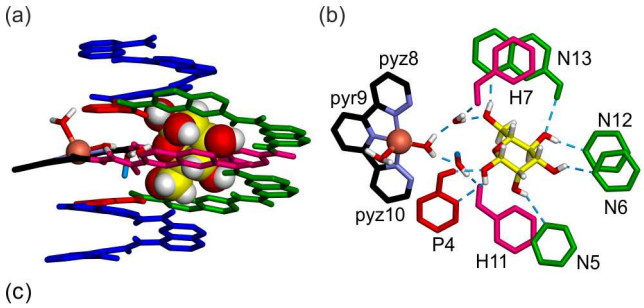

Fig. 4 (a) Side view of the solid-state structure of the complex formed between capsule ***M*-2-Cu^{2+}** and *β*-D-mannopyranose **5**; (b) top view showing the heterocycles that interact with the guest. Dashed blue lines indicate hydrogen bonds. Hydrogen bonding distances and angles can be found in the Supplementary Table S9. (c) Numbering of the monomers of sequence **2** used in this figure. Isobutoxy side chains and cavity-excluded solvent molecules and counterions are omitted for clarity. The capsule backbone is represented in sticks. Copper atoms are represented bronze scaled balls.

First-sphere metal coordination to assist molecular recognition has been exemplified before.[6n,13] Second-coordination sphere interactions between Cu^{2+} hydrates and carbohydrate guests is less common and is to be related to that previously observed for the binding of Ca^{2+} and Mg^{2+} hydrates within **1**.[9] It points at the strong benefits of polarizing hydrogen bonds through metal ions and also invites to considering stronger hydrogen bond donors and acceptors such as acidic phenols or pyridine N-oxides as main chain features of the foldamer backbones. The three crystal structures described here also constitute important milestones in the challenging area of sugar recognition by synthetic receptors,[6n,14] a field that had until recently[9f,15] suffered from a complete lack of solid state evidence.

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