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Structural Effects of Proline Substitution and Metal Binding on Hexameric Cyclic Peptoids

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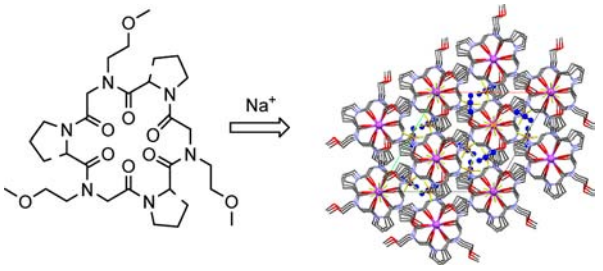
ABSTRACT



L-Proline and *N*-methoxyethyl glycine have been included in novel cyclic hexameric peptoids. Supramolecular coordination with Na^+ triggered the formation of the first 1D metal−organic framework based on peptoids.

For decades chemists have been fascinated by the remarkable functions and conspicuous beauty of natural and synthetic macrocycles.[1] The properties of these structures in areas as diverse as ion transport, crystal engineering, supramolecular chemistry, catalysis, and material sciences have greatly amplified their taxonomic and chemical diversity.

In the realm of macrocyclic architectures, cyclopeptoids[2] perfectly represent the whole subject: their biostability and potential diversity make them ideal candidates to evoke biological activities and unexpected properties. Ring formation also represents an effective strategy to facilitate crystal nucleation and growth: most of the high-resolution structures of peptoids originate from X-ray diffraction studies on macrocycles.[2,3] Conformational control and crystallization can be elicited by two further structural traits: inclusion, in the oligomeric sequence, of bulky[3a,d] or cyclic[3m,4] monomer units, and the establishment of relatively strong noncovalent intermolecular interactions (*i.e.*, metal complexation[3g,k,5]).

In this communication we probe the aptitude of rigid L-proline and of the chelating *N*-methoxyethyl glycine residues (included in cyclic hexapeptoid scaffolds) to trigger

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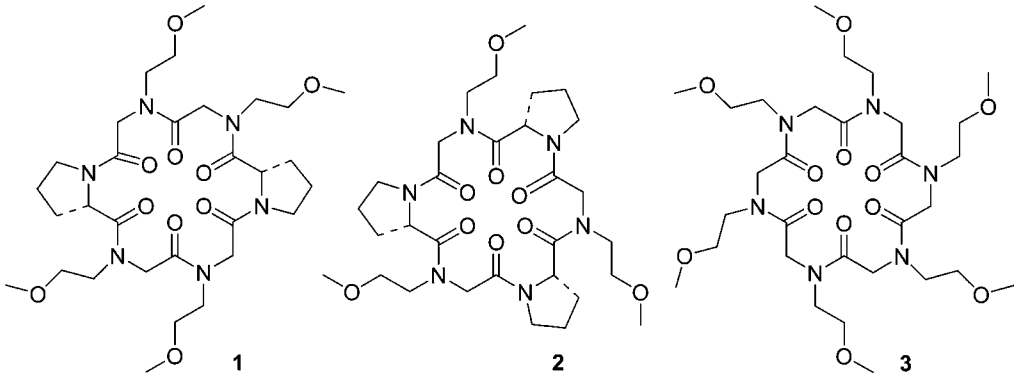

Figure 1. Structures of cyclic peptoids **1**–**3**.

the formation of metalated supramolecular frameworks.[6] We also show that symmetry represents a crucial factor facilitating self-assembly and a relevant prerequisite for the generation of interesting molecular architectures.

In the present investigation the hexameric cyclic peptoids **1**, **2**, and **3**[7] (Figure 1) have been considered as paradigmatic targets, being constituted by residues that potentially facilitate solid-state aggregation and display an increasing degree of symmetry.

The synthesis of prolinated **1** and **2** started from the on-resin construction of the precursors **4** and **5** (Figure 2).

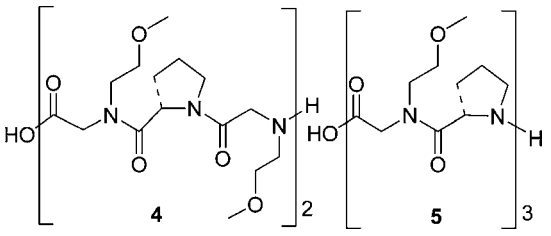

Figure 2. Linear precursors **4** and **5**.

Their solid-phase elaboration took advantage of the well-established mixed "sub-monomer"[8]/monomer approach. In particular, the *N*-methoxyethyl glycine monomer, prepared on resin, was coupled with *N*-fluorenylmethoxycarbonyl-L-proline using HATU as a condensing agent. Successive DIC- or HATU-induced couplings yielded the required **4** and **5** with purities greater than 90% (HPLC analysis; see Supporting Information (SI)). Head-to-tail macrocyclization of the linear **4**, performed in high dilution conditions in the presence of HATU,[3k,l] gave **1** as a complex mixture of conformers (rt, ^{1}H NMR analysis, Figure S1, SI). The addition of lithium picrate to a 9:1 $CD_3CN/CDCl_3$ solution of **1** resulted in a simplified ^{1}H NMR spectrum, reflecting the formation of a conformationally rigid C_1-symmetric[9] lithiated species[10] (Figure S3, SI).

Macrocyclization of the triprolinated **5** yielded **2** directly as metal complex after silica gel column chromatography.[11] Metal chelation was revealed by the presence of a 3-fold symmetric species in the rt ^{1}H NMR spectrum (Figure S8, SI) and later demonstrated by crystallization (*vide infra*). The geometry of the *N*-methoxyethyl glycine-Pro bond of the complex was inferred by the ^{13}C NMR resonance of the C^γ proline residue signal (δ = 25.0), diagnostic for a *trans* peptide junction.[10]

Metal-free **2** was obtained through a simple two-step, one-pot procedure (Figure 3).

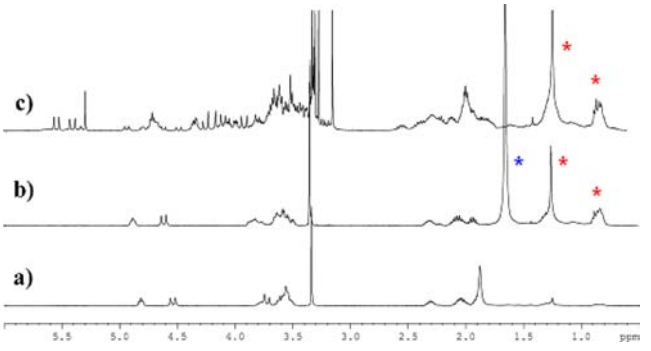

Figure 3. (a) ^{1}H NMR spectrum of **2** as Na^+ complex. (b) ^{1}H NMR spectrum of **2** as Ag^+ complex. (c) ^{1}H NMR spectrum of uncomplexed **2**. Residual water peak is labeled with blue *, residual "grease" peaks are labeled with red *.

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(7) For the synthesis of **3**, see: Della Sala, G.; Nardone, B.; De Riccardis, F.; Izzo, I. *Org. Biomol. Chem.* **2013**, *11*, 726–731.

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(9) It must be noted that the lack of symmetry in **1** as a lithium salt (despite the appearance of its C_2-symmetric formula) is related to a nonsymmetric (or non-C_2-symmetric) hexadentated carbonyls arrangement around the lithium cation.

A 0.006 M deuterated chloroform solution of the C_3-symmetric **2** (Figure 3a) was mixed with an equal volume of a 0.1 M $AgNO_3$ solution in water (in order to exchange the metal present in the complex with silver). The deuterated solution of the Ag^+ complex (retaining the C_3-symmetric pattern, Figure 3b) was then treated with Me_4NI. The immediate precipitation of the insoluble AgI instantly liberated **2** from silver complexation, giving a ^1H NMR spectrum (Figure 3c) showing a complex signal pattern (illustrating the presence of multiple conformers in slow exchange on the NMR time scale) and attesting to the lack of metal complexation.

The synthesis of the cyclic hexameric *N*-methoxyethyl glycine oligomer **3** and the formation of its Na^+ complex have been previously reported.[7]

Metalated macrocycles **1**–**3** were subjected to various crystallization conditions. While all the efforts to crystallize the nonsymmetric lithiated **1** were not successful, the metal complex of **2** was easily crystallized by slow diffusion of hexane in an acetonitrile solution. Small needle-like crystals, suitable for synchrotron radiation diffraction studies, were harvested. The obtained structure demonstrated the complexation of **2** with Na^+ and the presence of PF_6^-, as a counterion (from HATU).[12]

The arrangement of this cyclic α-peptoid is rather intriguing and intricate. In the solid state structure three cyclopeptoid rings, four Na^+ ions, and one acetonitrile molecule form a triple-decker salt sandwich metal complex (Figure 4) with a crystallographic 3-fold rotation symmetry.

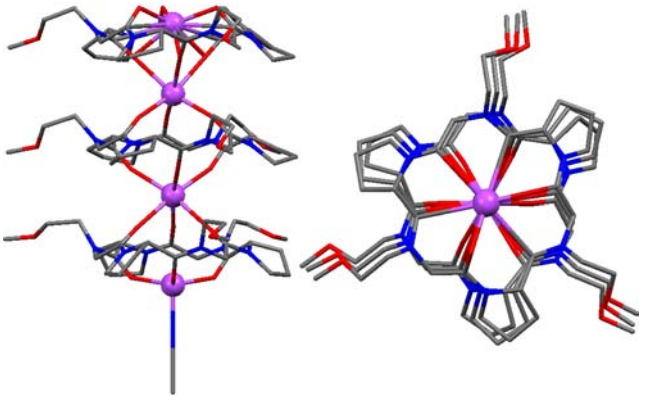

Figure 4. Triple decker Na^+ complex for **2**, as viewed along *a* (left) and *c* (right) axis. Hydrogen atoms have been omitted for clarity. Atom type: C, gray; N, blue; O, red; Na, magenta.

(10) Observation of the C^γ signals arising from the proline residues (δ = 25.8 and 25.4 in **1** as lithium salt) suggests a *trans* *N*-methoxyethyl glycine-proline peptoid junction. Resonances at δ = 21.7 and δ = 24.0 are, in fact, diagnostic for the amide *cis* and *trans* X-Pro peptide bond geometry, respectively. See: Sarkar, S. K.; Young, P. E.; Sullivan, C. E.; Torchia, A. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 4800–4803 and references cited therein.

(11) The cyclic hexapeptoid's high affinity for alkali metals induces complexation during the silica-gel column chromatography. See note 1 in the SI.

(12) See SI for details.

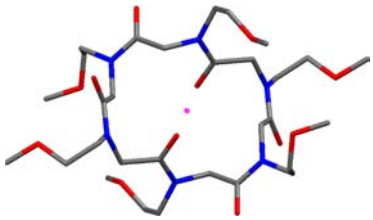

Figure 5. X-ray molecular structure for **3**. Hydrogen atoms have been omitted for clarity. Atom type: C, gray; N, blue; O, red. Inversion center in magenta.

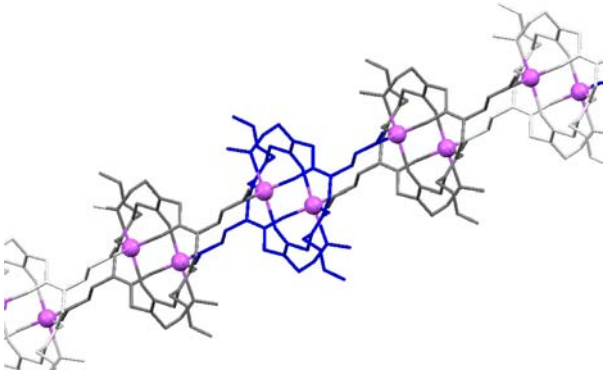

Figure 6. 1D polymer structure with the repeating unit in the center made by two sodium ions (in magenta) and one cyclopeptoid ring (in blue). Hydrogen atoms have been omitted for clarity.

The geometry of the amide linkages in all three cyclopeptoid macrocycles present in metal complex **2** is *trans*, with the carbonyl groups pointing toward the sodium cations, as previously observed by us in the structure of a cyclopeptoid strontium complex.[3k] The edge sodium ions complete the coordination sphere in two different ways (Figure 4, left): on one side by coordinating three alternate carbonyl groups and an acetonitrile molecule (bottom face of the complex: Na1 ion); on the opposite side (top side of the complex: Na4 ion) by linking all six carbonyl groups. The distances between the Na ions and the mean planes constituted by C and N atoms of the rings are as follows: Na1 1.93 Å, Na2 2.17 and 1.84 Å, Na3 2.76 and 2.45 Å, Na4 0.79 Å. The last distance strongly suggests a cation–π interaction between Na4 and the π-bond of the carbonyl groups (with Na4–O8 and Na4–C26 distances respectively 2.258(3) and 2.963(3) Å, Na4–O7 and Na4–C21 distances respectively 2.487(4) and 3.000(4) Å). Indeed a coordination mode similar to Na4 atom was observed for

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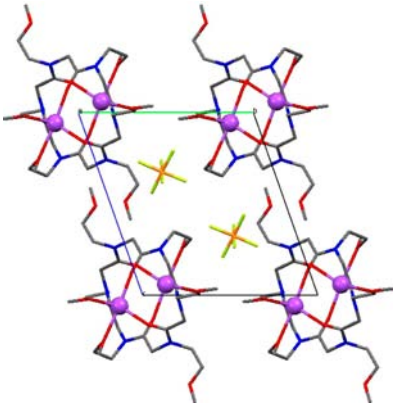

Figure 7. X-ray crystal structure for **3** as Na^+ complex as viewed along the *a* axis. Hydrogen atoms have been omitted for clarity. Atom type: C, gray; N, blue; O, red; Na, magenta; P, orange; F, green.

an enniatin B sodium 1:1 complex, where a central sodium ion is surrounded by six carbonyl oxygen atoms.[13]

The crystalline unit cell contains three triple-decker metal complexes, twelve PF_6^- ions, and nine acetonitrile molecules. The triple decker metal complexes are pillared along the *c* axis, while PF_6^- ions and acetonitrile molecules occupy interstitial spaces (Figure S11, SI). The *N*-methoxyethyl side chains are excluded by metal coordination, hampering crystal network extension.

The Na^+ complex of the highly symmetric cyclopeptoid **3** and its free form were successfully crystallized by slow evaporation from ethyl acetate and from ethyl acetate and acetonitrile, respectively.

While compound **3** exhibits a typical *tcctcc* peptoid bond conformation[2,3j,3l] (Figure 5),[12] its sodium complex shows unique features (Figures 6 and 7).[12]

In this metal adduct each sodium ion is coordinated to three carbonyl groups and to two methoxy group side chains (one belonging to the same cyclopeptoid molecule and the other from an adjacent molecule). Pentacoordinated sodium atoms are uncommon. Examples have been observed in G-quadruplex DNA.[14]

Side chain methoxy groups form a 1D polymeric chain extending along the *a* axis (Figure 6). In this coordination polymer, two side chains are folded toward the center of the cyclopeptoid ring to bind two sodium ions, two side chains overstretch outward to bind two contiguous sodium ions and extend the polymeric structure, and the remaining two other side chains point outward and are involved in crystal packing interactions. PF_6^- ions (from HATU) are located in the interstitial space among the chains (Figure 7).

The aggregative forces generate the first metal−organic framework (MOF) structure based on peptoids as linkers. This is particularly fascinating because peptoids, like peptides,[15] offer virtually unlimited structural diversity.

In conclusion, this communication shows that cyclic peptoids are a class of effective ligands for constructing new coordination networks due to their inherent structural properties and multiple binding sites. They represent excellent candidates for the preparation of infinite one-, two-, and three-dimensional solid-state supramolecular assemblies. Further studies are underway for the preparation of homochiral porous metal−peptoid frameworks as an advanced generation of robust biomimetic materials.

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Supporting Information Available. Experimental details, characterization and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.