Crystal Engineering

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Solid-State Conformational Flexibility at Work: Zipping and Unzipping within a Cyclic Peptoid Single Crystal

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Abstract: *A peptidomimetic compound undergoes a reversible single-crystal-to-single-crystal transformation upon guest release/uptake with the transformation involving a drastic conformational change. The extensive and reversible alteration in the solid state is connected to the formation of an unprecedented "CH–π zipper" which can reversibly open and close (through the formation of CH–π interactions), thus allowing for guest sensing.*

The biological processes of living systems rely on control of the dynamic behavior of biomolecules.[1] The intrinsic flexibility of proteins enables accurate guest recognition and specific substrate conversion.[2] Enzymatic activity can be tracked in protein crystals because of the presence of water channels that allow guest diffusion and dynamic fluctuation of active sites, while preserving crystal integrity and promoting catalysis.[3]

The design and synthesis of artificial systems able to mimic biological functions has been the aim of extensive research activity in the field of molecular nanotechnology.[4] In particular, one of the goals of crystal engineering is to identify crystalline materials that combine the recognition abilities of protein crystals with thermochemical stability.[4b]

Guest-induced single-crystal-to-single-crystal (SCSC) transformations have mainly been observed in metal–organic frameworks or coordination polymers.[5] In these cases the strength and directionality of the metal coordination bonds provide a robust architecture preserving the crystals from disruption in spite of large movements of the ligands.[6] Examples of guest-induced SCSC transformations are also reported for molecular compounds.[7] The observed dynamic behavior consists of positional or orientational rearrangements of the molecules inside the crystals. Banerjee et al.[8] described a reversible SCSC transformation in a cyclic peptide upon guest exchange by changing the columnar arrangement of the macrocycles from staggered to eclipsed. In a more recent example involving a cyclic peptoid, Kirshenbaum et al.[9] report only a negligible rearrangement of the host molecule during water uptake and release.

Herein we report the first example of a reversible SCSC transformation induced by guest removal involving a drastic conformational change of the molecular host. The organic compound **1** (Figure 1), decorated by strategically arrayed propargyl/methoxyethyl side chains, is a cyclic peptoid. The disruption of the host–guest interactions induces a noticeable movement (more than 110°) of two propargyl side chains, generating new stabilizing CH–π interactions[10] and forming an unprecedented reversible "CH–π zipper".

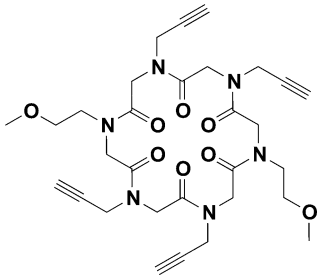

Figure 1. *Cyclo*-(Nme-Npa$_2$)$_2$ (**1**). Nme = *N*-(methoxyethyl)glycine, Npa = *N*-(propargyl)glycine.

Peptoids differ from peptides in the backbone position of the side chains, which are attached to the nitrogen atoms (giving *N*-substituted oligoglycines; Figure 2a).[11] The lack of the amide protons prevents the formation of NH···OC hydrogen bonds, and weaker interactions, such as CH···OC

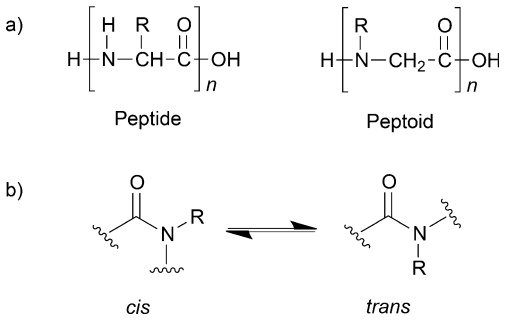

Figure 2. a) A comparison of peptide and peptoid structures. b) *Cis*/*trans* conformational isomerism in tertiary amides.

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hydrogen bonds[12] and CH–π interactions,[13] play a key role in the formation of secondary structures.[14]

Moreover, the presence of tertiary amide bonds adds further flexibility to the peptoid backbone: the *cis*/*trans* conformations are almost isoenergetic (Figure 2b).[14] Thus, head-to-tail cyclization represents a useful strategy to increase the conformational rigidity of linear oligomers.[15]

In a recent survey of the solid-state assembly of cyclic α-peptoids, we concluded that methoxyethyl and propargyl side chains induce a columnar arrangement of the peptoid macrocycles.[16]

This observation prompted us to design and synthesize compound **1** (Figure 1), displaying two distal methoxyethyl side chains and four propargyl side chains. Our goal was to verify the columnar arrangement of the macrocycles and to study possible host–guest properties as a prelude to their application in molecular storage, separation, and catalysis.

The linear precursor of **1** (see Scheme S1 in the Supporting Information) was prepared using the sub-monomer approach introduced by Zuckermann et al.[17] and cyclized under high dilution conditions with *O*-(7-azabenzotriazol-1-yl)tetramethyluronium hexafluorophosphate (HATU) as the coupling agent.[15i,k]

Compound **1** crystallizes from hot acetonitrile as an acetonitrile solvate (form **1A**) with a 1:2 ratio between the cyclopeptoid and acetonitrile molecules, as shown by single-crystal X-ray diffraction.[18] The macrocycle exhibits a *cctcct* (where *c* denotes *cis*, and *t* is *trans*) sequence of distorted amide bonds. Two methoxyethyl and two propargyl side chains point vertically with respect to the macrocycle plane, while two propargyl side chains extend horizontally.

As shown in Figure 3a (top), the molecules align in a columnar arrangement along the shortest *c* axis through CO···HC interactions involving the carbonyl groups of the peptoid backbone and the terminal hydrogen atom of the vertical propargyl side chain (CO···HC = 2.20 Å; O···H–C = 163°). As shown in Figure 3b (top; see also Figure S3), the acetonitrile molecules occupy the void space between the cyclopeptoid columns, forming channels parallel to the *c* axis. Acetonitrile molecules are linked together by means of CH–π interactions (N≡C···HC = 2.81 Å) and are only weakly bound to the host molecules by means of the methyl hydrogen atoms (CO···H_3C = 2.48 Å, C≡C···H_3C = 2.87 Å).

Differential scanning calorimetry (DSC) of crystals of form **1A** showed that acetonitrile molecules are released when the crystals are heated from 30 to 85 °C. Melting of the crystals occurs at 225 °C, followed by decomposition of the cyclic peptoid (Figure S4).

Thermogravimetric analysis (TGA) confirms the release of acetonitrile molecules between 30 °C and 65 °C (Figure S5). The measured percentage weight loss (about 12%) is consistent with the loss of two acetonitrile molecules per cyclopeptoid molecule.

Hot-stage microscopy (HSM) demonstrated that guest release (in the range 30–70 °C) does not affect the shape of the crystals but only their transparency (Figure 4; Movie S1). After thermal treatment on the hot-stage microscope, a single crystal was selected and analyzed by X-ray diffraction. The structure determination confirmed that all of the acetonitrile molecules were removed to give the desolvated form **1B** with no loss of crystal integrity (Figure S2).[18,19]

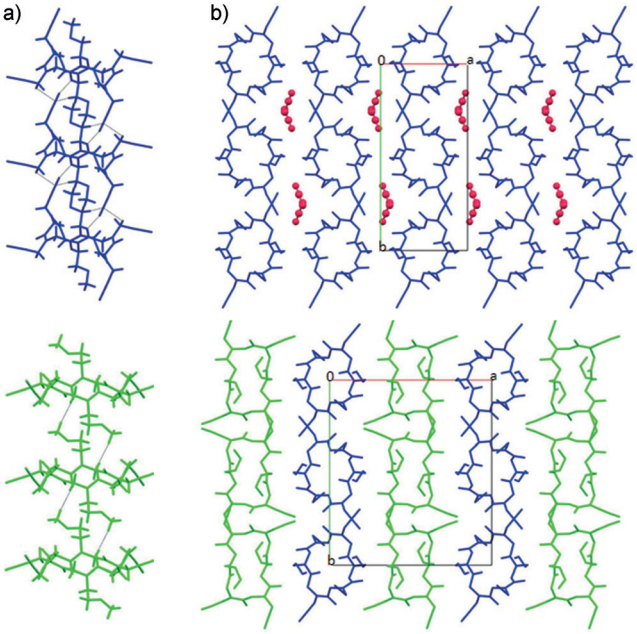

Figure 3. a) Columnar arrangement of cyclopeptoid molecules along the *c* axis in forms **1A** (top) and **1B** (type II molecules, bottom). CH–π and CH···OC hydrogen bonds are depicted as gray dotted lines. b) Crystal packing as viewed along the *c* axis in forms **1A** (top) and **1B** (bottom). Acetonitrile molecules are shown in red as a ball-and-stick model. Form **1B** contains two crystallographically independent molecules, type I (blue) and type II (green), respectively.

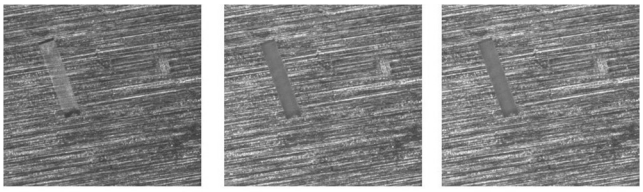

Figure 4. Images of a single crystal of **1A** during HSM upon heating from 30 °C to 70 °C and back to 30 °C.

In form **1B**, X-ray crystallography revealed that half of the cyclopeptoid molecules adopt a completely different conformation in order to efficiently occupy the space left behind by the acetonitrile molecules (Figure 3b, bottom).[20]

Indeed, the crystals of **1B** contain two crystallographically independent cyclopeptoid molecules (shown in blue and green; see Figure 3b). The blue molecules (type I) show only slight differences with respect to form **1A**, whereas the green molecules (type II) have undergone a drastic conformational change.

In type II (Figure 3a, bottom) the two vertical propargyl side chains have moved horizontally with respect to the plane of the macrocycle. The propargyl torsion angle (χ_1) changes from −118° (in form **1A**) to 129° in type II, with an overall variation of 113°. Type II molecules stack on top of each other with only the methoxyethyl side chains (CH_3···O = 2.57 Å,

O···H–C = 171.4°) located between the macrocyclic rings, as clearly shown in Figure 3a (bottom).

The dramatic change in the orientation of the side chain is accompanied by a backbone conformational adjustment. In particular, the type II molecules have an elongated shape that have adapted to form an ideal type I β-turn structure.[15k,21]

Desolvated crystals (form **1B**) are able to absorb acetonitrile molecules, as demonstrated by soaking a desolvated crystal in acetonitrile for a few seconds and analyzing it by single-crystal X-ray diffraction (Table S1). A desolvated single crystal was also monitored by polarized light microscopy during which time it was exposed to acetonitrile vapors. The acetonitrile uptake can be clearly detected in the recorded images (Figure 5b; Movie S2) showing the change in the transparency of the crystal with time.

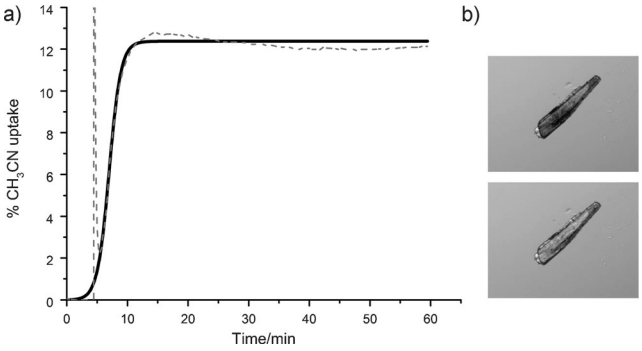

Figure 5. a) Sorption balance analysis on form **1B**. The dashed line is the experimental curve (the initial spike is due to the solvent injection). The solid line shows the sigmoidal curve fitted to the data. b) Polarized light micrographs of a crystal of form **1B** before (top) and after (bottom) exposure to acetonitrile vapors.

The reversibility was also verified by exposing desolvated crystals (**1B**) to acetonitrile vapors at 25 °C on a sorption microbalance (Figure 5a).[22] The weight percentage increase of 11.8 % agrees well with the stoichiometry within form **1A**. Adsorption/desorption cycles were repeated five times without loss of efficiency.

The dynamic behavior of the cyclopeptoid molecules in the crystal may be interpreted as a synchronized motion.[7c,23] The movement of the propargyl side chains to the equatorial plane (to fill the void volume left by the acetonitrile molecules) leads to intercolumnar CH–π interactions between methylene H atoms and propargyl triple bonds of adjacent columns (C≡C···HC = 2.80 Å, C···H–C = 164.4°), acting as a CH–π zipper, that is, where columns of type II molecules are held together by CH–π interactions (Figure 6).

The crystals release the guest molecules and the CH–π zipper is "closed" by rotating the vertical propargyl side chains by 113°. Upon subsequent exposure to acetonitrile vapor, guest uptake is facilitated by opening of the CH–π zipper by moving the propargyl side chain back again in a synchronized fashion.

This work shows how conformational flexibility in organic macrocycles may be exploited leading to functional materials that demonstrate both robustness and adaptivity. Easily

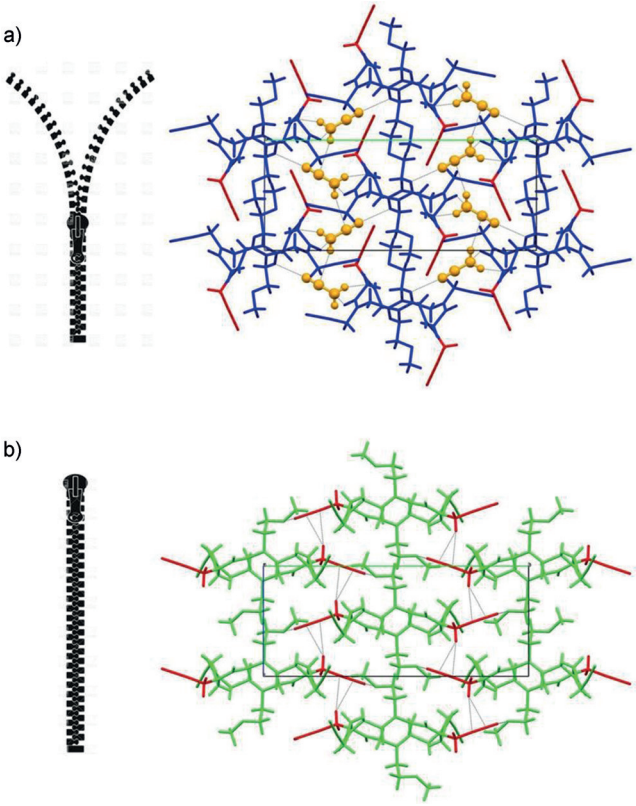

Figure 6. Open CH–π zipper in form **1A** (top) and closed CH–π zipper in form **1B** (bottom). Intercolumnar CH–π interactions in form **1B** replace the released acetonitrile molecules (yellow, ball-and-stick model). Moving propargyl side chains are shown in red, CH–π bonds as dotted gray lines.

tunable cyclic peptoids may represent very promising building blocks at the frontier between material science and biology and may be capable of reversible guest recognition and sequestration.

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Keywords: crystal engineering · host–guest systems · noncovalent interactions · peptoids · supramolecular chemistry

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[18] Diffraction data were collected at 100 K with a Bruker Smart diffractometer equipped with an APEXII CCD detector using Mo $K\alpha$ radiation. Form **1A**: Formula $C_{30}H_{38}N_6O_8 \cdot 2\,CH_3CN$, formula weight = 692.77, monoclinic, $P2_1/c$, $a = 9.773(5)$ Å, $b = 20.961(10)$ Å, $c = 8.500(4)$ Å, $\beta = 90.990(7)°$, $V = 1740.9(14)$ Å^3, $Z = 2$, $D_X = 1.322$ g cm^{-3}, $\mu = 0.096$ mm^{-1}, $R1$ $(I > 2\sigma_I) = 0.0465$ (2960), $wR2$ (all) = 0.1173 (3594), $\rho_{min} = -0.26$ e Å^{-3}, $\rho_{max} = 0.28$ e Å^{-3}. Form **1B**: Formula $C_{30}H_{38}N_6O_8$, formula weight 610.66, monoclinic, $P2_1/c$, $a = 17.887(3)$ Å, $b = 20.335(3)$ Å, $c = 8.4716(12)$ Å, $\beta = 93.160(2)°$, $V = 3076.7(8)$ Å^3, $Z = 4$, $D_X = 1.318$ g cm^{-3}, $\mu = 0.097$ mm^{-1}, $R1$ $(I > 2\sigma_I) = 0.0495$ (5009), $wR2$ (all) = 0.1148 (7960), $\rho_{min} = -0.26$ e Å^{-3}, $\rho_{max} = 0.28$ e Å^{-3}. CCDC1431223 (form **1A**) and 1431224 (form **1B**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[19] The loss of acetonitrile molecules is accompanied by an evident shrinkage of the crystal and a decrease in the unit cell volume of 11.6% (see the Supporting Information).
[20] Torsion angles before and after the acetonitrile removal are reported in Table S2.
[21] It is worth noting that in form **1B** type II, molecules display a rmsd value of 0.142 Å by superposition with a type I β-turn idealized peptide structure (see Table S3 and Figure S6).
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