Synthesis, structures, and properties of nine-, twelve-, and eighteen-membered *N*-benzyloxyethyl cyclic α-peptoids†

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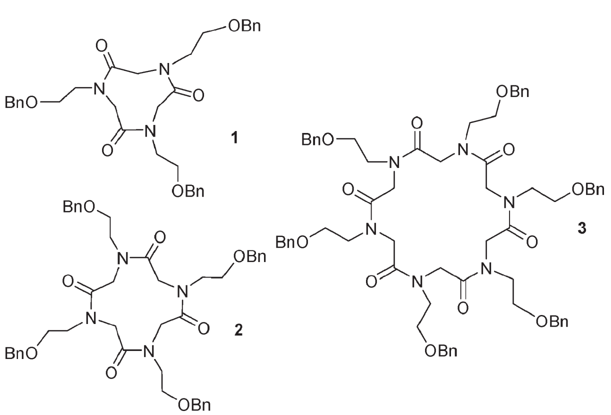
***N*-Benzyloxyethyl cyclic α-peptoids of various size were prepared and their conformational features were investigated by means of computational, spectroscopic, and X-ray crystallographic studies.**

Peptoids, an archetypal example of bioinspired peptidomimetics, show unique structural and physical properties.[1] The conformational ordering of their achiral polyimide backbone is dictated by stereoelectronic effects caused by *N*- (and *C*-) substitution[2] and/or by cyclization.[3–6] In particular, the prediction and the assessment of the covalent constraints induced by macrolactamization appears crucial for the design of conformationally restricted peptoid templates as preorganized synthetic scaffolds or receptors.

In this communication, we report the synthesis and the conformational features of cyclic tri-, tetra-, and hexa-*N*-benzyloxyethyl glycines (**1–3**). The structural studies were based on computational, spectroscopic, and X-ray crystallographic investigations. We will also discuss the complexing properties displayed by the cyclohexapeptoid **3**.



The studies on the cyclic peptoids (**1–3**) started with a preliminary lowest energy conformational search (Fig. 1). Molecular mechanics and dynamics calculations, followed by quantum mechanical (QM) refinement of the geometries and energies (see ESI† for details), predicted, for the highly strained cyclo-α-tripeptoid **1**, a C_3-symmetric "crown"[7] conformation (previously found for the all-*cis* *N*,*N*′,*N*″-triallyl-*cyclo*-triglycine)[4] and, for the 12-membered **2**, a center of symmetry (*i*) due to a *cis-trans-cis-trans* (*ctct*) "chair"[8] arrangement. The prediction of an all-*trans* amide geometry for **3** was tentative, due to the multitudinous, energetically equivalent, possible backbone orderings.

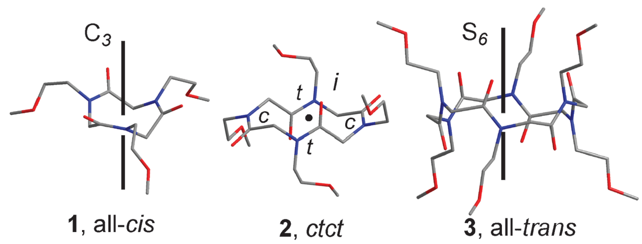
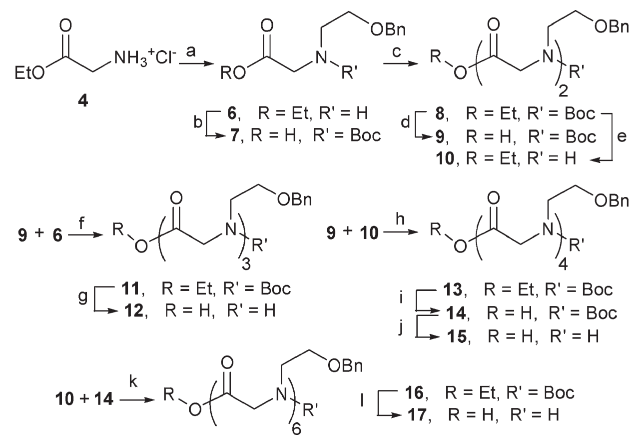


Fig. 1 Predicted lowest energy conformations for compounds **1**, **2** and **3** (atom type: C gray, N blue, O red); hydrogen atoms and phenyl groups omitted for clarity.

The synthesis of the linear *N*-benzyloxyethyl glycine oligomers was accomplished both in solution (Scheme 1) and through a



Scheme 1 Synthesis of **1–3**. Reagents and conditions: (a) $BnOCH_2CHO$ (**5**), Et_3N, $NaBH(OAc)_3$, CH_2Cl_2, 69%; (b) i. LiOH, dioxane–H_2O (1 : 1), ii. $NaHCO_3$, Boc_2O quant.; (c) **6**, BOP-Cl, Et_3N, CH_2Cl_2, 67%; (d) LiOH, THF, 92%; (e) HCl (4 M in 1,4-dioxane), AcOEt (1 : 1), quant.; (f) BOP-Cl, Et_3N, CH_2Cl_2, 58%; (g) i. LiOH, THF–H_2O (1 : 1) 76%, ii. HCl (4 M in 1,4-dioxane), AcOEt (1 : 1), quant.; (h) BOP-Cl, Et_3N, CH_2Cl_2, 63%; (i) LiOH, THF–H_2O (1 : 1) 65%; (j) HCl (4 M in 1,4-dioxane), AcOEt (1 : 1), quant.; (k) CIP, DIPEA, CH_3CN, 48 h, 54%; (l) i. LiOH, THF–H_2O (1 : 1) 80%, ii. HCl (4 M in 1,4-dioxane), AcOEt (1 : 1), quant.

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solid-phase approach ("monomer" approach). The key carboxy- and *N*-protected *N*-alkylated glycines (**6** and **7**, respectively) were easily obtained through reductive amination[9] and straightforward protecting group processing. Successive couplings and chemoselective deprotections yielded the required oligomers **12**, **15** and **17**.

Alternatively, HATU or PyBOP-induced oligomerization of *N*-fluorenylmethoxycarbonyl-*N*′-benzyloxyethyl glycine on 2-chlorotrityl resin (average coupling yield: 97%), gave the oligomers **12**, **15** and **17** with considerable purity (RP-HPLC and ESI-MS analysis) and in shorter times.

Head-to-tail macrocyclizations of the linear *N*-substituted glycines were attempted using a variety of condensing agents and high dilution conditions (2.0×10^{-3} M). The best results were achieved in the presence of PyBOP, FDPP or HATU in DMF.

The HATU-mediated cyclization of the linear **12** gave the highly strained *N*,*N*′,*N*″-tribenzyloxyethyl-*cyclo*-triglycine **1** in 15% yield.[10] The spectroscopic data (^{1}H- and ^{13}C-NMR) confirmed the predicted C_3-symmetric all-*cis* "crown" conformation (Fig. 1).[4] The GIAO[11] calculated ^{1}H-NMR chemical shifts, were in agreement with the experimental values (*e.g.* diastereotopic intra-annular glycine proton doublets: $\Delta\delta_{theor.}$ 0.74 ppm, $\Delta\delta_{exp.}$ 0.72 ppm, $CDCl_3$ solution, 400 MHz, see ESI†). Variable-temperature (VT) ^{1}H-NMR experiments demonstrated, for the glycine protons, a coalescence temperature at 405 K ($C_2D_2Cl_4$ solution, 300 MHz, $\Delta G^{\ddagger}$ = 19.0 ± 0.5 kcal mol^{-1} [12]).

Differently from the 9-membered cyclopeptoid **1**, cyclization of the *N*-substituted tetraglycine **15** proved easy to accomplish, giving **2** in 65% yield, using PyBOP or FDPP as the condensing agent. The presence of a centre of symmetry (Fig. 1) was inferred by the appearance, in the ^{1}H- and ^{13}C NMR spectra, of two independent resonance peak patterns. Theoretical prediction of the ^{1}H NMR values, performed at the QM level (see ESI†), showed full agreement with the recorded spectral data [*e.g.* diastereotopic intra-annular proton doublets: $\Delta\delta_{theor.}$: (a) 2.34 ppm, (b) 0.12 ppm; $\Delta\delta_{exp.}$: (a) 1.94 ppm, (b) 0.08 ppm, respectively; $C_2D_2Cl_4$ solution, 300 MHz, see ESI†]. VT ^{1}H-NMR studies indicated no hint of coalescence up to 425 K ($C_2D_2Cl_4$ solution, 300 MHz) for the intra-annular protons doublets. Finally, a single crystal X-ray analysis‡ (Fig. 2), demonstrated a *ctct* "chair" tetralactam core geometry in agreement with the theoretical prediction (Fig. 1).[13]

The synthesis of **3** proceeded smoothly both in the presence of PyBOP or FDPP (>97% yield, RP-HPLC analysis, see ESI†).

The complexity of the rt ^{1}H NMR spectrum recorded for the cyclic **3** invoked the contemporary presence of more than one conformer in slow exchange on the NMR time scale (Fig. 3a).[14] The conformational disorder in solution was seen as a propitious

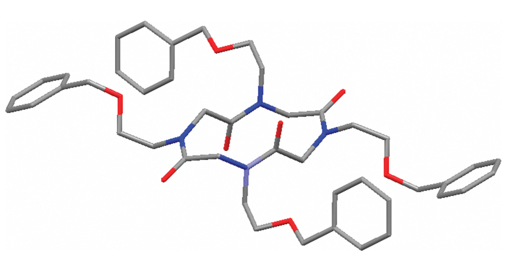

Fig. 2 X-Ray crystal structure of **2** reflecting the *ctct* stereochemical arrangement (atom type: C gray, N blue, O red). Hydrogen atoms have been omitted for clarity.

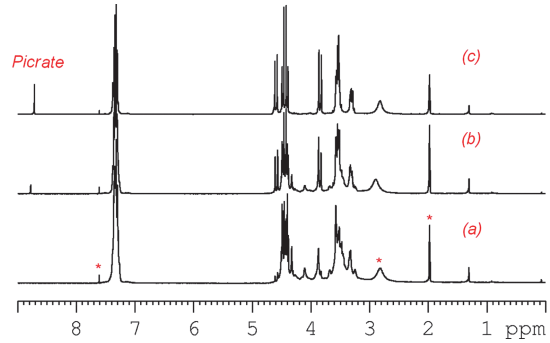

Fig. 3 ^{1}H NMR spectra of free **3** (a) (CD_3CN–$CDCl_3$ 9 : 1 solution, 25 °C, [**3**] = 4.0 mM, 400 MHz) and in the presence of 0.5 eq. (b) or 1.5 eq. (c) of sodium picrate. Residual solvent peaks are labelled with *.

auspice for the complexation studies. In fact, the stepwise addition of sodium picrate to **3**, induced the formation of a new chemical species, whose concentration increased with the gradual addition of the guest (Fig. 3b and c). The conformational equilibrium between the free host and the sodium complex, resulted in being slower than the NMR time scale, giving, with an excess of guest, a remarkably simplified ^{1}H NMR spectrum, reflecting the formation of a 6-fold symmetric species (Fig. 3c).

A conformational search on **3** as a sodium complex suggested the presence of an S_6-symmetry axis passing through the intracavity sodium cation (Fig. 4). The electrostatic (ion–dipole) forces stabilize this conformation, hampering the ring inversion up to 425 K.

The conformation of the corand **3** is influenced also by dipole–dipole interactions. In fact, gradual addition of an excess of the hydrogen bond donors ammonium and benzylammonium picrates to a 9 : 1 CD_3CN–$CDCl_3$ solution of the free host, froze **3** in a 6-fold symmetric species (^{1}H NMR, 400 MHz, Fig. 5a and b).

A QM refined conformational search demonstrated, for the hydrogen-bonded complexes, the structures reported in Fig. 6.

The association constants (K_a) for the complexation of **3** to the first group alkali metals and ammonium, were evaluated in H_2O–$CHCl_3$ following Cram's method (Table 1).[15] The results presented in Table 1 show a good degree of selectivity for the smaller cations, with a peak for Na^+.

We attempted crystallization of the first group alkali metal picrate salt adducts. After unsuccessful results, we obtained needle like crystals, suitable for X-ray structure analysis, of **3** as a 2 : 3 complex with strontium picrate.‡ The structure obtained, the first to be solved for a metal complex of a cyclic

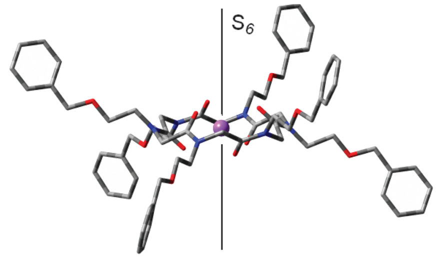

Fig. 4 Picture of the predicted lowest energy conformation for the complex **3** with sodium. The peptoid bonds display an all-*trans* geometry (atom type: C gray, N blue, O red, Na magenta). Hydrogen atoms have been omitted for clarity.

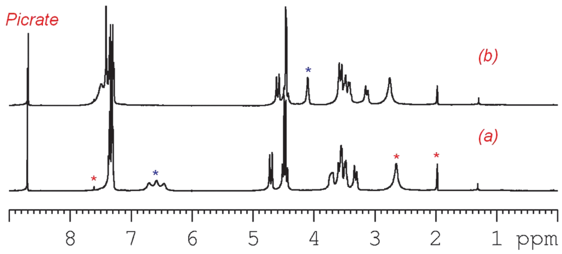

Fig. 5 ^{1}H NMR spectra of **3** (CD_3CN–$CDCl_3$ 9 : 1 solution, 25 °C, [**3**] = 4 mM, 400 MHz) in the presence of 4.0 eq. of (a) ammonium and (b) benzylammonium picrate (* NH_4^+ (a), and $PhCH_2NH_3^+$ (b) protons). Residual solvent peaks are labelled with *.

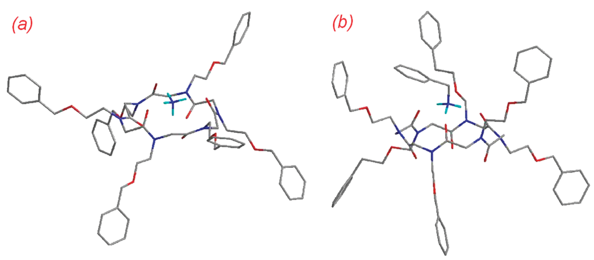

Fig. 6 Predicted lowest energy conformations for the complex between **3** and: (a) ammonium and (b) benzylammonium picrate (atom type: C gray, N dark blue, O red, polar H sky blue). The non-polar hydrogen atoms have been omitted for clarity.

Table 1 *R*, K_a, and $\Delta G°$ for cyclopeptoid host **3** complexing picrate salt guests in $CHCl_3$ at 25 °C; figures within ±10% in multiple experiments, guest : host stoichiometry for extractions was assumed as 1 : 1

Picrate salt	R[a]	$K_a/10^{-3}$ M^{-1}	$-\Delta G°$/ kcal mol^{-1}
Li^+	0.17	950	8.1
Na^+	0.35	3300	8.9
K^+	0.24	940	8.1
Rb^+	0.126	410	7.7
Cs^+	0.085	210	7.2
NH_4^+	0.18	380	7.6

[a] [Guest]/[host] in $CHCl_3$ layer at equilibrium.

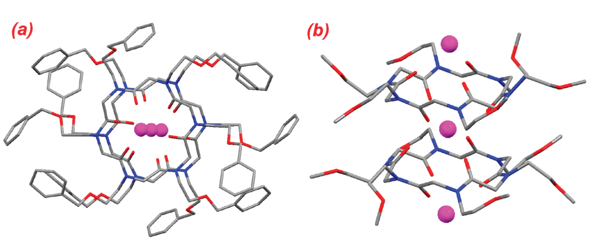

Fig. 7 X-Ray crystal structure of $\mathbf{3}_2\cdot[Sr(Picr)_2]_3$ complex. (a) Top view. Hydrogen atoms and picrates have been removed for clarity. (b) Side view. Hydrogen atoms, picrates, and phenyl groups have been omitted for clarity. Atom type: C gray, N blue, O red, Sr magenta.

peptoid, showed a unique all-*trans* peptoid bond configuration (Fig. 7), with the carbonyl groups alternately pointing toward the strontium cations and forcing the *N*-linked side chains to assume an alternate pseudo-equatorial arrangement.

The macrolactam core of the solid state construct is in excellent agreement with the theoretical studies, consolidating the supposed S_6-symmetry of the host in the sodium, ammonium and benzylammonium complexes.

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Notes and references

‡ Crystal data for **2**. Formula: $C_{44}H_{52}N_4O_8$, FW = 764.90, monoclinic, space group $C2/c$(no. 15), Z = 4, a = 18.554(3), b = 5.387(2), c = 40.021(5) Å, β = 98.171(5)°, V = 3959.5(17) Å^3, D_x = 1.283 g cm^{-3}, μ_{calc} = 0.089 mm^{-1}.
Crystal data for $\mathbf{3}_2\cdot[Sr(Picr)_2]_3$. Formula: $C_{168}H_{168}N_{30}O_{66}Sr_3\cdot 2H_2O$, FW = 3958.20, monoclinic, space group $P2_1/n$, Z = 2, a = 18.895(5), b = 24.546(3), c = 9.252(3) Å, β = 96.304(11)°, V = 8875(3) Å^3, D_x = 1.481 g cm^{-3}, μ_{calc} = 0.355 mm^{-1}.

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