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Cyclic Peptoids as Topological Templates. Synthesis *via* Central to Conformational Chirality Induction

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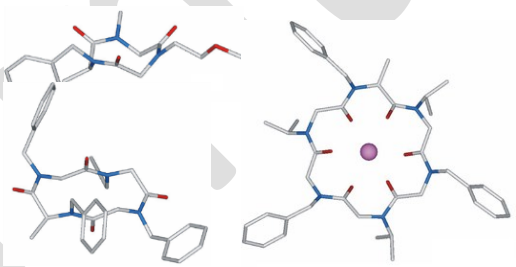
Supporting Information Placeholder

ABSTRACT: Central to conformational chirality induction was utilized for the synthesis of diastereopure cyclic peptoids containing an *N*-benzyl alanine residue. Molecular modelling, NMR spectroscopy, single crystal X-ray diffraction studies and HPLC with chiral stationary phase demonstrated the easy formation of free and sodium/benzylammonium complexed cyclic oligomers through strategic incorporation of a single stereogenic center in the oligomeric backbone. The synthesis of cyclic peptoids with defined conformational chirality and appropriate side chain topology is now possible.



The adaptable morphology of macrocyclic peptoids (cyclic oligomers composed of *N*-substituted glycine monomer units)[1] suggests their function as mimics of biomolecules,[2] supramolecular building blocks,[3] and catalytic agents.[4] The precise control of their conformation[5] is of crucial importance to capitalize on their geometric attributes. However, formation of racemic mixtures of conformationally unstable chiral macrocycles[6,7] plagues the design of architecturally defined oligomeric peptoids affecting their possible use as topological templates[8] and functional molecules.[2-4]

While the selection of appropriate side chains,[5,9] the formation of metal complexes,[3a,10] or macrocyclization[11] are conventional methods to stabilize peptoids' conformation, the insertion of stereogenic centers in the backbone[12,10b] has rarely been utilized to rigidify structures.[13]

In the present communication we illustrate, with the help of NMR spectroscopy, molecular modelling and single-crystal X-ray diffraction analysis, the remarkable chiral induction triggered by a *single* stereogenic center on the backbone of cyclic trimeric, tetrameric and hexameric peptoids **1-5** (Figure 1). The unique conformational features, the specific display of chelating ligands and the defined asymmetric orientation of the side chains in cyclic peptoids makes these preorganized platforms ideal candidates for use in molecular recognition studies and as potential topological templates.

The striking effects of an intra-annular stereogenic center insertion in a cyclopeptoid scaffold can be immediately appreciated comparing the conformational properties of the trimeric cyclopeptoid **1**, containing the *N*-benzyl alanine[14] residue, with those of the corresponding purely peptoidic **7** (Scheme 1).

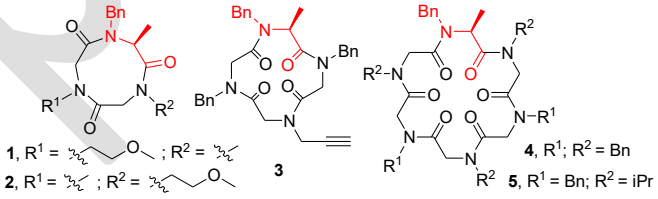
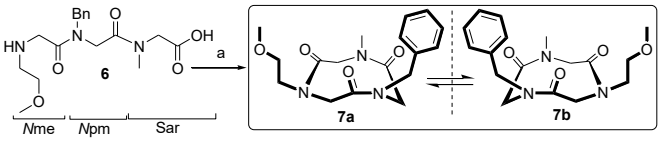


Figure 1. Schematic structures of molecular targets **1-5**. Highlighted in red is the *N*-benzyl alanine residue.

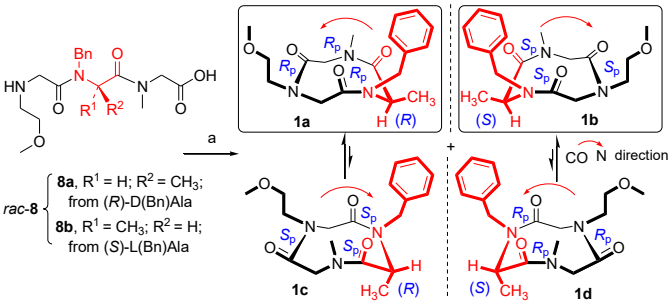
Cyclization of the achiral H-(*N*me-*N*pm-Sar)-OH (**6**)[15] furnished a racemic mixture of the expected "crown"[12a] conformational enantiomers cyclo-[(*cis*,R_p)*N*me-(*cis*,R_p)*N*mp-(*cis*,R_p)Sar] and cyclo-[(*cis*,S_p)*N*me-(*cis*,S_p)*N*mp-(*cis*,S_p)Sar],[6] **7a** and **7b**, respectively. The racemic mixture was evidenced by gradual addition of Pirkle's alcohol ((*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol as chiral solvating agent,[6] ^{1}H NMR analysis, Fig. S12 of SI section). The relatively low conformational energy barrier (T_c = 383 K, $C_6D_4Cl_2$, 300 MHz, $\Delta G^{\ddagger}$ = 17.9 kcal mol^{-1}, see SI) between the two enantiomorphous forms hampered resolution on HPLC with chiral stationary phase.[16] The substitution of the *N*-benzyl glycine with an *N*-benzyl alanine residue[14] completely changed the conformational stability of the trimeric scaffold.

From the cyclization of linear chiral racemic H-(*N*me-*rac*-(Bn)Ala-Sar)-OH (*rac*-**8**, Scheme 2) a pair of "crown"[17] enantiomers **1a**/**1b** ((cyclo-[(*cis*,R_p)*N*me-(*cis*,R_p)D(Bn)Ala-(*cis*,R_p)Sar)]/ (cyclo-[(*cis*,S_p)*N*me-(*cis*,S_p)L(Bn)Ala-(*cis*,S_p)Sar)], respectively, with the alanine methyl group in a

pseudo-equatorial position) and their diastereoisomers **1c/1d** ((cyclo-[(*cis*,S_p)*N*me-(*cis*,S_p)D(Bn)Ala-(*cis*,S_p)Sar)]/(cyclo-[(*cis*,R_p)*N*me-(*cis*,R_p)L(Bn)Ala-(*cis*,R_p)Sar)], respectively, with the alanine methyl group in a pseudo-axial position)[18] were expected.



Scheme 1. Synthesis of conformational enantiomers **7a**/**7b** from achiral precursor **6**. Reaction conditions: a) HATU (4 eq.), DIPEA (6.2 eq.), 23%. Residues abbreviations: *N*me = N-(methoxyethyl)glycine; *N*pm = N-(benzyl)glycine; Sar: sarcosine.



Scheme 2. Synthesis of **1a**-**1d** from chiral racemic precursor **8**. Reaction conditions: a) HATU (4 eq.), DIPEA (6.2 eq.), 56-69%, see SI.

To our surprise, the cyclization reaction only yielded the **1a**/**1b** enantiomer pair. Their structure was inferred by key ROE correlations involving the three intra-annular pseudo-axial protons (see SI) and by DFT (Density Functional Theory) calculations. **1a/1b** enantiomers (E = 0 kcal mol^{-1} in DMSO) show a much higher stability than their conformational diastereoisomers **1c/1d** (ΔE = 6.9 kcal mol^{-1} in DMSO, as reported in Figure 2, see SI for computational details and atomic coordinates). This conspicuous energy difference would lead to more than 99.9% of **1a/1b** in solution respect to **1c/1d**.

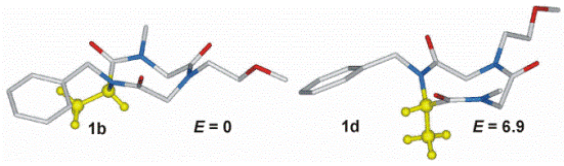


Figure 2. Minimum energy structures of conformational diastereoisomers **1b** and **1d** and their respective internal energies calculated in DMSO and expressed in kcal mol^{-1}. Hydrogen atoms have been omitted for clarity except for the alanine residue (in yellow). Atom type: C light grey (yellow for alanine residue), N blue, O red.

The racemate **1a**/**1b** was resolved by HPLC using a chiral stationary phase (Figure 3). The retention times of the enantiomers were coincident with those of the enantiopure macrocycles (showing opposite CD spectra) individually synthesized from the linear chiral non-racemic **8a** and **8b** (Scheme 2, see SI).

We were able to obtain single crystals suitable for X-ray diffraction studies for the enantiopure **1a** and **1b**, and the racemic mixture **1a/1b**. Noteworthy, the enantiopure compounds crystallize as enantiomorph crystals in the space group $P2_12_12_1$ and the corresponding absolute configuration of the stereogenic centers could be determined from the X-ray diffraction data. On the other hand the racemic mixture **1a/1b** provided crystals in space group *P*-1 with two crystallographically independent molecules in the asymmetric unit. In all cases molecules assemble with a *T*-shape arrangement as a consequence of $CH_2\cdots OC$ hydrogen bonds (previously reported for other cyclic trimeric peptoid oligomers).[3c]

For the non-palindromic nature of amide-based oligomers, cyclization of linear reverse sequences leads to constitutional cycloisomers. The cyclization of H-(Sar-L(Bn)Ala-*N*me)-OH (**9**), a retro-inverso isomer[19] of **8a**, gave the cyclic tripeptoid **2** (cyclo-((*cis*,R_p)Sar-(*cis*,R_p)L(Bn)Ala-(*cis*,R_p)*N*me), Scheme 3). Although containing an (*S*) stereogenic center, **2** is topologically similar to **1a** (containing an (*R*)-D(Bn)Ala residue). **2** and **1a** are cycloretro-enantiomers.[19] In *conformationally stable* peptoid scaffolds the absolute three-dimensional orientation of the side chains can be modified playing on both the backbone stereogenic center or their primary sequence.

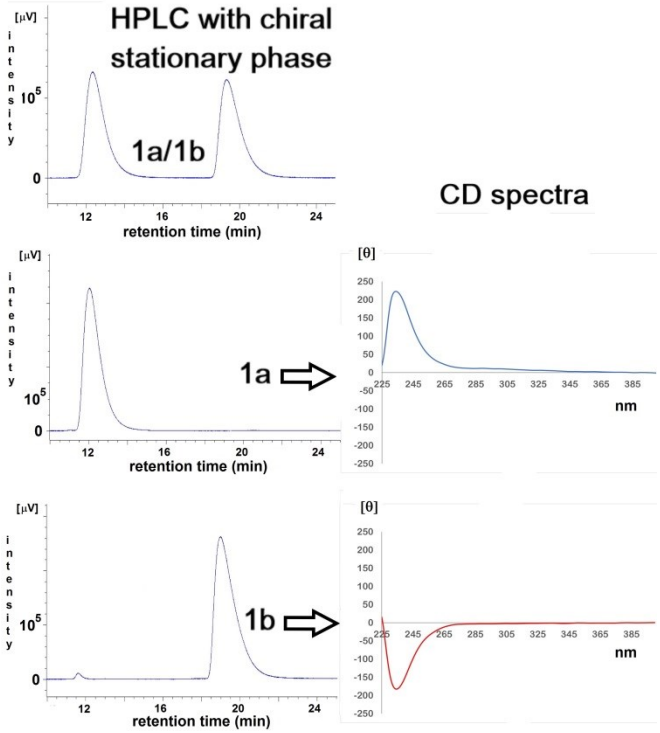


Figure 3. Resolution of the racemic mixture **1a**/**1b** (synthesized from *rac*-**8**) in comparison with chiral non-racemic **1a** and **1b** (synthesized from the enantiopure linear precursors **8a** and **8b**). HPLC chromatograms using CHIRALPAK AD-H column. Conditions: 85:15 hexane:isopropanol; flow: 1 mL min^{-1}, 220 nm (see SI) and their respective CD spectra (in chloroform, [θ] in deg·cm^2/dmol).

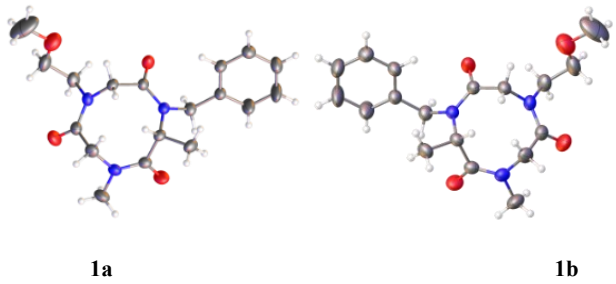
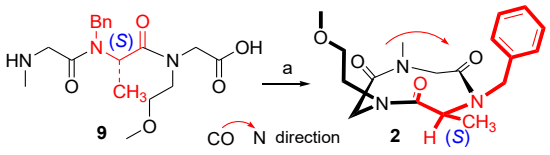


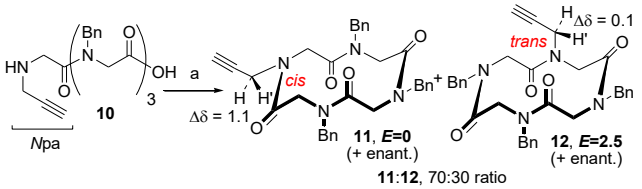
Figure 4. X-ray molecular structures of the enantiomorph cyclic peptoids **1a** and **1b** Atom type: C grey, N blue, O red, H white. Thermal ellipsoids are drawn at 30% probability level.



Scheme 3. Cyclization of **9** to give **2**. Reaction conditions: a) HATU (4 eq.), DIPEA (6.2 eq.), 46%.

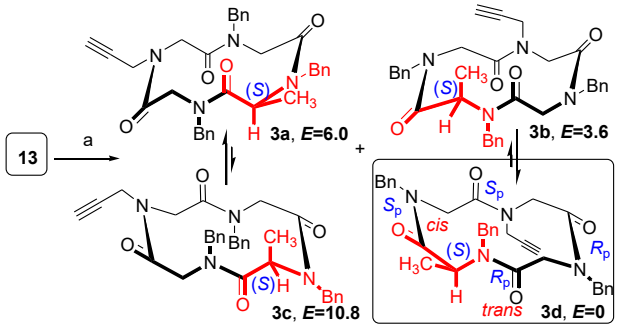
Cyclic trimeric peptoids constitute ideal platforms for molecular recognition. The rigid cone shape and the properly oriented carbonyls in **1b** favored the formation of a complex with the benzylammonium ion (as tetrakis[3,5-bis (trifluoromethyl)phenyl]borate –TFPB– salt, see Fig. S1 of SI for qualitative studies) in fast equilibrium with the free host on the NMR time scale. To the best of our knowledge this preliminary result represents the first case of molecular recognition in cyclic trimeric peptoid.

Interesting findings also emerged by cyclization of *N*-benzyl,*N*-propargyl tetrameric peptoids. High dilution cyclization of the linear achiral H-(*N*pa-*N*pm$_3$)-OH (**10**, Scheme 4) yielded an unseparable mixture of the two *cis,trans,cis,trans* conformationally stable diastereoisomers **11** and **12**[20] (plus their respective enantiomers,[21] not reported). The *c*/*t* amide bond geometries were assigned on the basis of the ^{1}H NMR Δδ observed for the side chains' methylene diastereotopic protons (larger Δδ indicated *cis* peptoid junctions, small Δδ implied *trans* amide bonds).[7] The preferential formation of the cyclic tetramer **11** (with the propargyl group located on the *cis* amide bond) was corroborated by comparison of calculated internal energies (**11**, E = 0 kcal mol^{-1}; **12**, ΔE = 2.5 kcal mol^{-1}, see SI).



Scheme 4. Cyclization of **10** to give **11** and **12** (their respective enantiomers are not reported). Reaction conditions: a) HATU (4 eq.), DIPEA (6.2 eq.), 69%. The reported internal energies differences (in Kcal mol^{-1}) were calculated in chloroform. Residues abbreviation: *N*pa = N-(propargyl)glycine.

Cyclization of the chiral linear **13** (H-(*N*pa-*N*pm-L(Bn)Ala-*N*pm)-OH), differing from **10** for the presence of a Cα-methyl group, was expected to yield four inequivalent stereoisomeric cyclopeptoids (**3a-d**, Scheme 5).



Scheme 5. Cyclization of (*S*)-**13** to give possible conformational isomers **3a-d**. The reported internal energies differences (in Kcal mol^{-1}) were calculated in chloroform. Reaction conditions: a) HATU (4 eq.), DIPEA (6.2 eq.), 30%.

In this case, the remarkable stereodirecting effects of the alanine residue induced the formation of a single detected isomer: the cyclo-((*trans*,R_p)L(Bn)Ala-(*cis*,S_p)Sar-(*trans*,S_p)*N*pa-(*cis*,R_p)*N*pa) **3d**,[20] (^{1}H NMR analysis). Its structural assignment was based on NMR data (Δδ values suggested the presence of an axial *N*-propargyl side chains, which excluded compound **3a** and **3c**) and on the grounds of theoretical studies (showed by the E values reported in Scheme 5). Qualitative NMR studies indicated the formation of a supramolecular complex between **3d** and the benzylammonium ion (^{1}H NMR analysis, Fig. S2). The only reported case of molecular recognition by cyclic tetrapeptoids is related to benzene.[22]

The stabilizing influence of the alanine residue on the conformation of cyclic nine- and twelve-membered oligoamides, was not observed in the chiral *N*-benzyl and alternated *N*-benzyl,*N*-isopropyl (*N*pe,*N*ip) hexameric cyclic peptoid probes **4** and **5**.[23] Their respective ^{1}H NMR spectra showed, in fact, multiple conformations in slow equilibrium on the NMR time scale (Figure 5a and d). However, addition of one equivalent of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFPB)[10c] induced the formation of 1:1 complexes[7] with Na^+ (Figure 5b and e). In the two complexes (in slow equilibrium with the free host in the NMR time scale) the cyclic peptoids displayed an all-*trans*[6,7,10c] [**4**·Na]$^+$/[**5**·Na]$^+$ amide bond conformation, a relatively high apparent[7] association constants (K_a = 5.2 × 10^4 M^{-1}, ΔG^0 = –6.4 Kcal mol^{-1}, and K_a = 2.7 × 10^4 M^{-1}, ΔG^0 = –6.0 Kcal mol^{-1}, for [**4**·Na]$^+$ and [**5**·Na]$^+$, respectively),[24] and stable conformational chirality (see CD spectra in Fig, S20 and 22, SI).

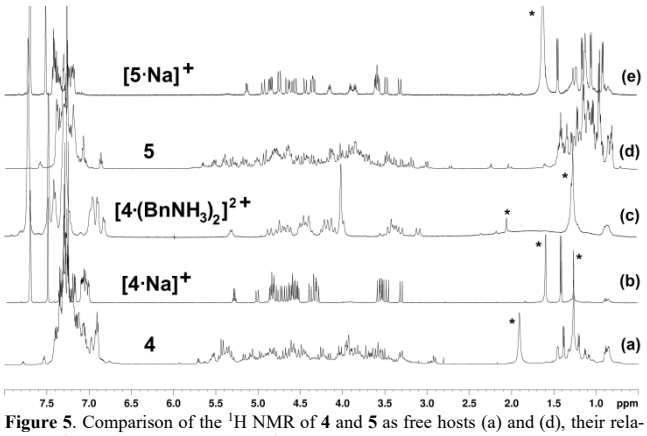


Figure 5. Comparison of the ^{1}H NMR of **4** and **5** as free hosts (a) and (d), their relative Na^+ [(b) and (e)] and $BnNH_3^+$ (c) complexes. Water and lipid impurities are marked with a black asterisk.

According to the ΔE values calculated in chloroform, the complexes with pseudo-axial methyl groups are thermodynamically unfavored (ΔE = +2.4 kcal mol^{-1} and +2.1 kcal mol^{-1} for [**4a**·Na]$^+$ and [**5a**·Na]$^+$, respectively, Figure 6), therefore, on the basis of modelling studies, the planar amide configurations of the chiral complex [**4**·Na]$^+$ and [**5**·Na]$^+$ were assigned as: cyclo-((*trans*,R_p)L(Bn)Ala-(*trans*,S_p)*N*pm-(*trans*,R_p)*N*pm-(*trans*,S_p)*N*pm-(*trans*,R_p)*N*pm-(*trans*,S_p)*N*pm) and cyclo-((*trans*,R_p)L(Bn)Ala-(*trans*,S_p)*N*ip-(*trans*,R_p)*N*pm-(*trans*,S_p)*N*ip-(*trans*,R_p)*N*pm-(*trans*,S_p)*N*ip), respectively.

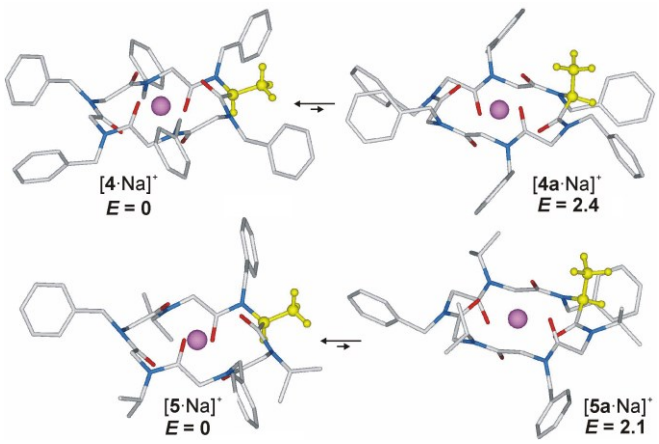


Figure 6. Minimum energy structures of chiral metal complexes [**4**·Na]$^+$/[**4a**·Na]$^+$ and [**5**·Na]$^+$/[**5a**·Na]$^+$ and their respective energies (in kcal mol^{-1}). Hydrogen atoms have been omitted for clarity except for the alanine residue (in yellow). Atom type: C light grey (yellow for alanine residue), N blue, O red, Na^+ magenta.

Peptoid **4** recognizes alkylammonium ions, as demonstrated by quantitative titration with $BnNH_3^+$ $TFPB^-$ (Figure 5c; Fig. S3 of SI reports the quantitative titration in $CDCl_3$). A 1:2 host:guest complex, with $K_{ass} = 7.0 \times 10^6$ M^{-2}, $\Delta G^0 = -9.3$ Kcal mol^{-1}, was formed.

In summary, the strategic incorporation of a chiral *N*-substituted amino acid in a peptoid backbone and the advantageous possible synthesis of retro-inverso analogs, represents a new conceptual approach for the construction of unique chiral preorganized molecular platforms that can play a major role in supramolecular chemistry and as bioactive molecules. The full assessment of their potentials will be our next challenge.

Supporting Information

Experimental procedures, characterization/structural data, and atomic coordinates (PDF). CCDC 1588736-1588738 contain the supplementary crystallographic data for this paper.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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(17) Small amounts of "boat" conformers were evidenced in non-polar solvents, as reported by Kessler in Ref. 12a.

(18) **1a**/**1c** and **1b**/**1d** pairs are diastereoisomeric conformational isomers: they have the same configuration of the stereogenic center and opposite planar configurations at the amide stereogenic sites. No sign of coalescence was observed for the intra-annular methylene groups up to 120° C (^{1}H NMR, $C_6D_4Cl_2$, 300 MHz, see SI).

(19) A *retro-inverso isomer* is an isomer in which the direction of the sequence is reversed and the chirality of the residue(s) is inverted. A *cycloretro isomer* is a cycloisomer in which the sequence is reversed and the chirality of the residue(s) is inverted. Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1–7.

(20) No sign of coalescence were revealed for **11**, **12**, **3d**, $[\mathbf{4}{\cdot}Na]^+$/$[\mathbf{5}{\cdot}Na]^+$ in $C_6D_4Cl_2$ solutions up to 120° C (^{1}H NMR, 300 MHz, see SI).

(21) The unequal substitution of the cyclic tetrameric peptoid breaks the symmetry of the *ctct* rings inducing the formation of enantiomeric pairs for both the conformational isomers **11** and **12**. To the best of our knowledge this is the first reported case of conformational asymmetric cyclic tetrapeptoids devoid of stereogenic centers.

(22) Sugihara, T.; Imanishi, Y.; Higashimura, T. *Biopolymers,* **1975**, *14*, 733–747.

(23) Most of the hexameric cyclic peptoids show multiple conformations in slow equilibrium in the NMR time scale: (a) Dale, J; Titlestad, K. *Chem. Commun.* **1969**, 656–659. (b) Titlestad, K. A *Acta Chem. Scand. B* **1975**, *29*, 153-167, plus refs. 6 and 10c.

(24) The template effect of Na^+ ion on the purely peptoidic derivatives of **4** and **5** (with identical *N*-side chain substitution) has been discussed on Ref. 6 and 7, respectively.