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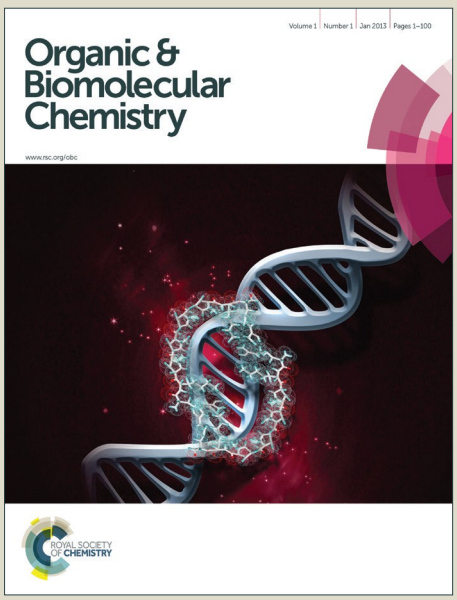

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ARTICLE

Synthesis and complexing properties of cyclic benzylopeptoids – a new family of extended macrocyclic peptoids†

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An efficient protocol for the solid-phase synthesis of six members of a new class of extended macrocyclic peptoids (based on the *ortho*-, *meta*- and *para*-*N*-(methoxyethyl)aminomethyl phenylacetyl units) is described. Theoretical (DFT) and experimental (NMR) studies on the free and Na^+-complexed cyclic trimers (**3**–**5**) and tetramers (**6**–**8**) demonstrate that the annulation of rigidified peptoid can generate new hosts with the ability to sequestrate one or two sodium cations with affinities and stoichiometries defined by the macrocycle morphology. Ion transport studies have been also performed in order to better appreciate the factors promoting transmembrane cation translocation.

Introduction

On a molecular standpoint, the functions of all living systems are based on mutual contacts of complementary three-dimensional atomic surfaces. Naturally occurring apoenzymes,[1] nucleic acids,[2] ionophoric macromolecules,[3,4] and most of the artificial supramolecular objects[5] have the common attribute to condense, in a proper space (designed by evolution or human inspiration), well-defined traits dictated by stable folding.[6-9] The acquisition of functional shapes is also attained in a promising family of artificial oligoamides: the peptoids[10] (Figure 1). In this mouldable class of inspiring peptidomimetics, molecular morphologies are defined by proper functionalization of the synthetically tuned *N*-alkylated amide moieties.[6]

In recent times, it has been demonstrated that the conformational control of *N*-substituted glycine oligomers can be further enforced by the insertion of aromatic rings in the oligoamide backbone. Benzanilides,[11-13] *para*-cyclophanamides,[14-16] and arylopeptoids[17-25] (Figure 1) are examples of new types of compounds with promising potentials due to their rigidified frame. In particular, arylopeptoids offer an interesting case of a new artificial taxonomic order. In these oligomeric aminomethyl benzamides attractive architectures emerge from *E*/*Z* peptoid bond conformational control[20,22,23,25] and cyclization. The last case has recently been examined by Hjelmgaard and Faure.[26] In their elegant work they demonstrated that the cyclization of relatively inflexible linear trimeric *para*-substituted arylopeptoids brings to the cyclic hexamers **1** and not to the expected cyclic trimers **2** (Figure 2). Moreover, the cyclization of trimeric *ortho*-isomers proceeds with very low yields (for the increased "congestion" of the backbone).

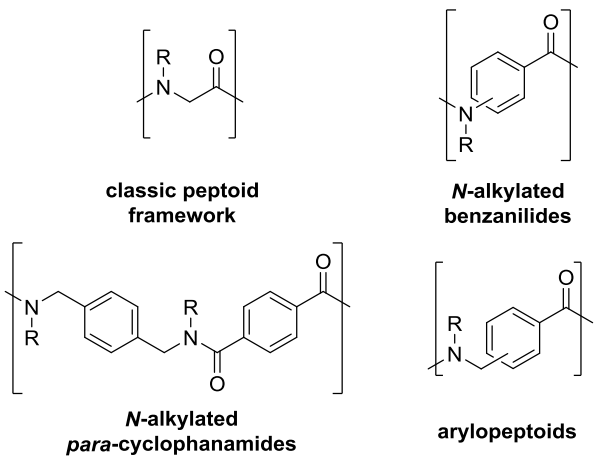

Fig. 1 Peptoids and tertiary oligoamides with aromatic backbones.

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† Electronic Supplementary Information (ESI) available: experimental synthetic procedures, ^{1}H- and ^{13}C NMR spectra, 2 D and variable temperature experiments, HPLC chromatograms, computational data and ionophoric studies. See DOI: 10.1039/x0xx00000x

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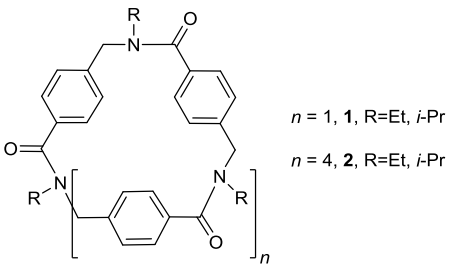

Fig. 2 *para*-Series of properly *N*-substituted arylopeptoids.

In our endeavour in the field of the classic cyclic peptoids,[27,28] we proved their innate ability to act as complexing agents,[27,29] to perform catalysis,[30,31] to form elegant molecular[32] and metal-organic frameworks[33] and promote ion transport.[34,35] Nonetheless, we felt that the horizons of chemical space could be magnified by the use of different building blocks. We thus chose to replace the *N*-alkylamino-acetyl unit of the peptoid backbone by an *N*-alkylaminomethyl phenylacetate monomer (Figure 3). The oligomerization and cyclization of *ortho*-, *meta*- *para*-substituted *N*-alkylaminomethyl phenylacetate units prelude to a new family of "extended peptoids" (termed "benzylopeptoids") with potential as ion complexing agents and, possibly, as ionophores and/or organocatalysts.

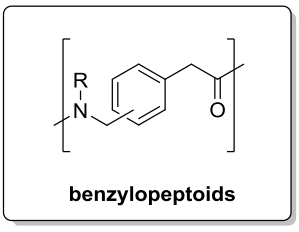

Fig. 3 Structural unit of "benzylopeptoids".

Preliminary theoretical calculations demonstrated that the formal addition of a benzylene group in the *N*-alkylglycine unit would have a beneficial effect for both the formation of the elusive *para*-substituted "extended" cyclic trimers and on the cyclization of the crowded *ortho*-substituted trimeric isomers. The *ortho*-substituted oligomers represent a challenging synthetic target and the scarce literature available on the subject[22,36-38] illustrates the intrinsic difficulties to forge these sterically demanding aromatic oligoamides.

Thus, with the aim to unveil the full potential of the newly conceived "extended peptoids"[11-26] in the field of supramolecular chemistry, herein we report the theoretical studies, the efficient monomers' syntheses, the solid-phase oligomerization and the cyclization of six members of a new class of cyclic oligomeric *N*-methoxyethyl(aminomethyl) phenylacetamides: the cyclic banzylopeptoid trimers **3–5** and tetramers **6–8** (Figure 4). The different size of the target compounds were meant to explore their complexing abilities in the presence of the sodium cation, chosen as the reference ion. The amphiphilic methoxyethyl side chain was selected in order to favour possible ionophoric activity.

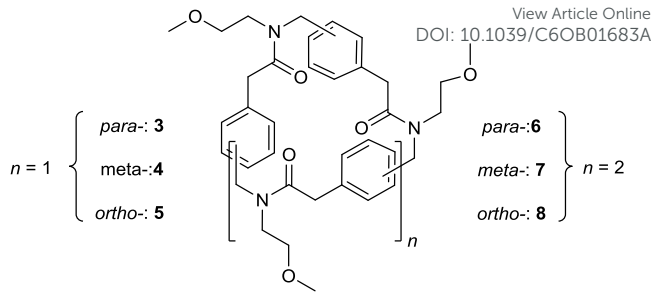

Fig. 4 Structures of cyclic benzylopeptoids **3–8** (*i.e.*: cyclic oligomeric *N*-substituted aminomethyl phenylacetamides).

The unequal substitution of the benzylopeptoids implied a tailored synthetic strategy with properly protected aromatic amino acid building blocks. In fact, in the case of the *ortho*-isomer, the spatial vicinity of cross-reactive functional groups required lactamization-free procedures. For all the monomers, the solid-phase synthesis relied on the classic Fmoc-based "monomeric" protocol.

Theoretical (DFT) and experimental (NMR) studies of the Na^+-complexed forms identified well-defined molecular architectures *in silico* and in solution for most of the host/guest adducts.

With the present contribution we enlarge the new field of the aryl-based "exdended" peptidomimetic foldamers and we clarify the minimal requirements for transmembrane ion transport. In this contribution we demonstrate how oligomers of rigid building blocks can undergo cyclization to generate fairly stable complexes of remarkable symmetry and superb beauty.

Results and discussion

Theoretical studies

The absence of stabilizing intramolecular non-covalent bonds (typical of most peptoid-based frameworks)[32,39] induces to multitudinous, energetically equivalent, conformational minima (even in the presence of rigid backbone units).[26] The ample variety of possible isoenergetic conformers is exemplified by the well-known complexity of the peptoids' NMR spectra (where the resonances of multiple conformations, in slow equilibrium respect to the NMR time scale, overlap in the one dimensional spectra).[27-29]

The situation reverses in the presence of cations (*i.e.* sodium ion). The stabilizing interaction of the positive ion with the carbonyl oxygen atoms lone pairs stiffens the macrorings' conformations and forces the host/guest complexes towards few (or a single) species.

Figure 5 reports the most stable conformation of the trimeric oligoamides **3–5** (see ESI† for computational details). While the *para*-substituted cyclic oligomer **3** appears too large and the *ortho*-benzylopeptoid **5** too small to host the Na^+, it seems that the *meta*-benzylopeptoid **4** has the optimal ring size for the interaction with the sodium cation. Indeed, according to the modelling studies, Na^+ would be located out of the plane defined by oxygen atoms in the *ortho*-benzylopeptoid **5**, while in the *meta*-benzylopeptoid **4** would lie almost on the same plane. As for *para*- benzylopeptoid **3**, the distance among oxygen atoms would be too large to give a simultaneous tricoordination to the metal.

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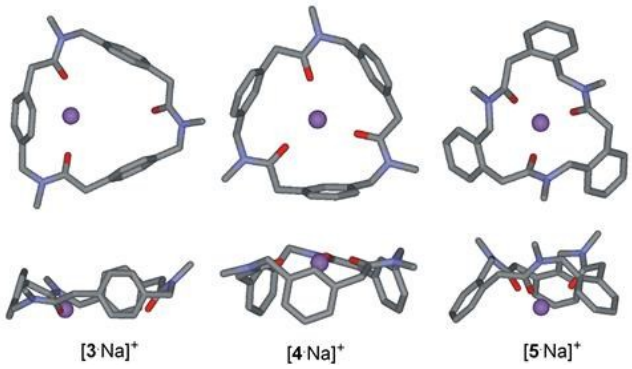


Fig. 5 Minimum energy structures of Na^+ complexes of compounds **3**–**5** (top and side views). For simplicity's sake, the *N*-linked side chain has been modelled as $–CH_3$. Hydrogen atoms have been omitted for clarity. Atom type: C grey, N light blue, O red, Na^+ blue.

The values of the interaction energies in $CHCl_3$, reported in Table 1, corroborate the visual impressions. In the three isomers it is evident an intrinsic C_3-symmetry of the complexes (in the case of the *para*-isomer the C_3-symmetry is "dynamic", because of the free movement of the sodium ion).

In the case of the bigger cyclic tetramers, the ample macrocycle inner space has the propensity to accommodate one or even *two* ions. The most stable conformations of the monosodium and disodium host/guest adducts are shown in Figure 6 and the energies are reported in Table 1.

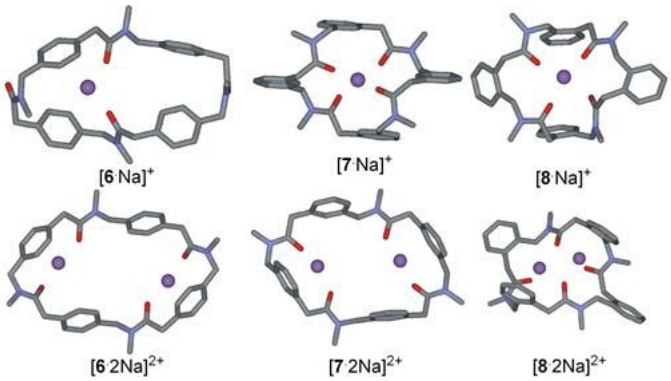


Fig. 6 Minimum energy structures of Na^+ complexes of compounds **6**–**8** with one or two coordinated Na^+. For simplicity's sake, the *N*-linked side chain has been modelled as $–CH_3$. Hydrogen atoms have been omitted for clarity. Atom type: C grey, N light blue, O red, Na^+ blue.

Table1 Host/guest interaction energies of trimers **3-5** with one Na^+ ion, and of tetramers **6-8** with one or two Na^+ ions. Energies are calculated in $CHCl_3$ and expressed in kcal/mol. In parentheses are reported the studied complexes.

	para-substitution	*meta*-substitution	*ortho*-substitution
Trimeric oligomers + Na^+	-16.2 ([**3**·$Na]^+$)	-33.1 ([**4**·$Na]^+$)	-32.2 ([**5**·$Na]^+$)
Tetrameric oligomers + Na^+	-23.8 ([**6**·$Na]^+$)	-32.0 ([**7**·$Na]^+$)	-24.1 ([**8**·$Na]^+$)
Tetrameric oligomers + $2Na^+$	-38.4 ([**6**·$2Na]^{2+}$)	-32.3 ([**7**·$2Na]^{2+}$)	-30.0 ([**8**·$2Na]^{2+}$)

Even if some of these geometries show a clear C_2 symmetry, any prevision about the behavior of the complexes in solution would be hazardous due to the possible fast shift of the sodium ion(s) through the four carbonyl groups and the high degree of freedom associated to the single bonds of the tetramers.

In the case of cyclic tetramers, host/guest interaction energies in $CHCl_3$ are always higher for disodium with respect to monosodium complexes, even for *ortho*-benzylopeptoid **8**, where the lack of free space keeps the two positive ions very close (Table 1). In the *para*- and *meta*-benzylopeptoid disodium complexes **6** and **7** the Na^+ coordination is helped by π(aromatic)-cation interactions. According to our calculations the interaction energies ($-\Delta E$) for the disodium complexes increase in the order **8** < **7** < **6**, reflecting the expansion of the ring inner space. On the contrary no monotonous behaviour is observed for monocoordinated tetramers, due to the unexpected stability of *meta*-benzylopeptoid complex.

Based on the reported calculation results, we expect the formation of monosodium complexes for the trimeric entities **3**-**5** (with the *meta*-benzylopeptoid monosodium complex favoured). For the tetramers **6**-**8** a single and a double sodium ion interaction seems possible.

With the comforting data from the preliminary theoretical calculations, we were ready to proceed towards the next steps: the synthesis of the cyclic benzylopeptoids and the experimental study of their complexing abilities.

Synthesis

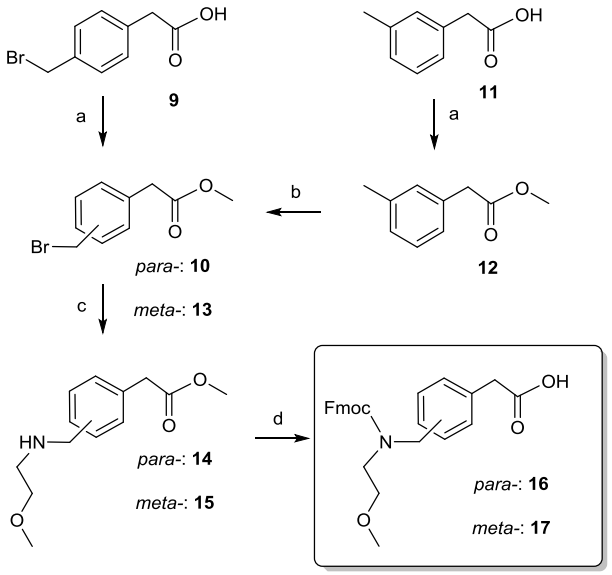
The "submonomer" approach[40] for the solid-phase synthesis of linear "extended peptoids" (as in the case of the arylopeptoids) is known to be a difficult task for two main reasons: the reactivity of the benzyl group does not match that of the bromoacetate, and the oligomerization conditions are substrate-specific.[22-24,41] Therefore, we decided to construct our oligoamides using the more reliable "monomer" approach.[42] The supposed easy elaboration of the Fmoc-protected monomers and the powerful strategies refined for the solid-phase condensation of the less reactive secondary amines[43] were considered good auspices for the success of our synthetic endeavour.

Two parallel routes were planned for the three differently substituted monomers. While for the *para*- and *meta*- isomers we chose the methyl as the carboxyl protective group, for the more challenging *ortho*- isomer we selected the more hindered *t*-butyl ester (in order to avoid possible base-induced intramolecular macrolactamizations).[22]

Scheme 1 outlines the synthesis of *para*- and *meta*-substituted monomer units. The synthesis started with the carboxyl group methylation of the commercially available *para*-(bromomethyl)phenylacetic acid (**9**) to give the corresponding methyl acetate (**10**).[44] The *meta*-isomer was elaborated in two steps: first the methylation of the inexpensive *meta*-tolylacetic acid (**11**), and then the NBS-mediated benzylic bromination (in the non-toxic ethyl acetate). Both the fairly stable brominated intermediates

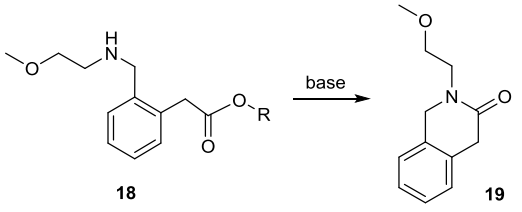
(**10** and **13**) were subjected to the amination reaction in the presence of five equivalents of methoxyethylamine (in order to prevent polyalkylation adducts) and were isolated from the column chromatography as free amines (the eluents contained 1% of triethylamine).

Both the *para*- and *meta*-methyl phenylacetates (**14** and **15**, respectively) were hydrolyzed with lithium hydroxide and the free amino groups were protected as 9-fluorenylmethoxycarbonyl (Fmoc) derivatives. The overall yields for the monomers **16** and **17**, ready for the solid-phase oligomerization, were 31% and 18%, respectively.



Scheme 1 Synthesis of monomers **16** and **17**. Reagents and conditions. (a) methanol, chlorotrimethylsilane (**10**: 97%; **12**: 98%); (b) *N*-bromosuccinimide, benzoyl peroxide, ethyl acetate (**13**: 55%); (c) methoxyethylamine, DMF (**14**: 70%; **15**: 76%); (d) i) $LiOH \cdot H_2O$, 1,4-dioxane/water; ii) $NaHCO_3$, DMAP, Fmoc-Cl, (**16**: 46%; **17**: 44%).

As previously stated, the synthesis of the *ortho*-isomer needed a different approach. The possible intramolecular amidation of the close cross-reactive ester/amine groups (Scheme 2) was considered a major risk for the success of the synthetic strategy.



Scheme 2 Possible base-induced lactamization of the *o*-substituted intermediate.

In order to preserve the relatively electrophilic carbonyl ester from the amine nucleophilic attack, we selected the bulky *t*-butyl group as the carboxyl protective group. Scheme 3 summarizes the synthesis of the *ortho*-((2-methoxyethylamino)methyl)phenylacetic acid (**25**) starting from the commercially available *ortho*-tolylacetic acid (**20**). The classic DCC-mediated esterification gave us the *t*-butyl ester (**21**). Radical bromination and subsequent S_N2 halogen displacement, in the presence of methoxyethylamine, produced the fairly stable aminoester **23**. Fmoc protection and acid-induced removal of the *t*-butyl ester afforded the target monomer **25** in 25% overall yield.

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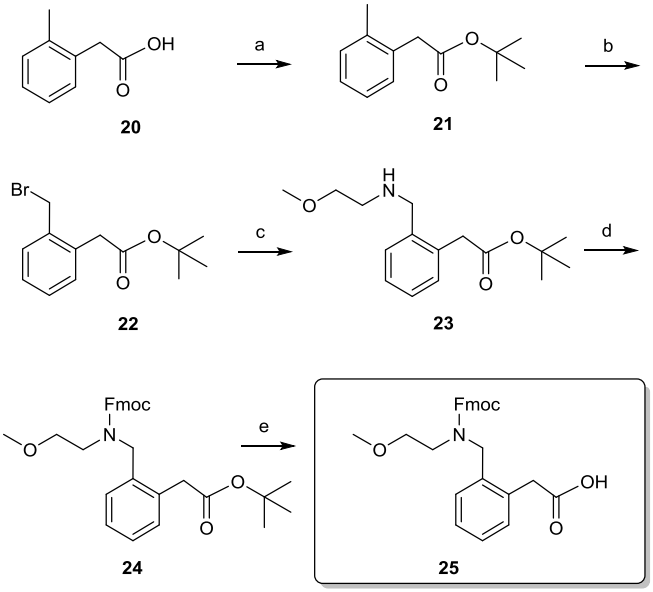

Scheme 3 Synthesis of monomer **25**. Reagents and conditions. (a) *t*-butanol, DCC, CH_2Cl_2 (68%); (b) *N*-bromosuccinimide, benzoyl peroxide, ethyl acetate (67%); (c) methoxyethylamine, DCM (78%); (d) $NaHCO_3$, DMAP, Fmoc-Cl, 1,4-dioxane/water; (e) trifluoroacetic acid/DCM 1:5 (71% two steps)

The Fmoc protected monomers (**16**, **17**, and **25**) were oligomerized on the 2-chlorotrityl resin. The yields per coupling were excellent (>98%, based on the chloranil test) and gave the linear trimeric (**26–28**) and tetrameric (**29–31**) oligomers in good overall yield (Scheme 4, HPLC analysis, purity >95%, see ESI†, Figures S17-18).

The fairly pure crude oligomers (**26–31**, HPLC analysis, see ESI†, Figures S17-18) were efficiently cyclized in high dilution conditions ($3 \cdot 10^{-3}$ M, HPLC purity, after the work up: >95%, see ESI†, Figures S19-20) using HATU as the coupling agent (Scheme 4). After the work-up, the crudes from the cyclization reactions gave excellent HPLC chromatograms and acceptable yields. We were pleased to isolate the elusive cyclic *para*-benzylopeptoid trimer **3** and to obtain the sterically hindered (trimeric and tetrameric) *ortho*-isomers (albeit in lower yields than the corresponding *meta*- and *para*-benzylopeptoids, see Scheme 4).¶

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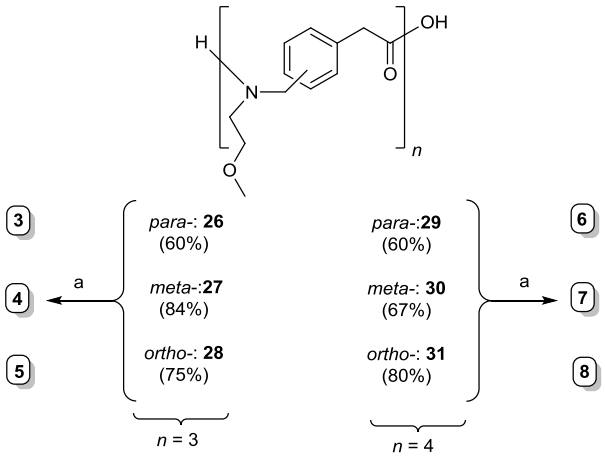

Scheme 4 The six linear *N*-substituted aminomethyl benzylamide oligomers **26–31** (the yields, in parentheses, were calculated on the basis of the resin loading) and their cyclization products. Reagents and conditions. (a) HATU, DIPEA, DMF (**3**: 65%; **4**: 53%; **5**: 32%; **6**: 57%; **7**: 72%; **8**: 26%).

Complexing studies

The *r.t.* ^{1}H- and ^{13}C NMR spectra, recorded for the six cyclic benzylopeptoids **3**-**8**, showed a very complex peaks pattern due to the slow (on the NMR time scale) interconversion of multiple conformations.

While no hint of ^{1}H NMR spectral simplification was evidenced treating the oligomers **3–8** with increasing amounts of sodium picrate (in a 4.0 mM $CD_3CN/CDCl_3$ 9:1 solution) or lowering the temperature of the recorded spectra, evident signal coalescence was observed in the presence of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFPB, $CDCl_3$ solution).[45]

The NaTFPB is an ideal cationic guest for multiple reasons: it is commercially available, it can be easily prepared from cheap starting materials, it is chemically stable, and, for its extremely low solubility in $CDCl_3$ as a free guest, it represents an ideal reagent for the facile evaluation of the host/guest stoichiometry (through simple integration of the ^{1}H NMR resonances).

Figure 7 reports the striking difference in the ^{1}H NMR spectrum of the representative cyclic trimeric benzylopeptoid **4** by addition of one equivalent of NaTFPB (the titration experiments for **3**-**5** are reported in the ESI†, Figures S11-S13). The Na^+ has a conspicuous template effect and the preorganization of the cyclic trimer facilitates the formation of the host/guest adduct, lowering the entropic costs of the interaction. Being the $[\mathbf{4}\cdot Na]^+$ complex C_3-symmetric, it has to display an all-*trans* or an all-*cis* peptoid junction. A ROESY experiment inferred the tertiary amide geometry of the complex as all-*trans*. A key cross correlation demonstrated that the framework -Ph-C$\underline{H_2}$-C=O and the side chain N-C$\underline{H_2}$-CH_2-methylene groups were on the same side (Figure 8, see ESI†, Figure S8). The results of the minimum energy search in the preliminary theoretical studies (reported in Figure 5) pointed towards an all-*trans* peptoid bond conformations also for the C_3-symmetric $[\mathbf{3}\cdot Na]^+$ and $[\mathbf{5}\cdot Na]^+$ host/guest complexes.‡

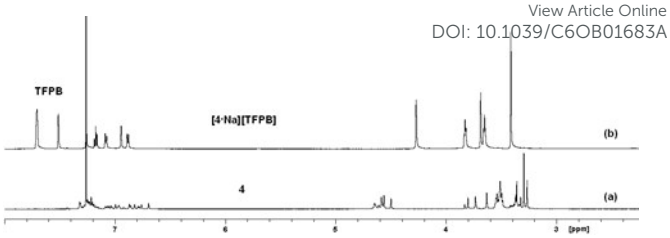

Fig. 7 ^{1}H NMR spectra of free **4** (a) ($CDCl_3$ solution, 298 K, [**4**] = 4.0 mM, 600 MHz) and (b) in the presence of 1.0 equivalent of NaTFPB.

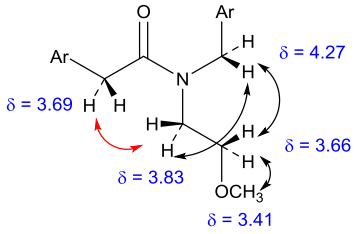

Fig. 8 ROE effects (600 MHz) in the case of [**4**· Na][TFPB]. In red the key cross correlation inferring the *trans* peptoid conformation.

Highly simplified ^{1}H NMR spectra were also recorded for compounds **6–8**, by addition of one and two NaTFPB equivalents (See ESI†, Figures S14-S16).

Figure 9 reports the representative formation of the C_4-symmetric host/guest adducts in the case of the *ortho*-substituted benzylopeptoid **8**. The interaction between the sodium cation(s), freely moving among the four carbonyl groups, and the cyclic host makes the four *N*-(methoxyethyl)aminomethyl phenylacetyl units equivalent (Figure 9).§

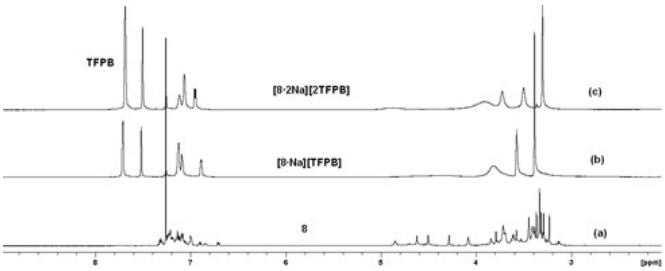

Fig. 9 ^{1}H NMR spectra of free **8** (a) ($CDCl_3$, solution, 298 K, [**8**] = 4.0 mM, 600 MHz), in the presence of 1.0 (b) and 2.0 equivalents (c) of NaTFPB.

Once again, DFT outputs as well as ^{13}C NMR of the corresponding trimeric (**3**-**5**) congeners (in particular of the sp^3 methylene carbons' and the carbonyls' resonances, see ESI†, Table S4) suggested a peptoids' all-*trans* conformation of the host/guest adducts. Quantitative ^{1}H NMR experiments were performed on the trimeric and tetrameric *ortho*-, *meta*-, and *para*-series in order to determine the association constants (K_a) (see ESI†, Figures S1-S6).[46] Table 2 reports the K_a and the corresponding Gibbs free energies values for the complexes formation. The data are compatible with the highest stability attributed to the trimeric *meta*-isomer **4** (as

anticipated by the preliminary theoretical studies). The unexpected higher stability of the *para*-isomer **3** respect to the *ortho*-benzylopeptoid **5** (missed by the calculations) is probably due to entropic/dynamic reasons (the higher rigidity of the *para*-isomer stabilizes the preformed cavity; moreover, the sodium cation can freely move through the *three* available carbonyls, further increasing the stability of the host/guest adduct).

Table2 Experimentally calculated (^{1}H NMR experiments) K_a values and $\Delta G°$ (kcal/mol) for the benzylopeptoids **3**-**5** with one Na^+ ion and **6**-**8** with two Na^+ ions.

	[**3**·Na]$^+$	[**4**·Na]$^+$	[**5**·Na]$^+$	[**6**·2Na]$^{2+}$	[**7**·2Na]$^{2+}$	[**8**·2Na]$^{2+}$
K_a *	$1.7 \cdot 10^3$ M^{-1}	$15.1 \cdot 10^3$ M^{-1}	$0.4 \cdot 10^3$ M^{-1}	$76.3 \cdot 10^3$ M^{-2}	$47.0 \cdot 10^3$ M^{-2}	$301 \cdot 10^3$ M^{-2}
$\Delta G°$	–4.4	–5.7	–3.5	–6.6	–6.4	–7.5

*Figures within ±10% in multiple experiments.

In the case of the cyclic tetrameric oligomers **6-8,** the preliminary theoretical studies predicted the formation of the *bis*-sodium adducts. However, the complexity of the structures, the unaccounted entropic contributions and the lack of the dynamic term in the calculations, underestimated the stability of the *ortho*-substituted oligomer **8** (which, in the experimental studies, showed the highest $K_a/\Delta G°$ values).

When the ^{1}H NMR complexation experiments were performed in more polar deuterated solvents (CD_3COCD_3 or CD_3CN), we observed no spectral simplification. Stronger coordinating solvents, in fact, dramatically reduce the complexing abilities of the benzylopeptoids **3**-**8** (whose K_a are from one to three order of magnitude lower than the corresponding classic hexameric cyclic peptoids).[27,31] The weaker association constants (due to the lower number of carbonyl donor groups present in the host molecules) justify the failed initial complexing experiments made in the presence of sodium picrate in $CD_3CN/CDCl_3$ 9:1 solutions.

Having demonstrated the innate abilities of all the members of this new class of extended peptoids, we decided to check their possible activity as transmembrane ion translocators.

Ionophoric activities

The ionophoric activity across a phospholipid membrane of compounds **3**-**8** was investigated with the HPTS assay (HPTS = 8-hydroxypyrene-1,3,6-trisulfonic acid).[47] The pH-sensitive fluorescent dye is trapped in large unilamellar liposomes (100 nm diameter, 95:5 egg phosphatidylcholine (EYPC) and egg phosphatidylglycerol (EYPG) lipid composition) prepared in HEPES buffer at pH 7.0 containing 100 mM NaCl (HEPES = 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid). Then a 0.6 units trans-membrane pH gradient is established, by external addition of NaOH, and the efficiency of the cyclopeptoids to dissipate the pH gradient across the membrane thanks to a facilitated cation transport is evaluated by monitoring the basification of the liposome internal water pool signalled by the increase of the HPTS fluorescence emission. All the tested cyclic benzylopeptoids did not show any measurable ion transport activity even when using as transportable cation the other alkali metal cations instead of Na^+ (see the supporting information section). We believe that, notwithstanding the conspicuous ion chelating properties in $CHCl_3$, the complexes stability are limited by the competition with the highly coordinating water molecules in the solutions where the ion transport tests are performed. Indeed, ion transport requires extraction of the hydrated cation from the bulk water, its dehydration and its stabilization through cation-carbonyl oxygen interactions during the transfer across the membrane. The lack of half of the carbonyl groups (when compared with the known cyclic hexa- and octapeptoids ion transporters) and the higher rigidity of the benzylopeptoids greatly reduces the ion affinities and leaves free coordinating positions on the metal ion thus hampering possible ion capture and translocation across the phospholipid membrane.

Conclusions

Accurate modelling of synthetically accessible artificial systems can bring to novel molecular architectures with unpredictable properties. The present study demonstrates that the strategic positioning and the number of the carbonyl donor groups in conformationally mobile, *ortho*-, *meta*- and *para*-*N*-(methoxyethyl)aminomethyl phenylacetamides have a crucial effect on their complexing properties. The cyclotrimeric 24-, 21-, and 18-membered ring oligomers **3–5** envelope the surface of the mid-size alkaline cation Na^+ and, with different degrees of selectivity, form 1:1 supramolecular complexes. The bigger cyclic tetrameric 32-, 28-, and 24-membered ring oligomers **6–8** can accommodate even two sodium cations.

The cation complexation properties of this new class of hosts encourages the efforts to synthesize new cyclic derivatives and evaluate their properties in ion recognition, transmembrane transport and, considering their activities in non-polar solvents, in catalysis.

Further studies are currently in progress in order to establish the interplay between the solid state benzylopeptoid structures and their complexing properties with the idea to shed light on this multifaceted new molecular continent.

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Notes and references

‡ The close proximity of the resonance peaks in the [**3**·Na]$^+$ and [**5**·Na]$^+$ host/guest complexes hampered their independent assignment via ROESY experiments.

§ In the case of the smaller *ortho*-substituted benzylopeptoid **8** just one sodium ion is able to simplify the appearance of the spectra. In this case, some r.t molecular motions are in the range of the NMR time scale (note the broadening of the

signals at around 5 ppm related to the resonance of the Ph-CH_2-N methylene singlet). Spectra taken at higher temperature (*i.e.*: 373 K, see ESI†) make sharper resonances.

¶ The formation of higher order cyclic oligomers (cyclohexamers or cyclooctamers) was minimized thanks to the slow addition of the linear oligomers (using the syringe-pump) in the HATU solution (see ESI†). The zoom-scan technique (HR-ESI of the pseudomolecular parent peaks of the cyclic oligomers) confirmed the high purity (>98%) of the cyclic trimers and tetramers (see ESI†, Table S2).

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