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 *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 annulation of the rigidified peptoids can generate new hosts with the ability to sequestrate one or two sodium cations with the 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

From a molecular standpoint, the functions of all living systems are based on the 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] show well-defined traits dictated by stable folding.[6–9] The acquisition of functional shapes is also attainable with a promising family of artificial oligoamides: the peptoids[10] (Fig. 1). In this mouldable class of inspiring peptidomimetics, molecular morphologies are obtained by appropriate functionalization of the synthetically tuned *N*-alkylated amide moieties.[6]

In recent times, it has been demonstrated that 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] (Fig. 1) are examples of new types of compounds with promising potential due to their rigidified frame. In particular, arylopeptoids offer an interesting case of a new artificial taxonomic class. With these oligomeric aminomethyl benzamides, attractive architectures emerge from *E/Z* peptoid bond conformational
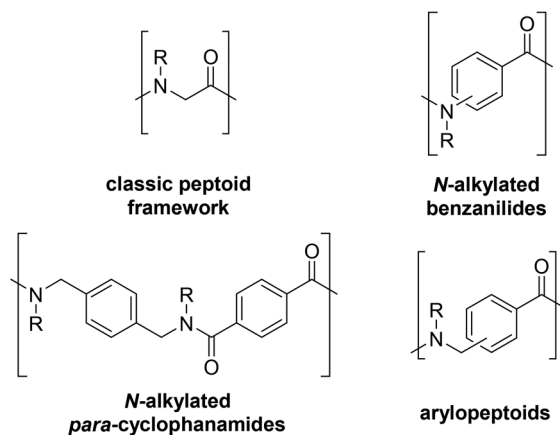

Fig. 1 Peptoids and tertiary oligoamides with aromatic backbones.

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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 produces cyclic hexamers **2** and not the expected cyclic trimers **1** (Fig. 2). Moreover, the cyclization of trimeric *ortho*-isomers proceeds with very low yields (due to the increased "congestion" of the backbone).

During our endeavours in the field of classic cyclic peptoids,[27,28] we proved their innate ability to act as complexing agents,[27,29] perform catalysis,[30,31] form elegant molecular[32] and metal–organic frameworks[33] and promote ion transport.[34,35] Nonetheless, we felt that the boundaries of chemical space could be stretched through the use of different building
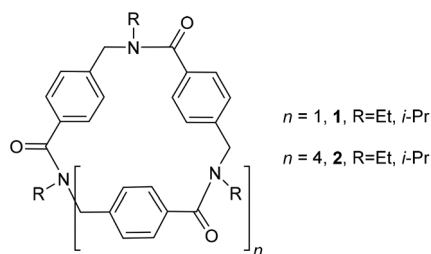
Fig. 2 A *para*-series of appropriately *N*-substituted arylopeptoids.

blocks. We thus chose to replace the *N*-alkylamino-acetyl unit of the peptoid backbone with an *N*-alkylaminomethyl phenyl-acetate monomer (Fig. 3). The oligomerization and cyclization of *ortho*-, *meta*- and *para*-substituted *N*-alkylaminomethyl phenylacetate units leads to a new family of "extended peptoids" (termed "benzylopeptoids") with potential as ion complexing agents and, possibly, as ionophores and/or organocatalysts.

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

Thus, with the aim of unveiling the full potential of the newly conceived "extended peptoids"[11–26] within the field of supramolecular chemistry, herein we report theoretical studies, efficient monomer syntheses, solid-phase oligomeriza-tion and cyclization of six members of a new class of cyclic oligomeric *N*-methoxyethyl(aminomethyl) phenylacetamides: the cyclic benzylopeptoid trimers **3–5** and tetramers **6–8** (Fig. 4). The different sizes of the target compounds were intended to help explore their complexing abilities in the pres-ence of sodium cations, chosen as the reference ion. The amphiphilic methoxyethyl side chain was selected in order to favour possible ionophoric activity.

The unequal substitution pattern of the benzylopeptoids implied a need for 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 the cross-reac-
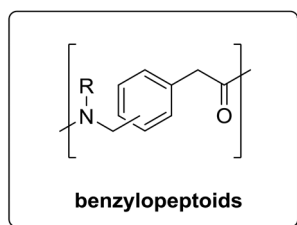
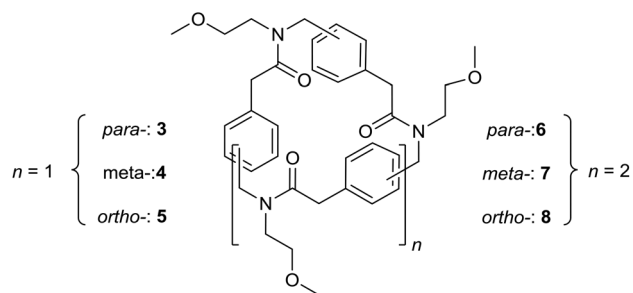

Fig. 3 Structural unit of the "benzylopeptoids".

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

tive functional groups meant that lactamization-free pro-cedures were required. 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 archi-tectures *in silico* and in solution for most of the host/guest adducts.

With the present contribution we enlarge the new field of aryl-based "extended" 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 multi-tudinous, energetically equivalent, conformational minima (even in the presence of rigid backbone units).[26] The large 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 with respect to the NMR time scale, overlap in one dimensional spectra).[27–29]

The situation reverses in the presence of cations (*i.e.* sodium ions). The stabilizing interaction of the positive ion with the carbonyl oxygen atom lone pairs stiffens the macror-ing's conformation and forces the host/guest complexes to exist as only a few (or a single) species.

Fig. 5 reports the most stable conformations of the trimeric oligoamides **3–5** (see the ESI† for computational details). While the *para*-substituted cyclic oligomer **3** appears to be 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 interaction with the sodium cation. Indeed, according to the modelling studies, Na^+ would be located out of the plane defined by the oxygen atoms in the *ortho*-benzylopeptoid
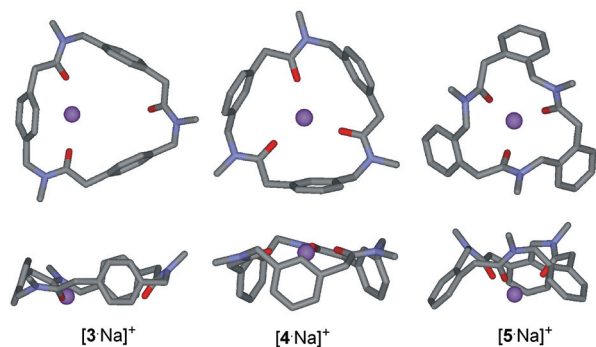
Fig. 5 Minimum energy structures for Na$^+$ complexes of compounds **3–5** (top and side views). For simplicity, the *N*-linked side chain was modelled as −CH$_3$. Hydrogen atoms have been omitted for clarity. Atom type: C grey, N light blue, O red, Na$^+$ blue.

Fig. 6 Minimum energy structures for Na$^+$ complexes of compounds **6–8** with one or two coordinated Na$^+$ ions. For simplicity, the *N*-linked side chain was modelled as −CH$_3$. Hydrogen atoms have been omitted for clarity. Atom type: C grey, N light blue, O red, Na$^+$ blue.
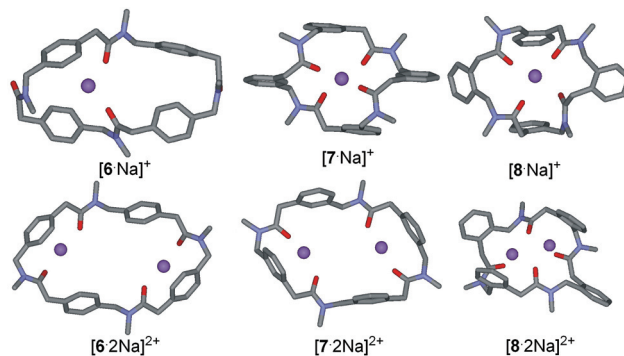
5, while in the *meta*-benzylopeptoid **4** it would lie almost on the same plane. As for the *para*-benzylopeptoid **3**, the distance between the oxygen atoms would be too large to allow simultaneous tricoordination to the metal.

The values of the interaction energies in CHCl$_3$, reported in Table 1, corroborate the visual impressions. For the three isomers, an intrinsic C_3-symmetry of the complex is evident (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 Fig. 6 and the energies are reported in Table 1.

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

In the case of the cyclic tetramers, the host/guest interaction energies in CHCl$_3$ are always higher for the disodium with respect to the monosodium complexes, even for *ortho*-benzylopeptoid **8**, where the lack of free space keeps the two positive ions very close together (Table 1). In the *para*- and *meta*-benzylopeptoid disodium complexes **6** and **7**, 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 steady trend in the behaviour was observed for the monocoordinated tetramers, due to the unexpected stability of the *meta*-benzylopeptoid complex.

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

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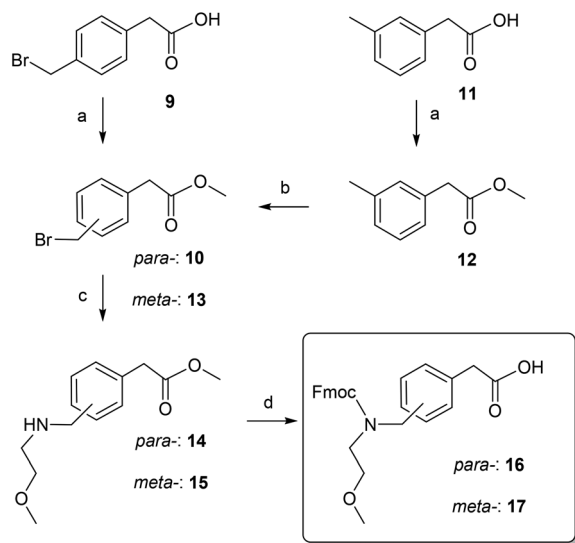
Synthesis

Using 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 a more reliable "monomer" approach.[42] The supposed easy elaboration of Fmoc-protected monomers and the powerful strategies that have been 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

Table 1 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^{-1}. The studied complexes are reported in parentheses

	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]$^{2+}$)

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·H₂O, 1,4-dioxane/water; (ii) NaHCO₃, DMAP, Fmoc-Cl, (**16**: 46%; **17**: 44%).

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

Scheme 3 Synthesis of monomer **25**. Reagents and conditions: (a) *t*-butanol, DCC, CH₂Cl₂ (68%); (b) *N*-bromosuccinimide, benzoyl peroxide, ethyl acetate (67%); (c) methoxyethylamine, DCM (78%); (d) NaHCO₃, DMAP, Fmoc-Cl, 1,4-dioxane/water; (e) trifluoroacetic acid/DCM 1 : 5 (71% over two steps).
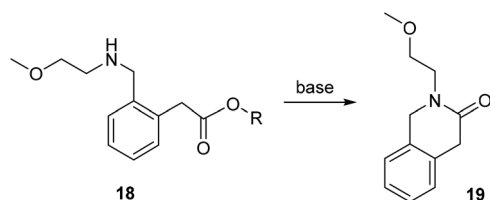
we chose the methyl ester as the carboxyl protecting group, for the more challenging *ortho*-isomer we selected the more hindered *t*-butyl ester (in order to avoid possible base-induced intramolecular lactamization).[22]

Scheme 1 outlines the synthesis of the *para*- and *meta*-substituted monomer units. The synthesis started with a carboxyl group methylation of the commercially available *para*-(bromomethyl)phenylacetic acid (**9**) to provide the corresponding methyl acetate (**10**).[44] The *meta*-isomer was elaborated in two steps: first, methylation of the inexpensive *meta*-tolylacetic acid (**11**), and then an NBS-mediated benzylic bromination (in nontoxic ethyl acetate). Both of the fairly stable brominated intermediates (**10** and **13**) were subjected to an amination reaction in the presence of five equivalents of methoxyethylamine (in order to prevent polyalkylation adducts) and the products were isolated after column chromatography as the free amines (the eluent contained 1% triethylamine).
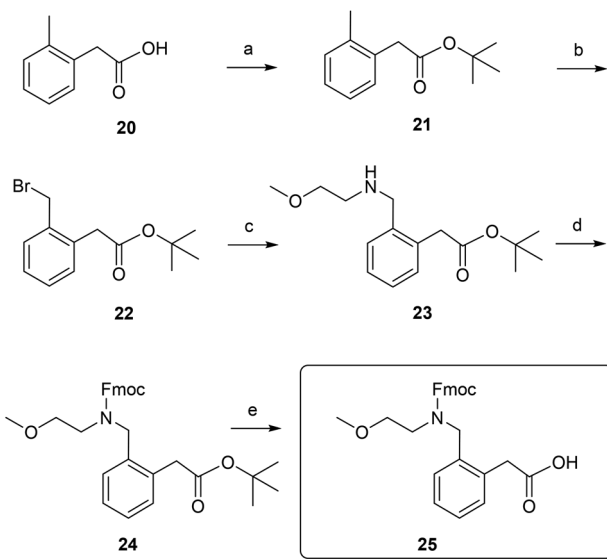
Both the *para*- and *meta*-methyl phenylacetates (**14** and **15**, respectively) were hydrolyzed with lithium hydroxide and the free amino groups were protected as 9-fluorenylmethoxycarbonyl (Fmoc) derivatives. The overall yield for the monomers **16** and **17**, ready for the solid-phase oligomerization, was 31% and 18%, respectively.

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

In order to protect the relatively electrophilic carbonyl ester from the amine nucleophilic attack, we selected a bulky *t*-butyl group as the carboxyl protecting group. Scheme 3 summarizes the synthesis of the *ortho*-((2-methoxyethylamino)methyl)phe-

nylacetic acid (**25**), starting from the commercially available *ortho*-tolylacetic acid (**20**). A classic DCC-mediated esterification provided the *t*-butyl ester (**21**). Radical bromination and a subsequent S$_N$2 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** with a 25% overall yield.

The Fmoc protected monomers (**16**, **17**, and **25**) were oligomerized using 2-chlorotrityl resin. The yields per coupling were excellent (>98%, based on a chloranil test) and the linear trimeric (**26–28**) and tetrameric (**29–31**) oligomers were obtained in good overall yield (Scheme 4; from HPLC analysis, purity >95%, see ESI, Fig. S17 and S18†).

The fairly pure crude oligomers (**26–31**) were efficiently cyclized under high dilution conditions (3 × 10⁻³ M; HPLC analysis, after the work up: purity >95%, see ESI, Fig. S19 and S20†) using HATU as the coupling agent (Scheme 4). We were pleased to isolate the elusive cyclic *para*-benzylopeptoid trimer **3** and to obtain the sterically hindered (trimeric and tetra-
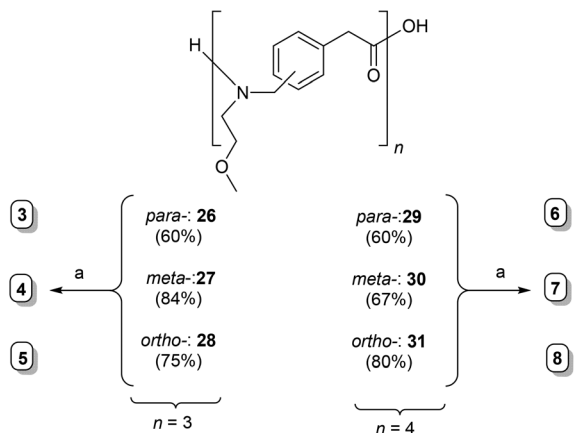
Scheme 4 The six linear N-substituted aminomethyl benzylamide oligomers 26–31 (the yields, in parentheses, were calculated on the basis of the resin loading) and their cyclization products. Reagents and conditions: (a) HATU, DIPEA, DMF (3: 65%; 4: 53%; 5: 32%; 6: 57%; 7: 72%; 8: 26%).

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) for the case of [4·Na][TFPB]. In red: the key cross correlation inferring the trans peptoid conformation.

meric) ortho-isomers (albeit in lower yields than the corresponding meta- and para-benzylopeptoids, see Scheme 4).‡
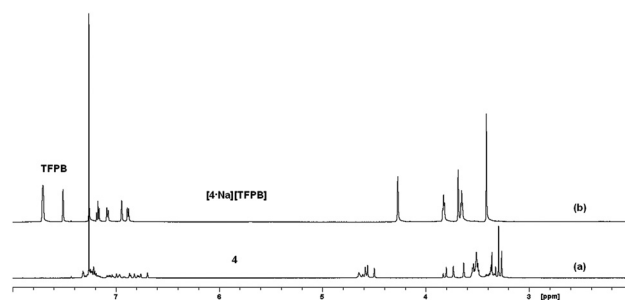
Complexing studies

The room temperature ^{1}H- and ^{13}C NMR spectra, recorded for the six cyclic benzylopeptoids 3–8, showed very complex peak patterns due to the slow (on the NMR time scale) interconversion of multiple conformations.

While no hint of ^{1}H NMR spectral simplification was observed on treating the oligomers 3–8 with increasing amounts of sodium picrate (using a 4.0 mM CD$_3$CN/CDCl$_3$ 9 : 1 solution) or on lowering the temperature for 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]
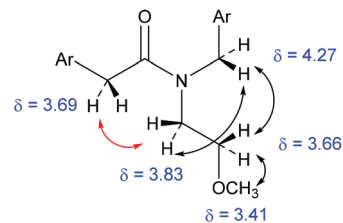
NaTFPB is a convenient cationic guest for multiple reasons: it is commercially available, it can be easily prepared from cheap starting materials, it is chemically stable, and, despite its extremely low solubility in CDCl$_3$ as a free guest, it represents an ideal reagent for facile evaluation of the host/guest stoichiometry (through simple integration of the ^{1}H NMR resonances).

Fig. 7 shows the striking differences in the ^{1}H NMR spectrum of the representative cyclic trimeric benzylopeptoid 4 that occur through the addition of one equivalent of NaTFPB (the titration experiments for 3–5 are reported in the ESI, Fig. 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. As the [4·Na]$^+$ complex is C_3-symmetric, it has to display an all-trans or an all-cis peptoid junction. A ROESY experiment inferred that the tertiary amide geometry of the complex is all-trans. A key cross correlation demonstrated that the framework –Ph–CH$_2$–C=O and the side chain N–CH$_2$–CH$_2$–methylene groups are on the same side (Fig. 8, see ESI, Fig. S8†). The results of the minimum energy structure search in the preliminary theoretical studies (reported in Fig. 5) pointed towards an all-trans peptoid bond conformation also for the C_3-symmetric [3·Na]$^+$ and [5·Na]$^+$ host/guest complexes.§

Highly simplified ^{1}H NMR spectra were also obtained for compounds 6–8, through the addition of one or two NaTFPB equivalents (see ESI, Fig. S14–S16†).

Fig. 9 shows a representative formation of the C_4-symmetric host/guest adducts using the case of the ortho-substituted benzylopeptoid 8. The interactions between the sodium cation(s), freely moving among the four carbonyl groups, and the cyclic host make the four N-(methoxyethyl)aminomethyl phenylacetyl units equivalent (Fig. 9).¶

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‡The formation of higher order cyclic oligomers (cyclohexamers or cyclooctamers) was minimized thanks to slow addition of the linear oligomers (using a syringe-pump) into the HATU solution (see ESI†). A zoom-scan technique (for the 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†).

§The close proximity of the resonance peaks for 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 occur 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 obtained at a higher temperature (i.e. 373 K, see ESI†) show sharper resonances.
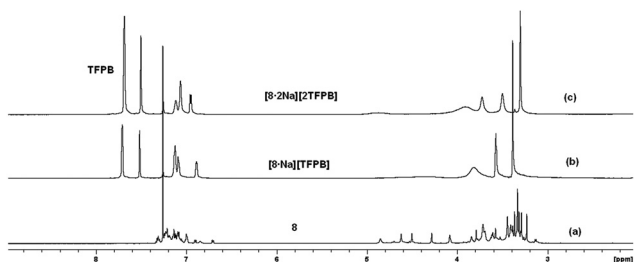
Fig. 9 ^{1}H NMR spectra of free **8** (a) (CDCl$_3$, solution, 298 K, [**8**] = 4.0 mM, 600 MHz), and in the presence of 1.0 (b) and 2.0 equivalents (c) of NaTFPB.

Once again, DFT outputs as well as ^{13}C NMR results for the corresponding trimeric (**3**–**5**) congeners (in particular, the sp^3 methylene carbon and the carbonyl resonances, see ESI, Table S4†) suggested a peptoid all-*trans* conformation of the host/guest adducts. Quantitative ^{1}H NMR experiments were performed for the trimeric and tetrameric *ortho*-, *meta*-, and *para*-series in order to determine the association constants (K_a) (see ESI, Fig. S1–S6†).[46] Table 2 shows the K_a and the corresponding Gibbs free energy values for the complex formation. The data are compatible with the highest stability being attributed to the trimeric *meta*-isomer **4** (as anticipated from the preliminary theoretical studies). The unexpected higher stability of the *para*-isomer **3** with respect to the *ortho*-benzylopeptoid **5** (missed during 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 among the three available carbonyls, further increasing the stability of the host/guest adduct).

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

When the ^{1}H NMR complexation experiments were performed in more polar deuterated solvents (CD$_3$COCD$_3$ or CD$_3$CN), 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 orders of magnitude lower than the corresponding classic hexameric cyclic peptides).[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 in the presence of sodium picrate in CD$_3$CN/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 using an HPTS assay (HPTS = 8-hydroxypyrene-1,3,6-trisulfonic acid).[47] This pH-sensitive fluorescent dye was trapped in large unilamellar liposomes (100 nm diameters, 95 : 5 egg phosphatidylcholine (EYPC) and egg-yolk 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 unit transmembrane pH gradient was established, through the external addition of NaOH, and the efficiency of the cyclopeptoids in dissipating the pH gradient across the membrane through facilitated cation transport was evaluated by monitoring the basification of the liposome internal water pool, signalled by an increase of the HPTS fluorescence emission. All of the tested cyclic benzylopeptoids did not show any measurable ion transport activity, even when other alkali metal cations were used as the transportable cation instead of Na$^+$ (see the ESI†). We believe that, notwithstanding the conspicuous ion chelating properties in CHCl$_3$, the stability of the complexes is limited by competition with the highly coordinating water molecules in the solutions used for the ion transport tests. Indeed, ion transport requires extraction of the hydrated cation from the bulk water, its dehydration and its stabilization through cation–carbonyl oxygen interactions during transfer across the membrane. The lack of half of the carbonyl groups (when compared with the known cyclic hexa- and octapeptoid ion transporters) and the higher rigidity of the benzylopeptoids greatly reduces the ion affinities and leaves free coordination 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 result in novel molecular architectures with unpredictable

Table 2 Experimentally calculated (^{1}H NMR experiments) K_a values and $\Delta G°$ values (kcal mol^{-1}) for the benzylopeptoids **3**–**5** with one Na$^+$ ion and for **6**–**8** with two Na$^+$ ions

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

^{a} Figures within ±10% throughout multiple experiments.

properties. The present study demonstrates that the strategic positioning and the number of 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** envelop the surface of the mid-sized 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 even accommodate two sodium cations.

The cation complexation properties of this new class of hosts encourage efforts to synthesize new cyclic derivatives and evaluate their properties in ion recognition, transmembrane transport and, considering their activities in non-polar solvents, 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 aim of shedding light on this multifaceted new type of molecules.

Acknowledgements

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