Macrocyclic Triazolopeptoids: A Promising Class of Extended Cyclic Peptoids

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ABSTRACT: Head-to-tail cyclization of linear oligoamides containing 4-benzylaminomethyl-1H-1,2,3-triazol-1-yl acetic acid monomers afforded a novel class of "extended macrocyclic peptoids". The identification of the conformation in solution for a cycldimer and the X-ray crystal structure of a cyclic tetraamide are reported.

The intrinsic attitude of macrocyclic systems toward recognition and complexation makes them formidable tools in supramolecular chemistry. New macrocyclic derivatives are continuously reported and investigated, confirming that every class has its own unique features and finds application in different fields. However, despite the multitude of the structures of known hosts (i.e., cyclodextrins, calixarenes, resorcinarenes, cucurbiturils, etc.), scant synthetic effort has been devoted to sequence-defined oligomerization processes. A modular accretion of bifunctional monomers is instead adopted for the synthesis of cyclic peptoids (cyclic oligomers of N-substituted glycines), a growing class of biomimetic compounds with enormous potential in catalysis, in material chemistry, as bioactive agents, and as precursors of azamacrocycles. The versatility of their synthetic method allows ample structural flexibility and facile introduction of rigid aromatic spacers into the peptoid oligoamide backbone, producing the valuable "extended peptoids" with excellent conformational properties (despite the absence of intramolecular H-bonding) and metal chelating abilities.

The richness of the heteroaromatic spacers available (furane, oxazoles, thiazole, etc.) can further expand the chemical space of the N-alkylated aromatic cyclic peptoids, and new studies are increasingly emerging in the past several years. Among the heteroaromatic spacer triazoles are ideal candidates. These intriguing heterocyclic compounds have broad use in the field of peptidomimetics. Because of their physicochemical resemblance to peptide bonds due to planarity and strong dipole moment, they have been used as amide bond isosteres in peptide science. In particular, their 1,4-disubstituted 1,2,3-regioisomers, built through the straightforward Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction, have already been used in peptoid chemistry for macrocyclization and conjugation with azido-functionalized bioactive compounds. Moreover, triazoles display various supramolecular interactions, such as hydrogen and halogen bond formation and metal coordination, which can reinforce the well-known complexation abilities of cyclic peptoids.

In this work, we report the synthesis and characterization of dimer 1, trimer 2, and tetraoligamide 3 (Figure 1), as first members of cyclic triazolopeptoids, and disclose the structural attitudes of this new class of macrocycles.

To take advantage of the submonomer-based approach to the solid phase, azidoacetic acid and N-benzylpropargyl amine were prepared in solution in high yields. In particular, the reductive amination, yielding propargyl-armed 5, shows the potential of the synthetic approach, which, in principle, can lead to differently decorated macrocycles.

Scheme 1 summarizes the synthetic steps toward triazolopeptoids 1–3. After the first submonomer 4 had been loaded, the (3+2) Cu(I)-catalyzed cycloaddition reaction smoothly afforded the first "extended" monomer on resin. This was acylated with azidoacetic acid 4 or bromoacetic acid 6, depending on the requested target(s). Iteration of cyclo-
addition/acylation steps afforded in one case (after the cleavage from the resin with HFIP 20% in DCM) the desired linear precursors 8 and 9 in quantitative yield. On the contrary, N-benzyl glycine addition and iteration of the synthetic steps produced linear precursor 10 in quantitative yield. HATU-induced macrocyclization under high-dilution conditions gave targets 1−3 in 34%, 28%, and 24% yields, respectively.

1H and 13C NMR spectral analysis of cyclodimer 1 showed the presence of a conformationally stable symmetric compound (Figure 2). The presence of tertiary amides in cyclic oligomers often induces the coexistence of several conformations in slow equilibrium on the NMR time scale. While smaller cyclic trimeric and tetrameric peptoids appear as single conformers (on the NMR time scale), larger oligomeric macrocycles (e.g., hexamers) show multiple conformations for the limited n → π* orbital contacts and weaker geometric constraints. To understand the structure of the observed conformer 1 and the interactions stabilizing its backbone, in-depth computational studies were performed.

According to the 2-fold symmetry revealed by the NMR spectra, cyclodimer 1 could adopt, in principle, a C$_2$- or S$_2$-symmetric all-trans or all-cis conformation (see Figure S12 and Table S1 for structures and energies, respectively). DFT calculations at the BP86/TZVP level identified the all-trans C$_2$-symmetric conformer (Figure 2e) as the most stable structure (the S$_2$-symmetric all-trans and the C$_2$- and S$_2$-symmetric all-cis conformers showed ΔG values that were 4.1, 6.5, and 5.7 kcal/mol higher, respectively, than that of the all-trans C$_2$-symmetric conformer).

In the "square" all-trans C$_2$-symmetric conformation, the two triazole rings act as H-bond acceptors of the CH$_2$ benzyl side chains and as carbonyl H-bond donors (Figure 2). Interestingly, the backbone conformation of the most stable conformer closely resembles [root-mean-square deviation 0.163 Å (Figure S15)] that observed by Ghadiri and co-workers for the analogous bis-triazole cyclic peptide (X-ray crystal structure, CSD code SURWUY).

The C$_2$-symmetry implied the presence of two enantiomorphous conformational isomers 1a and 1b (Figure 2d), which could be interconverted by simultaneous inversion of the two amide bonds and triazole rings.

Figure 1. Structures of new macrocyclic triazolopeptoids 1−3 reported herein.

Scheme 1. Synthetic Procedure for Linear Oligomeric Precursors 8−10, Prepared on 2-Chlorotryptic Chloride Resin 1% DVB, and Macrocyclic Targets 1−3

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As shown for cyclic peptoids, the presence of two conformational enantiomers can be revealed by $^1$H NMR, using a chiral solvating agent (to form diastereomeric supramolecular complexes). Gradual addition of Pirkle’s reagent [(R)-1-(9-anthryl)-2,2,2-trifluoroethanol] to a racemic solution of 1a and 1b in deuterated chloroform induced the splitting of most proton resonances (Figure 2b,c). Variable-temperature NMR (VT NMR) experiments in CDCl$_3$ showed the stability of the conformers up to 373 K (Figure S9).

$^1$H and $^{13}$C NMR analysis of cyclotrimers 2 and cyclic tetraamides 3 suggested, in analogy with the hexameric cyclic peptoids, closer in size, the contemporary presence of different conformers in slow equilibrium on the NMR time scale. Proof of their identity was obtained by HRMS and corroborated by X-ray diffraction analysis. The versatile synthetic approach of the linear precursors can afford precisely tailored macrocycles, both decorated with a wide range of side chains and containing aromatic side chains. Notably, the peptidic analogue of compound 3 (CSD code OKECUC), reported by Ghadiri in 2003, exhibited a completely different macrocycle conformation with the triazole moieties perpendicular to the plane of the macrocycle, featuring the tubular assembly of the macrocycles with ethanol molecules enclosed in the peptide nanotube.

In conclusion, we report the first members of a new class with short distances between the carbonyl groups of <3.22 Å (Figure S17) and O⋯C==O angles of 88.8(1)° and 81.5(1)° (Table S3), which are consistent with the values reported by Sarma and co-workers.

In the solid state, molecules of 3 align along the shortest $b$ axis (Figure 3) through hydrogen bonds involving N4 of the triazole ring and the methylene hydrogen atom of the backbone [C5⋯N4, 3.407(3) Å; C5H5B⋯N4, 2.53 Å; C5H5B⋯N4, 150.4°]. This results in an amphiphilic layered structure, where the backbone atoms constitute the hydrophilic region and the benzyl side chains the hydrophobic region. Finally, the interlayer interactions are mainly characterized by hydrophilic interactions and H–H contacts involving the aromatic side chains. Notably, the peptidic analogue of compound 3 (CSD code OKECUC), reported by Ghadiri in 2003, exhibited a completely different macrocycle conformation with the triazole moieties perpendicular to the plane of the macrocycle, featuring the tubular assembly of the macrocycles with ethanol molecules enclosed in the peptide nanotube.

In conclusion, we report the first members of a new class of intriguing “extended peptoid” macrocycles. Backbone conformations for smaller cyclodimer 1 and cyclic tetraamide 3 were supported by computational studies, NMR data, and X-ray diffraction analysis. The versatile synthetic approach of the linear precursors can afford precisely tailored macrocycles, both decorated with a wide range of side chains and containing aromatic side chains. Notably, the peptidic analogue of compound 3 (CSD code OKECUC), reported by Ghadiri in 2003, exhibited a completely different macrocycle conformation with the triazole moieties perpendicular to the plane of the macrocycle, featuring the tubular assembly of the macrocycles with ethanol molecules enclosed in the peptide nanotube.

ASSOCIATED CONTENT
Data Availability Statement
The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03062.

Figure 3. H-Bonded ribbon of 3 along the shortest $b$ axis (as viewed along the $a$ axis). H-Bonds are depicted as black dotted lines.
Experimental procedures, characterization data, HPLC chromatograms of the new compounds, and DFT and crystallographic studies (PDF)

Accession Codes
CCDC 2195045 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes
The authors declare no competing financial interest.

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Dedication
Dedicated to the memory of Piero Angela, a guide to the path of Science.

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