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From Cyclic Peptoids to Peraza-macrocycles: A General Reductive Approach

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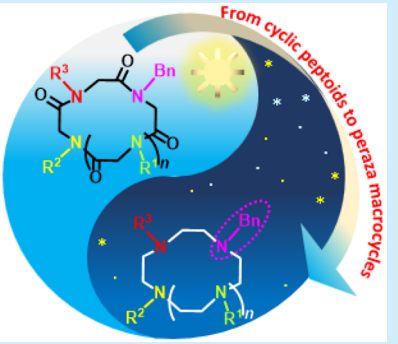
Supporting Information

ABSTRACT: Peraza-macrocycles form chelates of high thermodynamic and kinetic stability useful in diagnostic imaging (MRI, SPECT, PET), in coordination chemistry, and as catalysts. In this letter, we report an advantageous method to prepare these compounds via BH_3-induced reduction of cyclic peptoids. Using this procedure, 10 homo- and heterosubstituted aza-coronands, with different sizes and side chains, have been synthesized from the corresponding cyclic oligoamides. Solid structures of free, protonated, and Na^+ coordinated polyaza-derivatives have been disclosed by single-crystal X-ray diffraction analysis.



The past decades have witnessed an extraordinary proliferation of metal-based pharmaceuticals with a broad range of application in chemistry, biology, and medicine.[1] Complexes of toxic metals (such as Gd^{3+}, ^{99m}Tc, ^{90}Y) with peraza-macrocycles,[2] as the NOTA-BBN (**1**),[2e] HP-DO3A (**2**),[3] PEPA (**3**),[4] or the Me_6[18]aneN_6 (**4**,[2c] Figure 1), are valuable diagnostic and therapeutic tools for the detection and treatment of tumor lesions, metastases, and recurrences after cytoreductive therapy.[1]

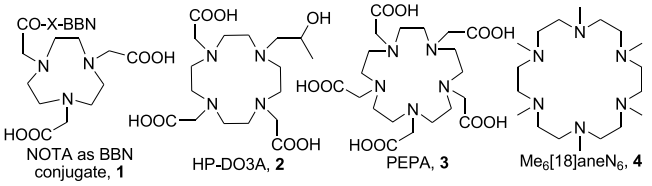


Figure 1. Schematic structures *N*-substituted peraza-macrocyclic ligands **1**−**4**.

The quest for new and more efficient ligands (to enhance diagnostic accuracy and reduce free metal exposure, especially for multiple follow-up examinations and in young patients) requires implementation of innovative synthetic methods.[2] Unfortunately, synthesis of hetero- or unsymmetrically substituted macrocycles relies on high cost cyclic precursors, laborious protecting group manipulation, and low-yield regioselective reactions.[2a,5] Moreover, substituted peraza-heterocycles are synthesized via alkylation of polyaza-cycloalkanes by ring opening of epoxides, by alkyl halides, or by Eschweiler−Clarke methylation.[2] These approaches severely limit the side chain diversity, also precluding the positional and stereochemical control of the appendages.[5f]

The need for a general synthetic route to more efficient peraza-macrocyclic chelators prompted us to plan an ingenious approach based on the intra-annular amide reduction of cyclic peptoids.[6] With this straightforward approach, *N*-side chains are installed early in the synthetic process and no time-consuming postsynthetic modifications are needed to decorate the designed polyaza-macrocycles (Figure 2). Two main advantages differentiate the reported method when compared with the classic ones:[2,5] (1) the rapid construction of small, medium, and large size aza-coronand employing the same procedure; (2) the remarkable expansion of the accessible chemical space (proportional to the number of commercially available primary amines, potentially inserted in the precursor linear oligomer).

With the present method, 10 macrocyclic scaffolds (from trimeric to heptameric homo- and heterooligomeric sequences), decorated with benzyl and methoxyethyl *N*-side chains, have been prepared. Furthermore, *N*-debenzylation of selected macrocycles gave synthetically useful secondary amine derivatives, useful as such or ready for possible alkylation reactions, with the aim to extend the accessible chemical space of these ligands.

The construction of polydentate macrocycles was accomplished through the classic "sub-monomer" solid-phase syn-

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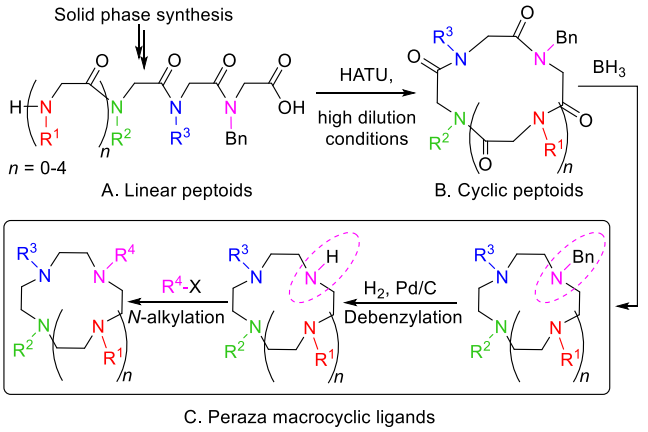
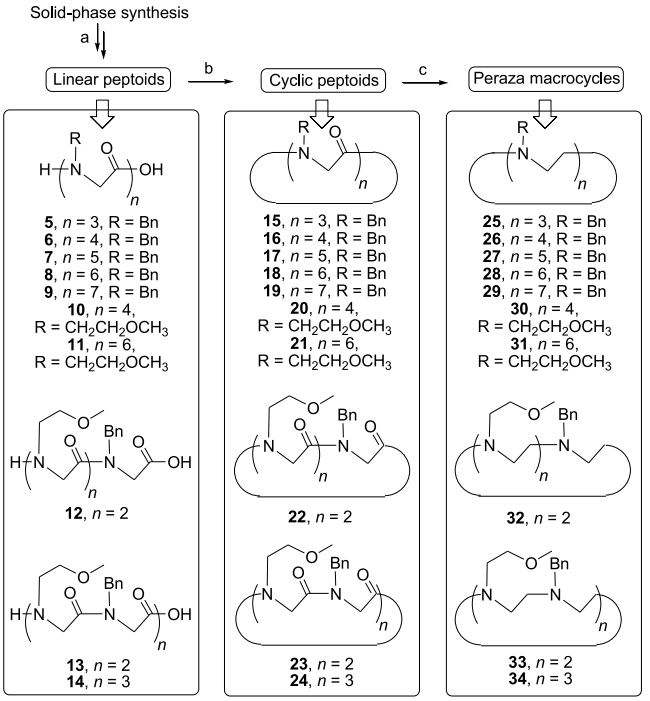


Figure 2. Synthetic route to peraza-macrocycles via oligomerization, cyclization, and reduction of peptoids.

thesis[7] followed by high dilution cyclization,[8] tertiary amide reduction, and, when applicable, *N*-debenzylation.[9]

Linear oligomers **5**−**14** were produced in good to excellent yields via solid-phase synthesis (from 64% to 100% yields, Scheme 1 and Table 1). HATU-mediated cyclization[8] gave macrocyclic peptoids **15**−**24** in high purity by precipitation or after chromatographic purification (see Supporting Information (SI)). Yields varied from 18% to 46%. Accurate NMR analysis showed the classic all-*cis* "crown" conformation for trimeric cyclic peptoid **15**[10] and **22** (Scheme 1).[8b] Homo- (**16**[8d,10] and **20**) and heterooligomeric **23**[8a] cyclotetramers were characterized by the *cis,trans,cis,trans* (*ctct*) "chair" arrangement, typical of these conformationally stable oligomers, as evidenced by NMR.[8b,d] Interestingly, precipitation of **23** from ethyl acetate gave the conformational isomer with the *N*-benzyl side chains on *cisoid* amide bonds, as attested in the NMR spectrum by the large $\Delta\delta$ values detected for the diastereotopic benzyl methylene protons (1.82 ppm;[11] see SI). Larger cyclic peptoids gave fairly complex NMR spectra due to the presence of multiple conformational isomers in slow equilibrium on the NMR time scale[8c] or the lack of symmetry.

Scheme 1. Synthesis of Peraza-macrocycles *via* Oligomerization, Cyclization, and Reduction Steps



a) i) bromoacetic acid, DIPEA, DCM; ii) $BnNH_2/CH_3OCH_2CH_2NH_2$, DMF; iii) bromoacetic acid, DIC; DMF, reiterate ii) and iii); iv) $HFIP/CH_2Cl_2$ 1:4; 0.290 mmol scale. b) HATU (4.0 equiv), DIPEA (6.2 equiv), DMF; 0.026 mmol scale. c) i) 1.0M BH_3-THF (5.0 equiv for each amide group), THF, reflux; ii) H^+; iii) OH^-; 0.025 mmol scale. See SI for general procedures and Table 1 for yields.

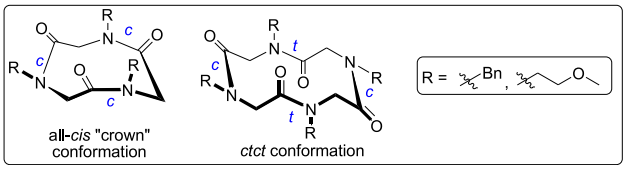


Table 1. Yields of Isolated Compounds for the Synthesis of Linear Peptoids (5−14), Cyclic Peptoids (15−24), Peraza-macrocycles (25−34), and Debenzylated Peraza-macrocycles (35−37)[a]

Synthesis of linear peptoids: % yield (compound)	Cyclization of linear peptoids: % yield (compound)	Reduction of cyclic peptoids: % yield (compound)	Debenzylation reaction: % yield (compound)
100 (**5**)[10]	35 (**15**)[10]	72 (**25**)[6,9]	–
100 (**6**)[8d,10]	46 (**16**)[8d,10]	75 (**26**)[17]	–
100 (**7**)[10]	42 (**17**)[10]	92 (**27**)	–
80 (**8**)[15]	46 (**18**)[15]	70 (**28**)[18]	–
90 (**9**)	37 (**19**)	77 (**29**)	–
91 (**10**)	34 (**20**)	78 (**30**)	–
64 (**11**)[16]	29 (**21**)[16]	91 (**31**)	–
100 (**12**)	18 (**22**)	70 (**32**)	95 (**35**)
100 (**13**)	32 (**23**)[8a]	100 (**33**)	98 (**36**)
100 (**14**)	23 (**24**)[8a]	80 (**34**)	89 (**37**)

[a]Reaction scales for each step are reported in Schemes 1 and 2. The synthetic steps involving the synthesis of 1,4,7,10-tetraazacyclododecane **36** (**13** → **23** → **33** → **36**) were repeated on a larger scale (~1.0 mmol) leading to comparable yields. See SI.

The key step for the synthesis of peraza-macrocyclic ligands was the tertiary amide groups reduction. We tested the efficiency of various reductive methods ($NaBH_4/I_2$; $NaBH_4$ in EtOH−TFE; $NaBH_4/Tf_2O$; see SI).[12] One reagent, however, surpassed all the others in terms of efficiency: the borane−THF complex, giving **25**−**34** in 70%−100% yield (Table 1).[6,13,14]

N-Debenzylation[9] of medium and large peraza-macrocycles **32**−**34** (in the presence of H_2 and Pd/C) gave the expected **35**−**37** in excellent yields (Scheme 2, Table 1), ready for subsequent *N*-alkylation reactions.[9]

The feasibility of the present approach, the large number and amount of accessible derivatives, and the limited literature examples of hexaperaza-macrocycles as free hosts prompted us to characterize one of the 1,4,7,10,13,16-hexaazacyclooctadecane derivatives synthesized with the reported procedure (compound **28**) by single-crystal X-ray diffraction analysis.

28 was crystallized by slow evaporation from a chloroform solution. In its solid state, the macrocycle adopts a round shape with the *N*-benzyl moieties almost perpendicular to the macrocycle mean plane (Figure 3). Interestingly, the Cambridge Structural Database[19] reports only one crystal structure for neutral hexa-*N*-substituted peraza-macrocycles[20] bearing four *N*-(2,3)-dihydroxybenzoyl groups and two *N*-methyl groups. In the latter case the macrocycle adopts a completely

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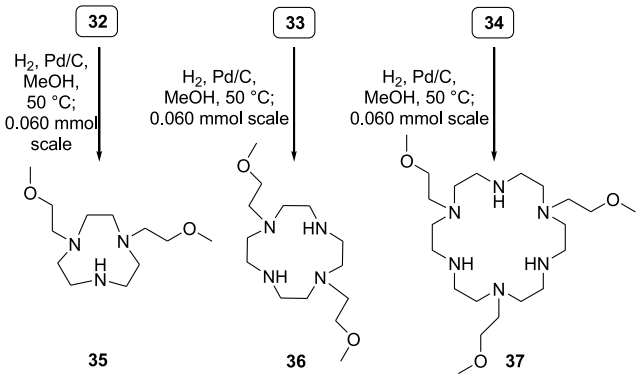
Scheme 2. Partially Substituted Peraza-macrocycles 35−37[a]



[a]See SI for general procedure and Table 1 for yields.

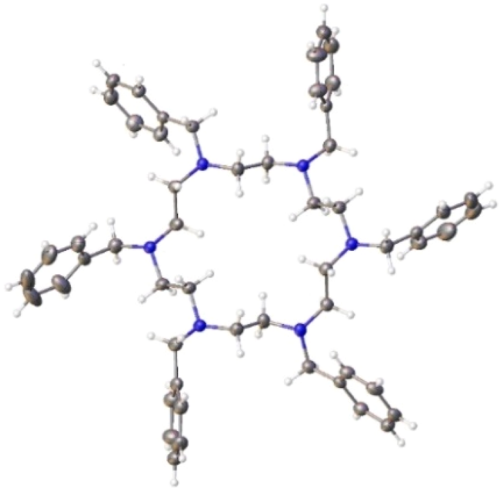


Figure 3. ORTEP drawing of compound **28**. Ellipsoids are drawn at 20% probability level. Atom type: C, gray; N, blue; H, white.

different ring conformation due to the presence of four amide nitrogen atoms. A conformation similar to that observed in **28** was found in the recently reported K^+ and Rb^+ complexes of hexa-*N*-methyl peraza-macrocycles.[2c]

We also attempted the crystallization of tridentate and tetradentate aza-coronands **25** and **26** in the presence of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFPB). Slow evaporation of chloroform solutions containing equimolar amounts of **25**/NaTFPB and **26**/NaTFPB afforded crystals suitable for X-ray diffraction analysis. In both cases no effort was adopted to avoid the presence of water in the solvent.

Single-crystal X-ray diffraction revealed the formation of two different species (protonated and sodiated) depending on the nature of the aza-macrocyclic host.

In the presence of the 1,4,7-triazacyclononane ligand **25**, the formation of a monoprotonated adduct ($[\mathbf{25}\cdot H]^+$ $TFPB^-$, Figure 4) was observed. In the case of the 1,4,7,10-tetraazacyclododecane (cyclen) ligand **26**, the expected Na^+ complex was obtained ($[\mathbf{26}\cdot Na]^+$ $TFPB^-$, Figure 5). Formation of different ion−molecule adducts is probably related to the exalted coordination abilities of the cyclen ligand.

Protonation of the tridentate 1,4,7-triazacyclononane macrocycle (due to the basic hydrolysis of water), and plausible precipitation of NaOH in chloroform solution, induced the formation of the $[\mathbf{25}\cdot H]^+$ $TFPB^-$, resembling the diprotonated

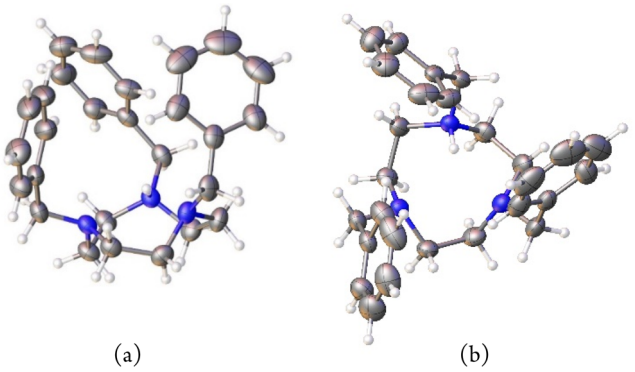


Figure 4. ORTEP drawing of compound $[\mathbf{25}\cdot H]^+$ $TFPB^-$: (a) side and (b) top view. Ellipsoids are drawn at 20% probability level. Atom type: C, gray; N, blue; H, white. For clarity, the TFPB anion is not shown.

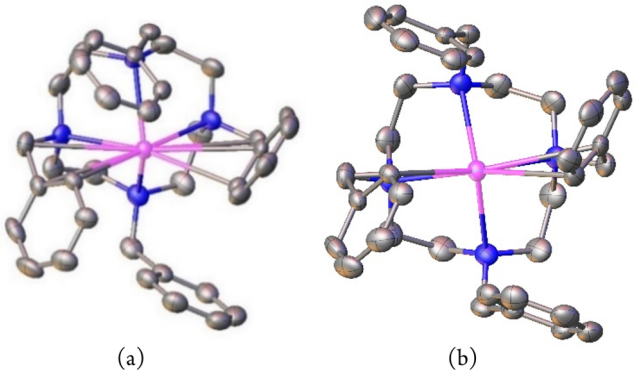


Figure 5. ORTEP drawing of compound $[\mathbf{26}\cdot Na]^+$ $TFPB^-$: (a) side and (b) top view. Ellipsoids are drawn at the 20% probability level. Atom type: Na, magenta; C, gray; N, blue. For clarity, hydrogen atoms and the TFPB anion are not shown.

adduct reported by Denat and co-workers,[9b] and showing the benzyl moieties folded toward the center of the macrocycle.

The X-ray crystal structure of compound $[\mathbf{26}\cdot Na]^+$ $TFPB^-$ (Figure 5) is dictated by the pseudo-octahedral coordination of the Na^+ cation. Four nitrogen atoms are coordinated to the cation (Na−N distances within 2.45−2.55 Å), and two opposite η^3 benzyl moieties complete the first coordination sphere (Na−C distances within 2.99−3.32 Å). The macrocycle conformation in $[\mathbf{26}\cdot Na]^+$ $TFPB^-$ is different from that evident in the free ligand[21] and similar to that observed by Habata and co-workers in argentivorous complexes.[17a]

NMR titration by stepwise quantitative additions of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFPB) to $CDCl_3$ solutions of cyclotetramer **26** showed the formation of a metalated species (see Figure S1) displaying an upfield shift of the benzyl ortho-protons (from 7.30 to 6.04 ppm) similar to that observed by Habata in the presence of Ag^+-ion.[17a]

In recent decades, peraza-macrocyclic compounds, and especially 1,4,7,10-tetraazacyclododecane and 1,4,7-triazacyclononane derivatives, have made a significant impact on the field of diagnostic imaging[1,2] and catalysis.[22] Less studied, due to the high price of the starting materials, the inefficient methods of selective derivatization, and the limitations of the current synthetic processes, are the 1,4,7,10,13-pentaazacyclopentadecane, the 1,4,7,10,13,16-hexaazacyclooctadecane, 1,4,7,10,13,16,19-eptaazacyclohenicosane ligands, and higher

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homologues. With the implementation of this new approach (that does not set any limits on the size of the macroring,[8a] type, and position of the side chains, if compatible with BH_3 and harsh acidic conditions), we believe that previously inaccessible ligands will be easily synthesized and it will surely increase the utilization of these macrocyclic ligands not only as useful MRI contrast agents but also in general catalysis and coordination chemistry, where advances have been heavily hindered by the nature of currently accessible derivatives.

Studies on the synthesis of chiral and *N*-bridged macro-/polycyclic derivatives are in progress. The results will appear in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02668.

Experimental procedures, characterization data, and HPLC chromatograms of the new compounds (PDF)

Accession Codes

CCDC 1941540−1941542 contain 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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