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Cage-like structures based on constrained cyclic arylopeptoids

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The access to cupola-like or tube-like structures from *ortho*- and *meta*-arylopeptoid macrocycles was explored through CuAAC reaction using a partially flexible bis(azide) and Cu^I-*N*-heterocyclic carbene as catalyst. NMR studies showed that a bis-triazolium bicyclic compound in the *ortho*-series adopts well-defined structure in polar aprotic and protic solvents. Besides, preliminary study revealed its potential for oxoanion recognition.

Molecular containers presenting cavities that can accommodate guests have been the focus of a growing interest in the past decades for their potential use in small molecule separation, gas storage and biomimetic catalysis.¹ Numerous three-dimensional ordered structures have been constructed by means of non-covalent interactions, such as hydrogen bonding² and metal–ligand coordination.³ In comparison, covalent assembly to build molecular containers and cages is less studied probably due to the synthetic challenge.⁴ A significant advance has been made in this field, with the introduction of dynamic covalent chemistry which relies on reversible covalent reactions to access the thermodynamically most favored species.⁵ However, the molecular architectures thus constructed may suffer from a lack of stability and structural diversity. Shape-persistent organic containers such as cyclodextrins, cyclophanes and calixarenes, with great potential for host-guest chemistry, have indeed been studied intensively. Considerable efforts have been made to enlarge ring sizes, backbone types and functional diversity of these synthetic receptors. We are interested in the design of organic 3D structures made from macrocyclic oligoamides to build molecular containers with structural and functional features giving rise to a particular kind of chemical behavior.⁶ Kubik unveiled the potential of bis(cyclopeptide) covalently connected as molecular anion containers.⁷ Recently, macrocycles processing *N,N*-disubstituted backbone amides instead of secondary amides, *i.e.* cyclopeptoids, were advantageously used

to access 3D-structures by Kirshenbaum and Bräse groups.⁸ Herein, we present an efficient route to access cupola-like structures made from cyclic *N*-substituted aminomethyl benzamide oligomers, *i.e.* cycloarylopeptoids,⁹ through double Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) process using a stable source of Cu(I) (Fig. 1). Literature reveals two strategies based on CuAAC reaction using large amount of [Cu(MeCN)₄],PF₆ catalyst to build cupola- or tube-like peptoid structures (Fig. 1). Kirshenbaum and co-workers use a cyclopeptoid containing an azide and an alkyne to access cupola- and tube-like structures in 27% and 4% isolated yields, respectively.⁸ To avoid homodimerization yielding tube-like compound, the reaction was conducted at high dilution. To favour the formation of tube-like structure, Bräse group uses two cyclic peptoids containing two azides and a bis-alkyne linker.¹⁰ The CuAAC process leads to compounds in yields ranging from 6 to 7%. We hypothesized that selectivity and reactivity could be improved by using a pre-organized cyclic structure including a proper choice of the distance between the alkynes connecting groups, and an oxidation resistant Cu^I catalyst. To construct the pre-organised macrocycles, we selected arylopeptoids (*i.e.* *N*-alkylated aminomethyl benzamide oligomers)¹¹ which are peptoid-inspired aromatic oligoamides.¹² Arylopeptoid macrocycles were shown to adopt well-defined conformation in solution; particularly in the *ortho* series.^{9,13} Therefore, we selected for this study, cyclic *ortho*- and *meta*-hexaarylopeptoids **IIa,b** available through cyclization of their linear counterpart **Ia,b** and catalyst (**III**), a Cu^I-*N*-heterocyclic carbene recognized to be stable for years when exposed to air (Fig. 2).¹⁴

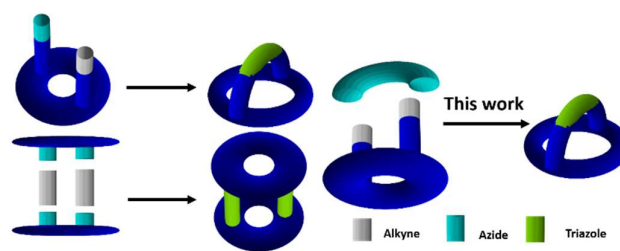


Figure 1. Strategies to access cupola- and tube-like 3D-structures.

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Electronic Supplementary Information (ESI) available: Experimental procedures and characterisation data; HPLC and NMR spectra; X-ray structure CCDC 2220978 (IIa); molecular modelling. See DOI: 10.1039/x0xx00000x

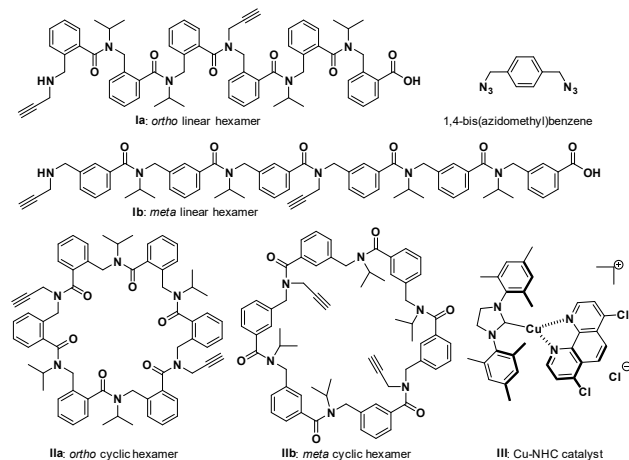


Figure 2. Structures of linear and cyclic arylopeptoids, azide and Cu(I) catalyst used.

The conformational study of these cyclic hexamers has been reported for a full substitution by isopropyl side chains.⁹ The cyclic *ortho*-hexamer displays a well-defined conformation in solution with a 6-fold rotational symmetry and a full *trans* arrangement of the backbone amides whereas the *meta* parent shows a high conformational flexibility. As partner for the CuAAC reaction, we have chosen the partially flexible 1,4-bis(azidomethyl)benzene because the azides inter distance (7.1 Å between the two N1) seems compatible with the cavity size in **IIa,b**. Linear arylopeptoids were synthesized on rink acid resin for **Ia** (*ortho* series) and 2-chloro trityl resin for **Ib** (*meta* series),¹⁵ using a submonomer strategy in 90 and 93% yield, respectively and HPLC purity > 96% (ESI for details). Cyclisation using HATU as coupling reagent in presence of DIPEA afforded **IIa** and **IIb** in 70 and 81% yields. Unexpectedly, **IIa** crystallized spontaneously from the chromatographic eluent MeOH/Water/TFA 80:20:0.1 but despite an exhaustive screening of solvents and techniques, crystal of **IIb** suitable for X-ray diffraction could not be obtained. Compound **IIa** crystallizes in the space group C2/c and displays an all *trans* conformation of the backbone amides with isopropyl and propynyl side chains pointing alternately up and down of the plan of the ring (Fig. 3). The crystal contains 3 water molecules occupying the cavity formed by tubular assembly of the macrocycles in the crystal packing. The distance between the two internal carbons of the alkyne groups is 12.7 Å.

Conformational preferences of the two cyclic hexamers were also examined in solution by NMR. As expected, ¹H NMR of **IIb** (*meta* series) shows signals coalescence in various solvents (chloroform-*d*, acetone-*d*₆, acetonitrile-*d*₃, methanol-*d*₄, dms-*d*₆), indicative of the

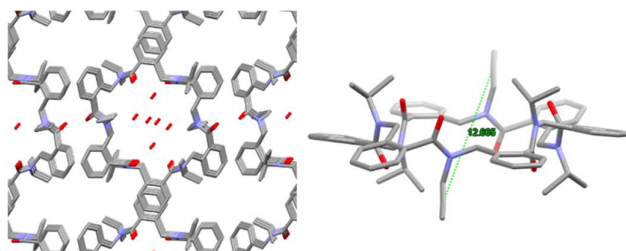
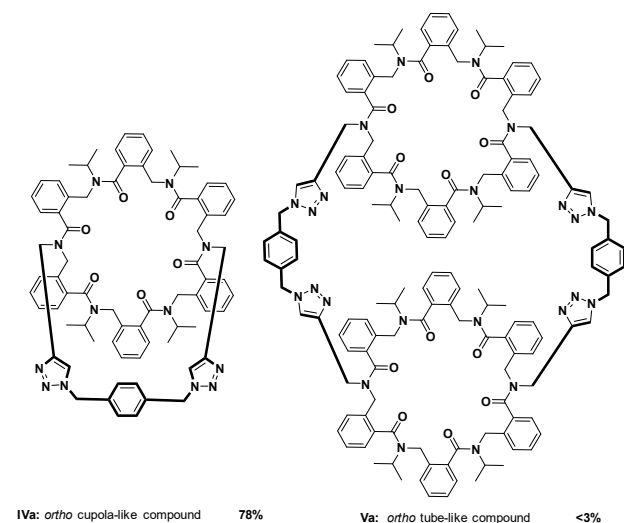
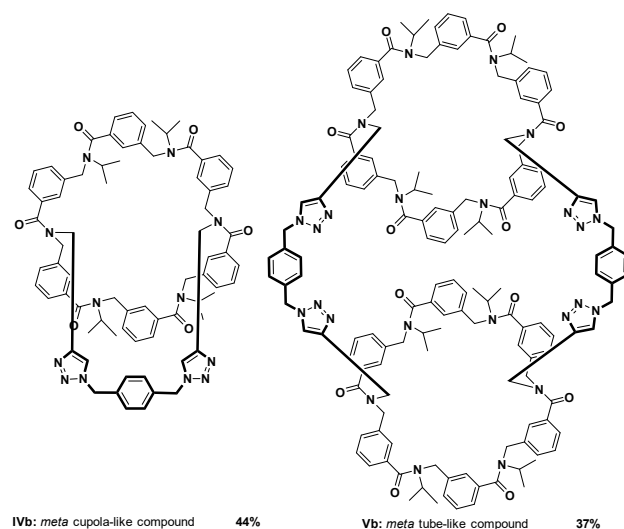


Figure 3. X-ray structure of **IIa**: crystal packing (left) and side view (right).

presence of several conformations interconverting at the NMR precession rate (Fig. S41, ESI). Regarding **IIa** (*ortho* series), the replacement of two isopropyl by the less bulky propargyl side-chains furnishes ¹H NMR spectra reflecting a relative conformational flexibility in acetone-*d*₆, acetonitrile-*d*₃, methanol-*d*₄ or dms-*d*₆ but better resolved and simplified spectrum in CDCl₃, suggesting the existence of a preferred conformation only in this polar aprotic solvent. Variable temperature NMR was performed on macrocycle **IIa** to better understand the dynamics of this cyclic system. Upon heating up to 398 K in dms-*d*₆, coalescence persists indicating the existence of high-energy barriers to cross in order to pass from one conformer to the other (Fig. S42, ESI). Indeed, the *ortho* substitution of the backbone aromatics actually decreases the degrees of freedom around the amide-aromatic bonds. At low temperature in CDCl₃, one predominant conformer is observed (Fig. S43, ESI). The number of AB systems from methylene groups and the 8 signals corresponding to the methyl protons from isopropyl side chains suggest one non-symmetric preferred conformation. Aromatic signals overlapping prevents from complete signals assignment and determination of the *N,N*-disubstituted amides conformation. The conformational heterogeneity observed in methanol and acetonitrile (CuAAC reaction solvents) suggests that conformers with propargyl groups either on the same or opposite side of the ring, are simultaneously present in solution. Besides, when the propargyl groups are on the same side, the C2 alkyne/alkyne distance is approximately 10 Å, a value compatible with the inter azide distance in 1,4-bis(azidomethyl)-benzene allowing the cupola-like structure formation by double CuAAC reaction (Fig. S56, ESI).

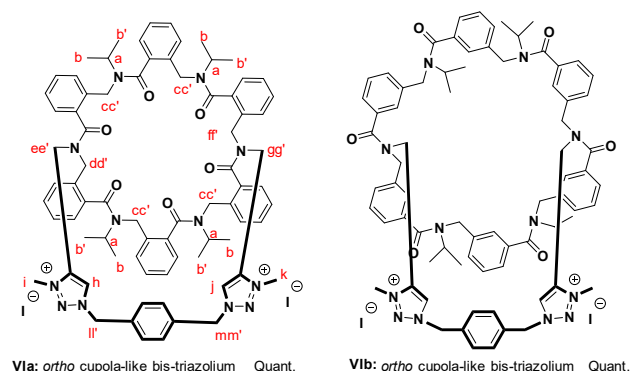
The CuAAC reaction between *ortho*-macrocycle **IIa** and 1,4-bis(azidomethyl)benzene was first catalysed with 100 mol% of [Cu(MeCN)₄]₂PF₆ furnishing 20% isolated overall yield of **IVa** and **Va** (8:2 ratio; Fig. 4) in agreement with literature concerning peptoid macrocycles.¹⁰ We observed a total disappearance of the starting material and formation of insoluble, white unidentifiable material that could result from polymerisation. The same reaction was then catalysed using 10 mol-% of catalyst **III** at 0.5 mM in methanol for 2 days.[†] To our delight, the reaction went to completion and afforded the bicycle **IVa** as major compound (78% isolated yield) and only traces amount of tricyclic compound **Va** (<3%) (Fig. 4).^{**} Impressively, the concentration could be increased from 5.10⁻⁴ M to 10⁻¹ M keeping good yield (70%) and surprisingly without affecting the ratio between cupola- and tube-like adducts. 1D and 2D NMR experiments on **IVa** at variable temperature revealed a certain level of structuration but the presence of more than one conformer in solution (Fig. S44-45, ESI).

The CuAAC reaction proceeded differently using the cyclic *meta*-hexaarylopeptoid **IIb**. Using [Cu(MeCN)₄]₂PF₆ catalyst (100 mol-% at 0.5 mM), although the starting material was totally consumed, the reaction afforded a mixture of bicyclic compound **IVb** and tricyclic compound **Vb** in a 3:7 ratio in 35% overall yield (Fig. 5). Gratifying, the use of catalyst **III** (10 mol-% at 0.5 mM) increased the overall yield to 82%, albeit the **IVb/Vb** ratio is switched down to ≈ 1:1 based on isolated compounds (Fig. 5). As for the *ortho* series, the proportion stayed constant when increasing the concentration to 10⁻¹ M. But, contrary to bicycle **IVa**, ¹H NMR spectra of compound **IVb** showed high level of coalescence indicative of conformational heterogeneity in solution (Fig. S45, ESI).

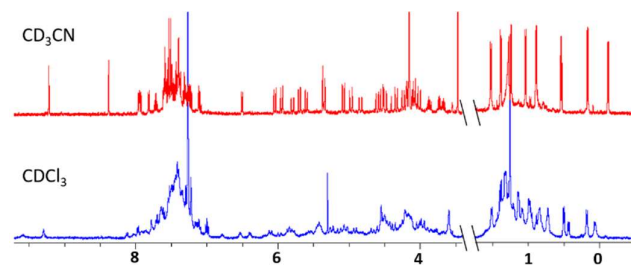
Figure 4. Bicyclic and tricyclic compounds obtained by CuAAC of *ortho*-macrocycle IIa.Figure 5. Bicyclic and tricyclic compounds obtained by CuAAC of *meta*-macrocycle IIb.

These new 1,2,3-triazole-containing structures might be of interest as confined receptors for anion recognition through C-H...anion bond interactions.¹⁶ To further enhance the H-bond donor capability and potentially favour anion- π interaction, the triazoles should be converted into triazoliums.¹⁷ Moreover, according our previous studies, the triazolium groups can also exert additional constraints through $n-\pi^*$ aromatic interaction and may lead to better defined and strongest structure.¹⁸ Therefore, the triazoles were treated with methyl iodide in MeCN at 70°C. For tube-like **Vb**, the expected compounds were detected by HPLC-HRMS but exhaustive decomposition occurred during the methylation either using methyl iodide or methyl triflate at room temperature. Oppositely, the cupola-like structures **IVa,b** afforded stable bis-triazolium-based compounds **VIa** and **VIb** in quantitative yields (Fig. 6). The comparison of ¹H NMR spectra of the triazolium-based compounds **VIa** and **VIb** clearly indicates highly defined structure in solution in the *ortho* series and conformational flexibility in the *meta* series. In contrast with NMR study of the bis-triazole bicycle **IVa**, while more

than two conformers of the bicyclic structure **VIa** seems to coexist in CDCl₃, ¹H NMR spectra in CD₃CN, MeOH and DMSO showed only one well-defined predominant conformation (approx. 90%; Fig. 7 and Fig. S46, ESI).

Figure 6. Cupola-like bis-triazolium compounds in the *ortho*- and *meta*-series.

1D and 2D TOCSY, HSQC, HMBC experiments were performed to enable protons assignment in CD₃CN (Fig. S47-52 and Table S1, ESI). All aliphatic protons are well discernible: the 10 methylene groups give rise to 10 distinct AB systems and the 8 methyl groups from isopropyl side chains give 8 doublets ranging from -0.14 to 1.52 indicative of a highly constrained non-symmetric well-defined structure. Variable temperature NMR studies also attest to the very high stability of the 3D-structure of **VIa**. No change into the ¹H NMR spectra was observed at low temperature *i.e.* 273 K in CD₃CN (Fig. S54, ESI). At high temperature till 388 K in DMSO, all signals stayed well-discriminated for the *ortho*-compound **VIa** while the *meta*-compound **VIb** gave a very simplified spectra indicative of a fast exchange rate between conformers at this temperature (Fig. S54 versus S55, ESI). Our attempts to crystallize **VIa** in various solvents proved unsuccessful. In order to propose a possible structure of the bicyclic bis-triazolium **VIa**, we used the Conformer-Rotamer Ensemble Sampling Tool (CREST) developed by Grimme and co-workers¹⁸ that can quickly explore the conformational space of molecules up to 1000 atoms. From an optimized structure of **VIa** (Table S3, ESI), low-energy candidates were generated. Despite the constrain of all amide bonds in *trans*, the program evaluated more than 12 000 possibilities to finally restrict them to 198 in a window of 6 kcal/mol (Fig. S57, ESI).

Figure 7. ¹H NMR spectra of bicyclic bis-triazolium compound **VIa.2I** (3 mM) in various solvent at 298K.

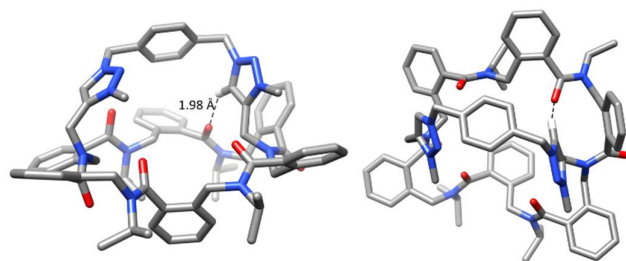


Figure 8. Proposed model structure of VIa obtained using CREST program: side view (left) top view (right); H-atoms omitted for clarity.

All of the proposed solutions show similar ring conformation with the isopropyl side chains on the same side of the aryloleptoid ring and the main variations occurring at the bridge with various orientations of the triazolium groups (Fig. S58, ESI). The structure presented (Fig. 8) is the lowest in energy consistent with the features observed by NMR in CD₃OD and CD₃CN, notably a non-symmetric structure, one triazolium implicated in a CH...O hydrogen bonding and an upfield shift of two methyl groups due to anisotropy cone generated by aromatic rings. Inspired by the Beer's group demonstrating that triazolium cages display strong affinity for oxoanions and especially sulfate, we briefly explored the NMR behaviour of IVa and VIa in presence of the tetrabutylammonium hydrogen sulfate salt.¹⁷ HSO₄⁻ is a harmful waste for which the development of selective receptors is needed. As expected, the bis-triazole precursor IVa did not show marked binding ability upon addition of TBAHSO₄ in CD₃CN or CDCl₃ (Fig. S59-60, ESI). Our anion exchange attempts using NH₄PF₆, as previously reported,¹⁹ to form VIa.2PF₆ from VIa.2I led to product degradation. We thus decided to perform the preliminary binding study on the bis-triazolium VIa.2I. Upon addition of TBAHSO₄ to VIa.2I in CD₃CN, no change in the well-defined ¹H NMR spectrum was observed, except a slight upfield shift of one triazolium proton of 0.1 ppm (Fig. S61, ESI). By contrast, in CDCl₃, a solvent in which several conformers of VIa are coexisting (Fig. 7), the addition of TBAHSO₄ led to an extraordinarily well-defined spectrum (Fig. 9 and Fig. S62, ESI). The number of signal sets are divided by two compared to the spectrum of VIa alone in CD₃CN, suggesting a single conformer exhibiting a 2nd-order symmetry which was confirmed by 1D and 2D-NMR analysis (Fig. S63-65 and Table S3, ESI).

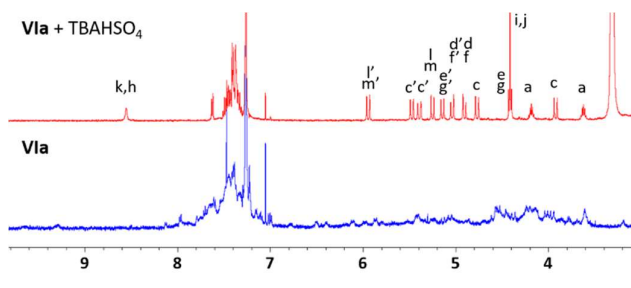


Figure 9. ¹H NMR spectra of bis-triazolium structure VIa (3 mM) in CDCl₃ at 298K alone and in presence of TBAHSO₄ salt (5 equiv.). Protons assignment according Figure 6.

In conclusion, we reported an efficient access to cage-like structures in the aryloleptoid series. As hypothesized, the spatial preorganization of the cyclic core - responsible for the selectivity displayed by *ortho*-aryloleptoids - and proper choice of the NHC catalyst III that outperforms the classical [Cu(MeCN)₄]⁺ are key

factors to selectively access well-defined cupola-like structures. The high level of organization observed in polar aprotic and protic solvents for the bicyclic bis-triazolium structure VIa.2I in the *ortho* series and its recognition of the oxoanion HSO₄⁻ by formation of a symmetric complex are particularly interesting and opens the way for the design and investigation of these novel aryloleptoid-type cage-like structures as receptors and molecular reactors.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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‡ Protic solvents are preferred as proton source to free the triazole from the copper(I)-triazolyl. Indeed, blank experiments show that no reaction occurs in pure CH₂Cl₂ or CHCl₃ and in absence of catalyst III. †† The proof of the total linkage is given by the lack of the strong azide band at 2100 cm⁻¹ in infra-red spectra for IVa,b and Vb.

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