One-step synthesis of chiral cages†

Vincent Steinmetz, François Couty and Olivier R. P. David*

Received (in Cambridge, UK) 23rd September 2008, Accepted 7th November 2008
First published as an Advance Article on the web 26th November 2008
DOI: 10.1039/b816628e

A novel type of hemispherical cage was synthesized in a one-pot procedure, which displayed good binding properties towards nickel(II).

In order to mimic enzymes, chemists have created various molecular architectures aimed at reproducing the major characteristics of those biological entities, namely the binding of specific guests followed by their chemical transformation in a regio, stereo and enantioselective manner.[1] To that end, rather simple molecules have been prepared which possess a three-dimensional arrangement defining a pocket able to accommodate cationic or anionic species, as well as neutral molecules, depending on the moieties present within the cage. Among the numerous architectures prepared to date, calix[6]trens of type **1** developed by Reinaud and Jabin[2] attracted our attention due to their ability to complex all three kinds of guests mentioned above. They are represented as their topological skeleton in Scheme 1 (I and V or Y symbolize bi- and tri-functional modules, respectively). This synthesis relied on the closing of a desymmetrized calix[6]arene **2** in which three of the six phenols are linked together with a "cap" of type **3** (route *a* in Scheme 1). We report herein an alternative approach to this type of topology, in which the macrocyclic crown in **1** is constructed around a preexistent cap **4** after ring-closure with three linkers **5** (route *b*).[3]

In order to prepare a bowl-shaped cage presenting topological structure **1**, synthesis of tripodal module **4** was envisioned using copper catalyzed Huisgen cycloaddition (CuAAC) since this would also introduce a tris-triazole motif that could serve as complexing entity.[4] As a bridging reaction (**4** + **3** × **5**), imine formation has already demonstrated its efficiency for building complex architectures[5] and we planned to take advantage of the chemistry of "trianglimines" developed by Gawronski and Kuhnert.[6] In addition, through this cyclocondensation, a chiral cage can be prepared by using a chiral linker for **5**. The combination of these two linking reactions (CuAAC and imine condensation) led us to the design of the star-like compound **9** bearing six aldehyde groups. This synthesis thus began with the preparation of azido-aldehyde **8** (V module) in four steps from dimethyl 5-hydroxyisophthalate. This compound was then reacted with tripropargylamine (Y module) in a threefold cycloaddition reaction using the standard $CuSO_4$–sodium ascorbate system.[7]

UniverSud Paris, Institut Lavoisier, Université de Versailles St Quentin-en-Yvelines, UMR 8180, 45 avenue des Etats-Unis, 78035 Versailles, France. E-mail: odavid@chimie.uvsq.fr; Fax: +33 (0)1 3925 4452; Tel: +33 (0)1 3925 4455

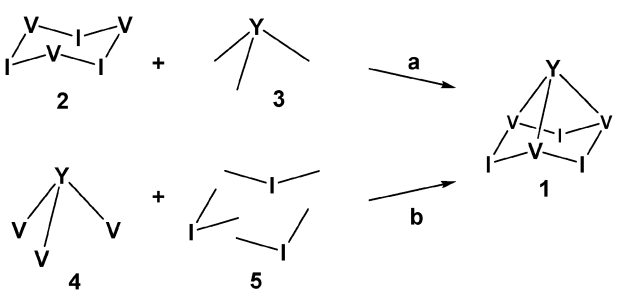
† Electronic supplementary information (ESI) available: Detailed experimental procedures, spectroscopic data. See DOI: 10.1039/b816628e/

Due to the poor solubility of the produced di-, tetra- and hexa-aldehydes, a DMSO–water mixture had to be employed to avoid premature precipitation of partially "clicked" compounds; tris-triazole **9** could then be isolated in fair yield. Formation of a cyclic hexa-imine was next attempted by reacting compound **9** with three equivalents of ethylenediamine (I module) in dichloromethane. Hexa-aldehyde **9** being only very slightly soluble in dichloromethane, completion of the reaction required full solubilization of the starting material and was observed only after three weeks. Gratifyingly, upon evaporation of the solution, a unique product was obtained that exhibited a set of signals in its ^{1}H NMR spectrum fitting the expected tricyclic hexa-imine structure **10** (Scheme 2).

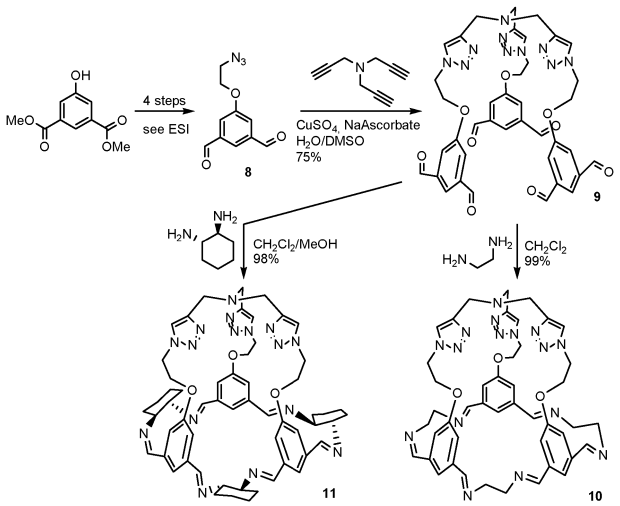
Similar polycondensation gave **11**, when (1*R*,2*R*)-1,2-diaminocyclohexane was used as the linking diamine. All spectroscopic data (^{1}H, ^{13}C, HRMS, IR) supported the depicted structures. Eventually, we found that a mixture of dichloromethane and methanol (9 : 1) readily dissolved compound **9**, and thus reduced the macro-imination reaction time to 12 h. Noteworthy is that dilute conditions were not necessary, and half-gram scale experiments could be run in 6 ml of the above mixture of solvents. Cage **11** proved stable indefinitely at room temperature, either in the solid state or in solution; furthermore the imines were resistant enough to allow purification over silica-gel.

Interestingly, the product **11** exhibited a set of signals in its ^{1}H NMR spectrum fitting with a chiral structure possessing a C_3 symmetry axis. In particular, the whole architecture appeared to be twisted in a propeller-like shape as shown by NMR spectroscopy. The proton NMR spectrum reproduced in Fig. 1 exhibits two signals for the iminic protons (noted Hj and Hj′), suggesting that three are pointing inward and three outward. The same differentiation was observed for the aromatic protons *ortho* to the oxygen substituent (Hg and Hg′), and for the diastereotopic methylene protons Ha and Ha′ remote from the chiral centers but strongly differentiated by the twisted shape.

With the aim of running the cycloaddition as well as the imine formation processes in a one-pot procedure, we sought



Scheme 1 Topological representation of the targeted cage.



Scheme 2 Assembly of tripod **9** and cages **10–11**.

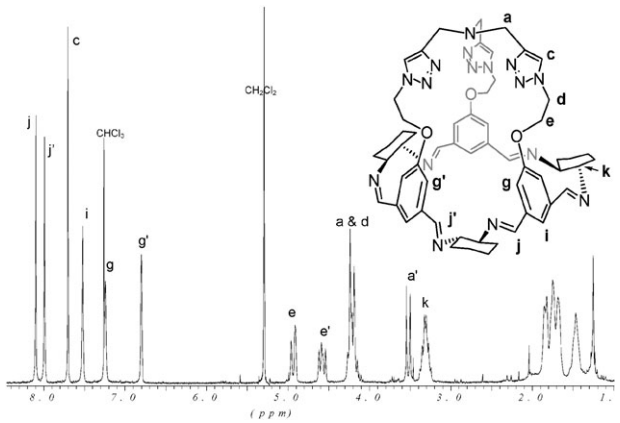
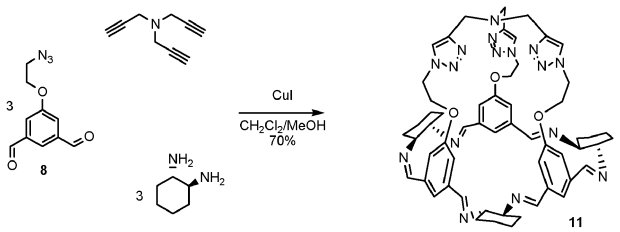


Fig. 1 Proton NMR spectrum of cage **11**.

for experimental conditions that would intersect the requirements for both reactions, hence allowing a direct assembly of the cage. This was realized by dissolving the three partners, trialkyne, diamine and azide **8**, in a dichloromethane–methanol mixture and by employing CuI as catalyst (Scheme 3). Pleasingly, after 12 h, cage **11** was produced, although partially complexed with copper ions. Decomplexation by treatment with sodium diethyl-dithiocarbamate, followed by flash chromatography, gave **11** in 70% yield.

The superposition of two reactions, one reversible and one irreversible, allowed the complete conversion of the different fragments into a unique and defined architecture. The constant equilibration of the imine functions allows the autorepair of an eventual "mistake" and drives the reaction to the thermodynamically stable compound.



Scheme 3 Direct assembly of Y, V and I modules into cage **11**.

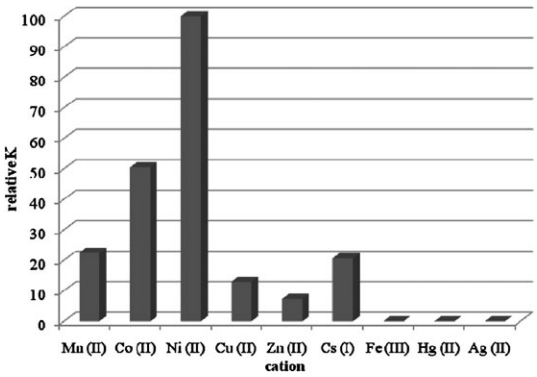


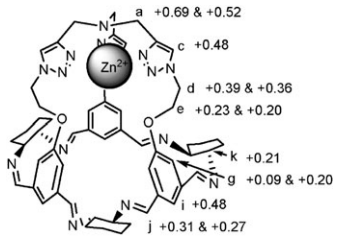
Fig. 2 Relative *K* values *versus* cation.

In order to evaluate the complexation abilities of the synthesized cage **11**, it was titrated with an array of metallic ions (Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cs^{+}, Hg^{2+}, Ag^{+}) (Fig. 2); quantification was accomplished by mass-spectrometry measurements.[8]

Nickel(II) was the most efficiently complexed cation, while other metals belonging to the same period are also recognized by **11** but with lower complexation constants. Importantly this binding takes place without observable degradation of the polyimine structure. Caesium also showed a non-negligible affinity, but, quite surprisingly, heavy metals like Hg(II) or Ag(I) and iron(III) were not at all complexed and promoted hydrolysis of the imines at high concentration. Finally, competition experiments employing equimolar quantities of all the cations tested above showed exclusive complexation of nickel(II).

Having demonstrated the ability of cage **11** to complex cations, we next wanted to gather some information on the nature of the complexation site. In fact, in cage **11**, no fewer than nineteen heteroatoms are potential binding sites. In particular, we wanted to know if the cation was complexed by the large macroimine crown or by the tris-triazole tripod. As attempts at crystallization of cage **11** with nickel(II) and other cations proved unsuccessful, we decided to use NMR techniques to ascertain the location of the complexation site. Zinc(II) was chosen as the cation because of its ease of manipulation and compatibility with the NMR method. Compound **11** is only sparingly soluble in acetone-d_6 but upon addition of one equivalent of zinc(II) triflate, complete solubilization occurred and a new set of signals was displayed in the ^{1}H NMR spectrum. Since the NMR data demonstrate that C_3 symmetry was retained, the cation is expected to be located along this axis. This observation excludes coordination by the imines as the interatomic distances are too great to allow complexation at the center of the macrocyclic crown. Secondly, comparison with the initial chemical shifts revealed the zinc(II) ion to be most probably located in the triazole region, as depicted in Scheme 4. In fact, if the oxygen atoms participate in coordination, important shifts should be observed for the He and Hg protons, which is not the case. Therefore, a tetradentate complexation with the three N3 atoms of the triazoles and with the apical nitrogen atom was assumed,[9,10] although this preliminary study does not unambiguously answer the question.

Having demonstrated the ease of preparation of chiral cages of type **11** and verified that complexation was effective with



Scheme 4 Proton shifts upon complexation of Zn(II), $\Delta\delta$ values in ppm.

this entity, we now plan to design related architectures fitted with chemical moieties able to act as organocatalyst, thus opening new perspectives for pseudo-enzymatic catalysis. Currently, the host–guest studies of these new cages with cations, as well as small organic molecules, are underway in our laboratory.

Notes and references

1 (*a*) W. B. Motherwell, M. J. Bingham and Y. Six, *Tetrahedron*, 2001, **57**, 4663–4686; (*b*) Y. Murakami, J.-I. Kikuchi, Y. Hisaeda and O. Hayashida, *Chem. Rev.*, 1996, **96**, 721–758.

2 (*a*) X. Zeng, N. Hucher, O. Reinaud and I. Jabin, *J. Org. Chem.*, 2004, **69**, 6886–6889; (*b*) U. Darbost, M.-N. Rager, S. Petit, I. Jabin and O. Reinaud, *J. Am. Chem. Soc.*, 2005, **127**, 8517–8525; (*c*) I. Jabin and O. Reinaud, *J. Org. Chem.*, 2003, **68**, 3416–3419; (*d*) O. Seneque, M.-N. Rager, M. Giorgi and O. Reinaud, *J. Am. Chem. Soc.*, 2000, **122**, 6183–6189.

3 For a similar strategy with C_{2v} symmetrical calix[4]pyrroles: C.-H. Lee, H. Miyaji, D.-W. Yoon and J. L. Sessler, *Chem. Commun.*, 2008, 24–34.

4 T. R. Chan, R. Hilgraf, K. B. Sharpless and V. V. Fokin, *Org. Lett.*, 2004, **6**, 2853–2855.

5 Striking examples are found in: (*a*) X. Liu, Y. Liu, G. Li and R. Warmuth, *Angew. Chem., Int. Ed.*, 2006, **45**, 901–904; (*b*) Y. Liu, X. Liu and R. Warmuth, *Chem.–Eur. J.*, 2007, **13**, 8953–8959; (*c*) O. Francesconi, A. Ienco, G. Moneti, C. Nativi and S. Roelens, *Angew. Chem., Int. Ed.*, 2006, **45**, 6693–6696; (*d*) P. Mal, D. Schultz, K. Beyeh, K. Rissanen and J. R. Nitschke, *Angew. Chem., Int. Ed.*, 2008, **47**, 8297–8301; (*e*) K. S. Chichak, S. J. Cantrill, A. R. Pease, S.-H. Chiu, G. W. V. Cave, J. L. Atwood and J. F. Stoddart, *Science*, 2004, **304**, 1308–1312.

6 (*a*) J. Gawronski, H. Kołbon, M. Kwit and A. Katrusiak, *J. Org. Chem.*, 2000, **65**, 5768–5773; (*b*) M. Chadim, M. Budesínský, J. Hodacová, J. Závada and P. C. Junk, *Tetrahedron: Asymmetry*, 2001, **12**, 127–133; (*c*) N. Kuhnert, G. M. Rossignolo and A. Lopez-Periago, *Org. Biomol. Chem.*, 2003, **1**, 1157–1170; (*d*) N. Kuhnert, A. Lopez-Periago and G. M. Rossignolo, *Org. Biomol. Chem.*, 2005, **3**, 524–537; (*e*) J. Gawronski, K. Gawronska, J. Grajewski, M. Kwit, A. Plutecka and U. Rychlewska, *Chem.–Eur. J.*, 2006, **12**, 1807–1817.

7 For reviews on alkyne-azide cycloaddition see: (*a*) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015; (*b*) V. D. Bock, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2006, 51–68.

8 For an example of quantification of binding constants by mass-spectrometry see: M. Desage-El Murr, S. Nowaczyk, T. Le Gall, C. Mioskowski, B. Amekraz and C. Moulin, *Angew. Chem., Int. Ed.*, 2003, **42**, 1289–1293.

9 For comparison of coordination behaviors of tripodal ligands see: C.-Y. Su, B.-S. Kang, T.-B. Wen, Y.-X. Tong, X.-P. Yang, C. Zhang, H.-Q. Liu and J. Sun, *Polyhedron*, 1999, **18**, 1577–1585.

10 For a discussion on the binding of tristriazole ligands with Cu(I) and (II) see: V. O. Rodionov, S. I. Presolski, D. Diaz Diaz, V. V. Fokin and M. G. Finn, *J. Am. Chem. Soc.*, 2007, **129**, 12705–12712.