ORGANIC
LETTERS

2007
Vol. 9, No. 24
4987−4990

A Ditopic Calix[6]arene Ligand with *N*-Methylimidazole and 1,2,3-Triazole Substituents: Synthesis and Coordination with Zn(II) Cations

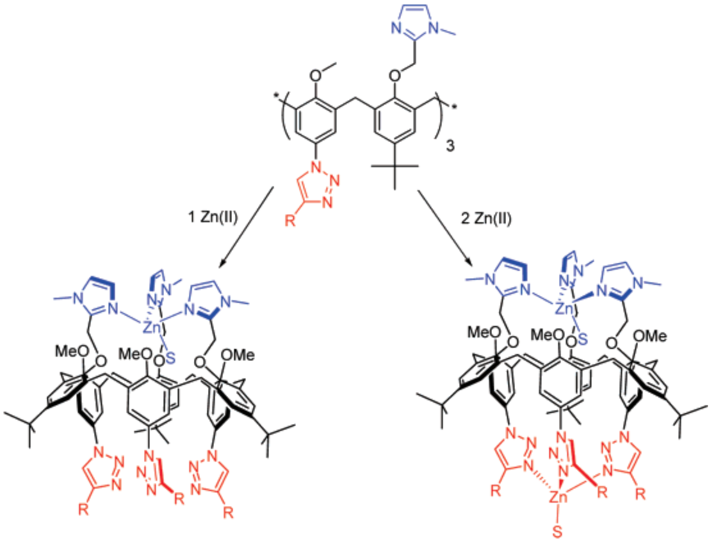
**Benoit Colasson,[†] Marion Save,[†] Petr Milko,[‡] Jana Roithová,[‡,§]
Detlef Schröder,[‡] and Olivia Reinaud*,[†]**

Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR CNRS 8601, Université Paris Descartes, 45 rue des Saints Pères, 75006 Paris, France, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 16610 Prague 6, Czech Republic, and Department of Organic Chemistry, Charles University in Prague, Faculty of Science, Hlavova 8, 12843 Prague 2, Czech Republic

olivia.reinaud@univ-paris5.fr

Received August 30, 2007

ABSTRACT



The first member of a new class of ditopic calix[6]arene has been synthesized, which is decorated with three *N*-methylimidazoles at the small rim and three 1,4-disubstituted-1,2,3-triazoles at the large rim. The coordination of a first Zn(II) cation selectively takes place at the small rim. Addition of a second equivalent results in the complexation of the three triazoles, providing a rare example of 1,2,3-triazole ligands embedded within a supramolecular system.

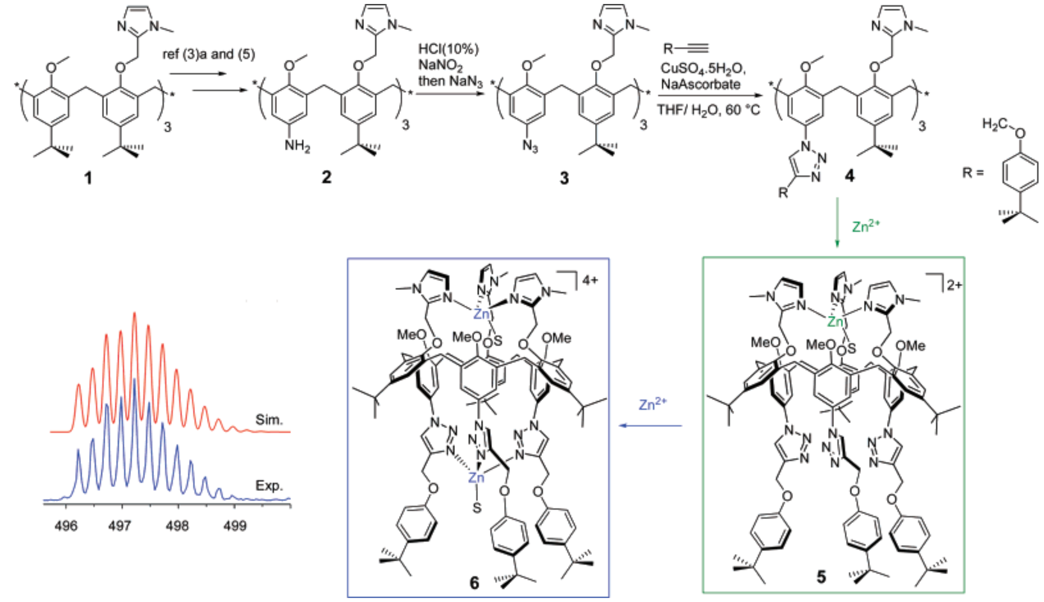
The versatility of calixarenes has been extensively used as their scaffolds present an hydrophobic aromatic core that can be functionalized easily.[1] In the past few years, we have reported a series of calix[6]arenes with appended ligands on the small rim offering a biomimetic N_3 environment for a metal cation.[2] Incorporation of the metal center rigidifies the cavity of the calixarene and offers a labile coordination site pointing toward the inside of the cavity enabling host−guest recognition studies. We were interested in implementing novel functionalities onto the large rim which could either be used as new recognition sites or could create a second

---

[†] Université Paris Descartes.
[‡] Academy of Sciences of the Czech Republic.
[§] Charles University in Prague.

10.1021/ol701850t CCC: $37.00

Scheme 1. Synthesis of the Triazole Calixarene **4**, the Monometallic Zinc Complex **5**, and the Bimetallic Zinc Complex **6**[a]



[a] S is either a solvent molecule (CH$_3$CN) or water depending on the experimental conditions. Bottom left: tetracation region of the ESI mass spectrum of a diluted solution of [$\mathbf{6}^{4+}$,4CF$_3$SO$_3^-$] in MeCN showing the isotope patterns for the tetracation [$\mathbf{6}$(CH$_3$CN)]$^{4+}$.

coordination domain. The presence of the phenolic units on the small rim offers simple methods to functionalize this part of the calixarene. On the contrary, selective functionalization of the large rim remains challenging. Among the few reactions, *ipso*-nitration and *ipso*-sulfonylation have proven to be very useful.[3] *Ipso*-nitration gives access to calixarene **2** on a large scale, making **2** a good precursor to explore new methods to decorate the large rim. We focused on the blooming Cu^{I}-catalyzed azide−alkyne cycloaddition (CuAAC)[4] for two reasons: (a) from the same calixarene building block **3**, we can rely on the high efficiency of the CuAAC to confer many different properties to the calixarenes and (b) the presence of the 1,2,3-triazoles on the large rim can offer a second coordination site, allowing the synthesis of bimetallic complexes.[5] The coordination chemistry of 1,4-disubstituted-1,2,3-triazoles has not yet been explored. To the best of our knowledge, only three recent papers deal with the use of triazole as a ligand.[6] Few other papers report their use for catalysis without emphasis on the nature of the complexes involved.[7] Here, we report the synthesis of a novel calixarene tris-imidazole ligand functionalized at the large rim with three triazole units. The coordination properties of this calixarene are described. Two binding sites have been shown to selectively interact with metal ions, thus giving a unique example of triazole ligands incorporated in a supramolecular system capable of host−guest recognition.

Synthesis of Triazole Calixarene 4. Calixarene **2** can be obtained on a gram scale. To generate calixarene **3** (Scheme 1), **2** was subjected to diazotation followed by nucleophilic substitution with sodium azide.[8] After workup, calixarene **3** bearing three azido groups was obtained in quantitative yield. **3** was then reacted with *t*Bu-4-(prop-2-ynyloxy)benzene[9] under standard conditions for CuCAAC. A 0.6 equiv quantity of the copper catalyst precursor was required for complete conversion. The ability of the three imidazole arms to coordinate either Cu(II) or Cu(I) and to form rather stable complexes may be the reason why the catalyst loading had to be increased. Calixarene **4** was obtained in 75% yield after flash chromatography. The ^{1}H NMR spectrum of calixarene **4** in CD$_3$CN at 300 K showed broad resonances due to slow conformational motions of the calixarene core on the NMR

---

(1) (a) Gutsche, C. D. *Calixarenes Revisited. Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, UK, 1998. (b) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, Holland, 2001. (c) *Calixarenes in the Nanoworld*; Harrowfield, J., Vicens, J., Eds.; Springer: Dordrecht, Holland, 2006.

(2) (a) Sénèque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2000**, *122*, 6183−6189. (b) Sénèque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2001**, *123*, 8442−8443. (c) Sénèque, O.; Rondelez, Y.; Le Clainche, L.; Inisan, C.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *Eur. J. Inorg. Chem.* **2001**, *10*, 2597−2604. (d) Sénèque, O.; Giorgi, M.; Reinaud, O. *Chem. Commun.* **2001**, 984−985.

(3) (a) Redon, S.; Li, Y.; Reinaud, O. *J. Org. Chem.* **2003**, *68*, 7004−7008. (b) Coquière, D.; Cadeau, H.; Rondelez, Y.; Giorgi, M.; Reinaud, O. *J. Org. Chem.* **2006**, *71*, 4059−4065.

(4) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3062. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(5) Coquière, D.; Marrot, J.; Reinaud, O. *Chem. Commun.* **2006**, 3924−3926.

(6) (a) Suijkerbuijk, B. M. J. M.; Aerts, B. N. H.; Dijkstra, H. P.; Lutz, M.; Spek, A. L.; van Koten, G.; Klein Gebbink, R. J. M. *Dalton Trans.* **2007**, 1273−1276. (b) Li, Y.; Huffman, J. C.; Flood, A. H. *Chem. Commun.* **2007**, 2692−2694. (c) Mindt, T. L.; Struthers, H.; Brans, L.; Anguelov, T.; Scheinsberg, C.; Maes, V.; Tourwé, D.; Schibli, R. *J. Am. Chem. Soc.* **2006**, *128*, 15096−15097.

(7) (a) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *17*, 2853−2855. (b) Liu, D.; Gao, W.; Dai, Q.; Zhang, X. *Org. Lett.* **2005**, *22*, 4907−4910. (c) Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.* **2006**, *10*, 3928−3934. (d) Bastero, A.; Font, D.; Pericàs, M. A. *J. Org. Chem.* **2006**, *7*, 2460−2468.

(8) Pagliai, F.; Pirali, T.; Del Grosso, E.; Di Brisco, R.; Tron, G. C.; Sorba, G.; Genazzani, A. A. *J. Med. Chem.* **2006**, *49*, 467−470.

(9) Howell, S. J; Spencer, N.; Philp, D. *Tetrahedron* **2001**, 4945−4954.

time scale. When the temperature was raised to 343 K, sharp peaks were observed and indicated a C_{3v} symmetry (Figure S1, Supporting Information).

Coordination Properties of Calixarene 4. The coordination of Zn(II) to calixarenes with the small rim functionalized with three *N*-methylimidazoles is well-described.[2] The Zn(II) center has a tetrahedral geometry with a fourth neutral exogeneous ligand encapsulated inside the cavity. This feature leads to the possibility of performing various host−guest studies with the ditopic system based on **4**. Therefore, we decided to use the diamagnetic Zn(II) cation to investigate the coordinating properties of calixarene **4** and especially the influence of the triazoles.

A UV−vis titration of a solution of calixarene **4** in CH_3CN with $Zn(ClO_4)_2$ was carried out (Figure 1). During the addition of the first equivalent of Zn(II), an isobestic point at 260 nm was observed. Upon addition of a second equivalent of Zn(II), the isobestic point disappeared concomitantly with a collapse of the band centered at 265 nm. Further additions of Zn(II) did not modify the spectrum. The profile of the absorbance at 250 nm vs equivalents of Zn(II) clearly indicates two distinct binding events with high K_a values ($K_{a1} > K_{a2} = 3 \times 10^5$, see the Supporting Information).

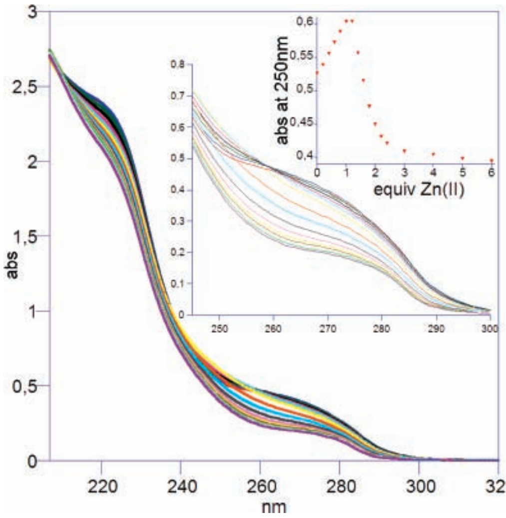


Figure 1. UV−vis titration of calixarene **4** (3×10^{-5} M in CH_3CN containing 10 mM Bu_4NClO_4, $T = 293$ K) with $Zn(OH_2)_6(ClO_4)_2$.

To identify the coordination sequence of two Zn(II) cations by calixarene **4**, the titration was monitored by ^1H NMR in CD_3CN (Figures 2 and S2). Upon titration with the first equivalent of Zn(II), the formation of a single new species was observed. The spectrum shows sharp resonances due to the rigidification of the calixarene core upon complexation. The resonances corresponding to the protons on the imidazoles are split into two peaks and the δ shift of the OMe groups (3.64 ppm) shows that they point away from the cavity. These observations account for the formation of a monometallic zinc complex, **5**, with the zinc cation being coordinated to the imidazoles and to a solvent molecule (MeCN) that is included in the calixarene cavity, as in the parent system based on calixarene **1** (Scheme 1).[2] The second equivalent of Zn(II) led to the formation of compound **6**. The resonance of the triazole protons underwent downfield shift ($\Delta\delta = 0.46$ ppm), whereas the imidazole signals remained unaffected. This is fully consistent with coordination of the second metal center to the triazole units. While the first Zn(II) cation spatially preorganizes the three triazoles through a conformational freeze, the coordination of the second Zn(II) forces them to move further toward the C_3 axis of the macrocycle as shown by the upfield shift of their aromatic protons ($\Delta\delta = -0.20$ ppm).

Mono- and bimetallic complexes **5** and **6** were isolated by reaction of **4** with 1 and 2 equiv of $Zn(OTf)_2$, respectively. Elemental analyses account for two and four triflate counteranions, respectively, with water to complete the coordination sphere of the metals. Synthesis of **6** was also achieved with $Zn(H_2O)_6(ClO_4)_2$. In pure CD_3CN, the ^1H NMR spectra of the two complexes were identical with those recorded in the course of the titration at 1 and 2 equiv of Zn(II). In a noncoordinating solvent such as $CDCl_3$, the spectra of **5** and **6** showed broad peaks, whereas new upfield shifted resonance in each case was observed, at −0.20 ppm for **5** and 0.44 ppm for **6**. These observations indicate that the bimetallic complex, as with the monometallic complex, hosts an exchangeable nitrile guest in the calixarene cavity (this was confirmed by saturation transfer experiments). According to Dreiding models, coordination of the second metal ion to all three central nitrogen atoms N2 of the triazoles is hardly feasible, whereas coordination to the N3 atoms does not appear to induce any major steric distortion for either a 4- or a 5-coordinate Zn center orienting its labile sites toward the microcavity provided by the triazole R substituents. Solvent molecules, and possibly one counteranion, are most probably completing the coordination sphere of this second Zn(II) center. These qualitative conclusions from the NMR data are fully supported by electrospray ionization (ESI) mass spectra of **6** dissolved in MeCN, which show three major signals, all with the expected isotope patterns: the dication **5** with MeCN bound, a trication signal containing two Zn(II) cations, one triflate counterion, and one MeCN, i.e., $[\mathbf{6}(CH_3CN)(CF_3SO_3)]^{3+}$, and finally a clear signal due to the acetonitrile complex of the free tetracation $[\mathbf{6}(CH_3CN)]^{4+}$ (see inset in Scheme 1). We further note that gaseous $[\mathbf{6}(CH_3CN)]^{4+}$ is one of the few examples of highly multiply charged transition-metal cations observed so far.[10]

Mapping the Cavity. Primary amines are good guests for calix[6]arene-based Zn(II) complexes.[2a] When 1 equiv of heptylamine was added to **5**, a set of well-resolved peaks appeared in the high-field region of the spectrum (Figure 3), accounting for its encapsulation in the calixarene cavity. Comparison of the shielding effect of the cavity between the mono zinc complex of calixarenes **4** and **1** clearly indicates that the functionalization of the large rim with substituted triazoles extends the cavity. Indeed, for positions 4 to 7 in the alkyl chain, the shielding effects for **5** are 0.5 to 1 ppm higher than those for the Zn(II) complex of **1**. In

---

[10] (a) Schröder, D.; Schwarz, H. *J. Phys. Chem. A* **1999**, *103*, 7385−7393. (b) Roithová, J.; Milko, P.; Ricketts, C. L.; Schröder, D.; Besson, T.; Dekoj, V.; Bělohradský, M. *J. Am. Chem. Soc.* **2007**, *129*, 10141−10148 and references cited therein.

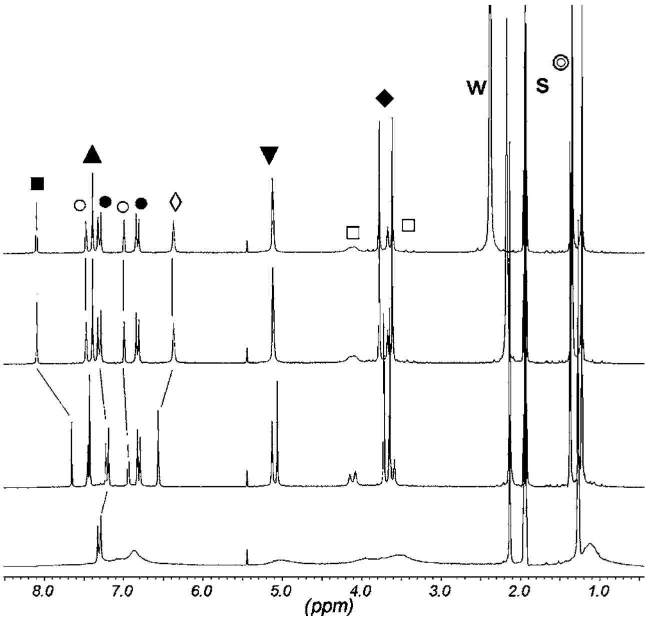


Figure 2. ^{1}H NMR (CD_3CN, 300 K) of the titration of calixarene **4** with $Zn(OH_2)_6(ClO_4)_2$. From bottom to top: before and after addition of 1, 2.25, and 4 equiv of Zn(II): (■) $H_{triazole}$, (○) H_{Im}, (▲) H_{ArtBu}, (●) H_{ph}, (◇) H_{Artria}, (▼) OCH_2 and CH_{2Im}, (□) CH_2Ar, (◆) OCH_3, and NCH_3, (◎) *t*Bu.

contrast, binding a second Zn^{2+} at the triazole site shortens the cavity. Indeed, whereas the addition of MeCN and EtOH into a $CDCl_3$ solution of the bimetallic complex led to their encapsulation into the calixarene core, their higher homologues (EtCN and PrOH) appeared to be too long and increasing their stoechiometry (vs **6**) only led to the decoordination of the triazole-Zn associated to their encapsulation in **5**.

In conclusion, we have synthesized a new triazole calixarene using the CuCAAC methodology. This synthetic pathway opens the possibility of extending the calixarene cavity and of implementing other functional groups with fluorescent, redox, or hydrophilic properties. The presence of the three triazole ligands enables the formation of a bimetallic Zn(II) complex that, despite the closure of the cavity, can accommodate an exchangeable nitrile guest. Complex **6** differs from the previously reported calix[6]arene-based bimetallic complex, where a $H_3O_2^-$ unit occupies the cavity and bridges the Zn(II) centers.[5] In the present system, the second metal ion orients its labile site in the opposite direction, being easily accessible to exogenous binding, although protected by the microenvironment defined by the triazole substituents. Hence, whereas the mononuclear complex offers an extended and tunable cavity for host−guest recognition, the dinuclear complexes provide a novel platform for studying biomimetic catalysis.

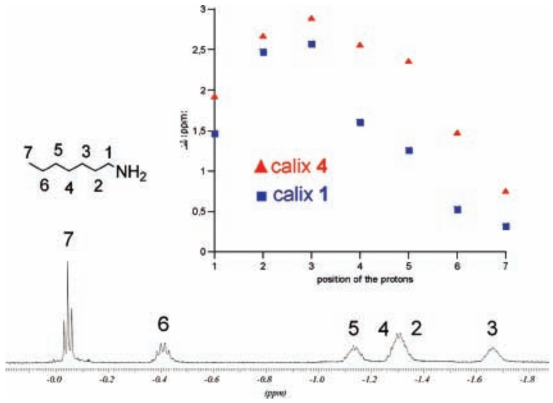


Figure 3. High-field region of the ^{1}H NMR spectrum of **5** with encapsulated heptylamine (500 MHz, $CDCl_3$, 300 K) and plot of the $\Delta\delta$ shifts [$\Delta\delta = \delta(\text{free}) - \delta(\text{encapsulated})$] for the guest's protons as a function of their position relative to the nitrogen for the zinc(II) complex of calixarene **1** and calixarene **4**.

Acknowledgment. This research was supported by CNRS and Agence National pour la Recherche (Calixzyme Project ANR-05-BLAN-0003) and by the Grant Agency of the Academy of Sciences of the Czech Republic (KJB400550704).

Supporting Information Available: Experimental procedures and spectral data for compounds **3**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701850T