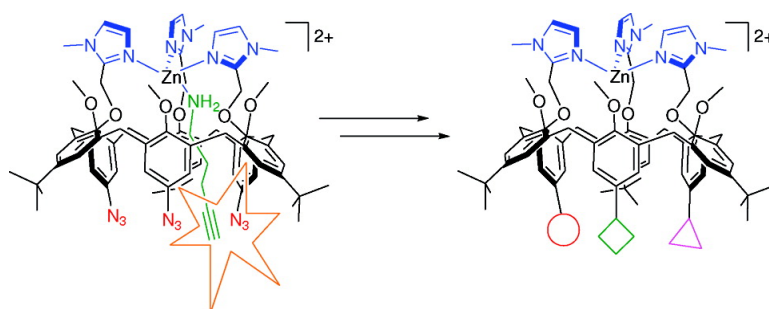Communication

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Selective Hetero-Trisfunctionalization of the Large Rim of a Biomimetic Calix[6]arene Using Host−Guest Chemistry as a Synthetic Tool

Benoit Colasson and Olivia Reinaud*

Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, CNRS UMR 8601 Université Paris Descartes, 45 rue des Saints Pères, 75006 Paris, France
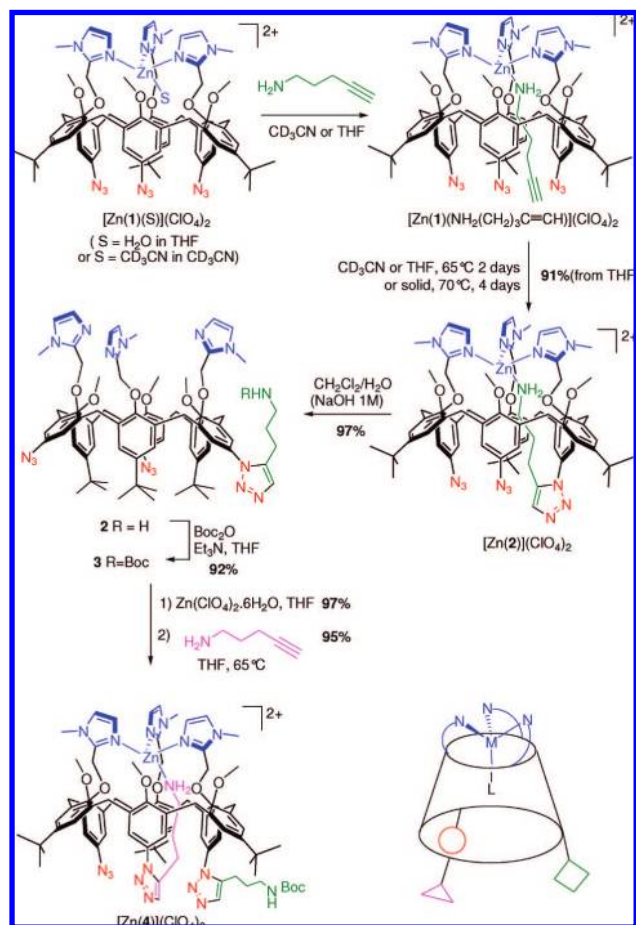
Received May 29, 2008; E-mail: olivia.reinaud@parisdescates.fr

Scheme 1

Template synthesis provides an access to complex molecular structures such as macrocycles, rotaxanes or catenanes.[1] For the past decade, we have developed biomimetic receptors based on calix[6]arenes.[2] The calix[6]arene macrocycle is functionalized at the small rim with three coordinating groups, mimicking the first coordination sphere of the enzymatic metal complex. The hydrophobic cavity of the macrocycle is reminiscent of the pocket of the enzyme governing the recognition event. We anticipated that the host−guest recognition event could be a good template strategy to achieve selective functionalization of the large rim of a calix[6]arene via the Huisgen 1,3-dipolar cycloaddition between an alkyne and an organic azide[3] (Scheme 1). Indeed, if the Cu(I)-catalyzed method is by far the most reliable,[4] the "original" thermal reaction has been successfully exploited in target-guided synthesis (TGS) for drug discovery.[5] In this strategy, the enzyme itself catalyzes the formation of its own inhibitor via the formation of a triazole link between two substrates interacting specifically with two domains of the enzymatic pocket. Taking advantage of the host−guest chemistry we have developed with the calix[6]arene-based "funnel complexes" and in analogy with the TGS, the guest would be the first substrate of the synthetic enzyme model, the second substrate being directly attached to the large rim of the calixarene.

We have recently reported the synthesis of a tris(azido)calix[6]arene (**1**) as a new precursor for the introduction of a second coordination sphere at the large rim. Indeed, the Cu(I)-catalyzed Huisgen reaction performed with compound **1** in the presence of three molar equivalents of an alkyne allowed the formation of a C_{3v} symmetrical tris-triazole derivative at the large rim that can coordinate a metal ion.[6] When the reaction was performed in a 1:1 ratio of tris(azido)calix[6]arene **1** and alkyne, a mixture of products was obtained. To favor the formation of a monoadduct, the zinc complex of ligand **1**, [Zn(**1**)(S)](ClO$_4$)$_2$, was prepared (Scheme 1). Addition of 1 equiv of 5-aminopentyne led to the quantitative formation of the 1:1 host−guest complex, [Zn(**1**)(NH$_2$(CH$_2$)$_3$C≡CH)](ClO$_4$)$_2$. This guest was chosen for two reasons: (i) primary amines are the best ligands for this family of Zn(II) funnel complexes and (ii) modeling studies suggested that three methylene groups linking the NH$_2$ donor and the triple bond would be optimal to place the latter in close proximity to the azido groups. When the complex was heated for 48 h in CD$_3$CN at 65 °C or placed as a solid in an oven at 70 °C for 4 days, a single product, [Zn(**2**)](ClO$_4$)$_2$, was formed as shown by ^{1}H NMR spectroscopy and ESI-MS analysis performed after demetalation (m/z = 1335.7 for [**2** + H]$^+$; Scheme 1). In addition to this product, unreacted complex [Zn(**1**)(S)](ClO$_4$)$_2$ was present (ca. 40%). We attributed this incomplete conversion to the decoordination of the amine in the competitive coordinating MeCN solvent and the partial degradation of the free amine.

Indeed, the reaction was brought to completion when performed in the presence of an excess of 5-aminopentyne (ca. 3 equiv) in the noncoordinating solvent THF after two days at 65 °C. Pure complex [Zn(**2**)](ClO$_4$)$_2$ was straightforwardly isolated by precipitation from the crude reaction mixture with Et$_2$O in 91% isolated yield. Its ^{1}H NMR spectrum, displayed in Figure 1 (bottom), clearly indicates the transformation of the encapsulated alkyne whose resonances appear in the high field region of the spectra. While the chemical shifts for H1 and H2 are almost unchanged compared to the starting complex, the resonance of H3 is about 1 ppm downfield shifted due to the regioselective formation of the 1,5-triazole ring (see Figure 1 for the H labeling). The overall profile also indicates that the symmetry of the complex has switched from pseudo C_{3v} to C_s and that enantiomerization of the helix at the metal center remains a fast process at room temperature. This shows that, in spite of the intramolecular coordination of the amine, the Zn complex remains flexible.
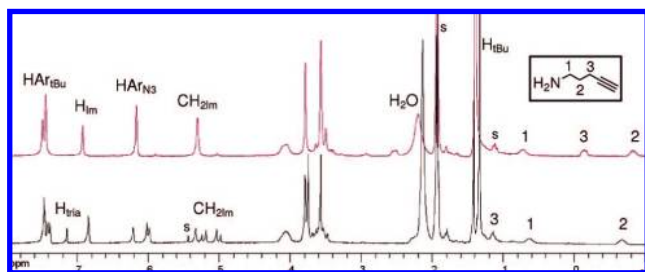
Figure 1. ^{1}H NMR spectra (CD$_3$CN, 250 MHz, 300 K). From top to bottom, [Zn(**1**)(NH$_2$(CH$_2$)$_3$C≡CH)](ClO$_4$)$_2$ and [Zn(**2**)](ClO$_4$)$_2$ (s = residual solvents, H$_{Im}$ and H$_{tria}$ stand for imidazole and triazole protons, respectively, and HAr$_{tBu}$ and HAr$_{N3}$ for the aromatic H of the calixarene units substituted at the large rim by the t-Bu and N$_3$ groups, respectively).

When a CD$_3$CN solution of **1** and an excess of 5-aminopentyne was heated for several days at 65 °C, neither product **2** nor other cycloadduct did form at all. This shows that under such conditions, the thermal intermolecular Huisgen cycloaddition does not occur and that the coordination of the amine to Zn(II) is necessary for the reaction to take place. Indeed, it allows the preorganization of the alkyne substrate in the vicinity of the azido substituent for the host and the guest to react intramolecularly. As a result, the effective concentration of the two reagents increases and the close contact between the azide and the alkyne decreases the activation barrier, especially the entropic contribution. The fact that no bis- or tris-functionalized calixarene was detected is quite remarkable. It is attributable to both the intramolecular nature of the process and the "protecting" effect of the intramolecular coordination of the amine to Zn(II) in complex [Zn(**2**)](ClO$_4$)$_2$. The favored coordination of the reacted amino guest prevents the inclusion of a second amine and reaction of a second azido group of the calixarene with an alkyne. By analogy with the TGS, this scorpionate-like structure can be seen as an inhibited form of our model compound.

With such a tool in hand, we continued the functionalization of the large rim of the calixarene (Scheme 1). To accommodate another reactive alkyne in the cavity, the amine had to be protected. This was done in two steps: demetalation of [Zn(**2**)](ClO$_4$)$_2$ to recover the free ligand **2** and then reaction of the amine with Boc$_2$O to yield **3**. Once protected, the amine cannot coordinate the Zn(II) ion. Complex [Zn(**3**)(H$_2$O)](ClO$_4$)$_2$ was finally reacted with 5-aminopentyne in THF to yield [Zn(**4**)](ClO$_4$)$_2$ with high yield and selectivity. At this stage, three different groups are present at the large rim of the calixarene: the remaining azido group, a Boc-protected amine and a coordinated primary amine. The ^{1}H NMR spectrum of complex [Zn(**4**)](ClO$_4$)$_2$ displayed particularly sharp and well defined resonances at high temperature. At low T, specific resonances became very broad, whereas others remained almost unchanged (see SI for discussion). This is indicative of the left/right inversion of the helix at the level of the tris-imidazole zinc core that was slowed down.[2b] Most interestingly, the methylene groups of the encapsulated amine appeared diastereotope, whatever the temperature (as illustrated by the central H2 displayed Figure 2). This clearly shows that the three different groups at the large rim create a chiral environment inside the cavity that is sensed by the amino-guest.

In conclusion, we have reported an efficient method for the controlled, stepwise functionalization of the large rim of a
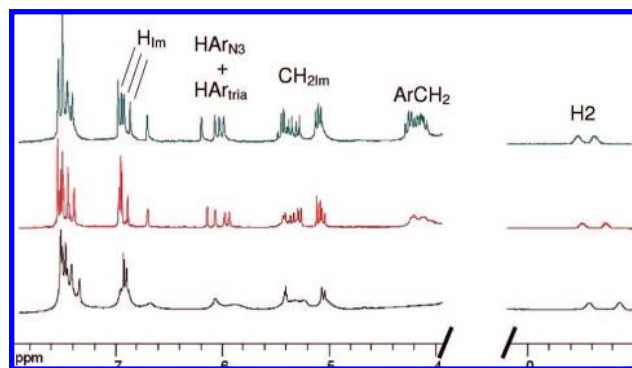

Figure 2. ^{1}H NMR spectra (CD$_3$CN, 500 MHz) of [Zn(**4**)](ClO$_4$)$_2$ at different temperatures: From top to bottom: 340, 300, and 260 K (H$_{Im}$ stands for imidazole protons, and HAr$_{tria}$ and HAr$_{N3}$ stand for the aromatic H of the calixarene units substituted at the large rim by the triazol and N$_3$ groups, respectively).

calix[6]arene. Our strategy relies on the host−guest properties of our system, which associates metal-template and molecular inclusion to favor an intramolecular reaction and inhibit a possible second turnover. It provides an easy access to monofunctionalized macrocyclic hosts that can be derivatized into a wide range of structures. It also opens the route to inherently chiral calix[6]arenes presenting an ABC pattern at the large rim.[7] The use of other alkyne guests is currently investigated, with the perspective of studying the effects of the chirality introduced at the large rim for enantioselective recognition and catalysis. Finally, we believe that this host−guest driven chemistry, as a mean to introduce selectively one function on a platform, will find some resonances in other supramolecular systems.

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

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JA803878G