JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Supramolecular Assistance for the Selective Monofunctionalization of a Calix[6]arene Tris-carboxylic Acid-Based Receptor

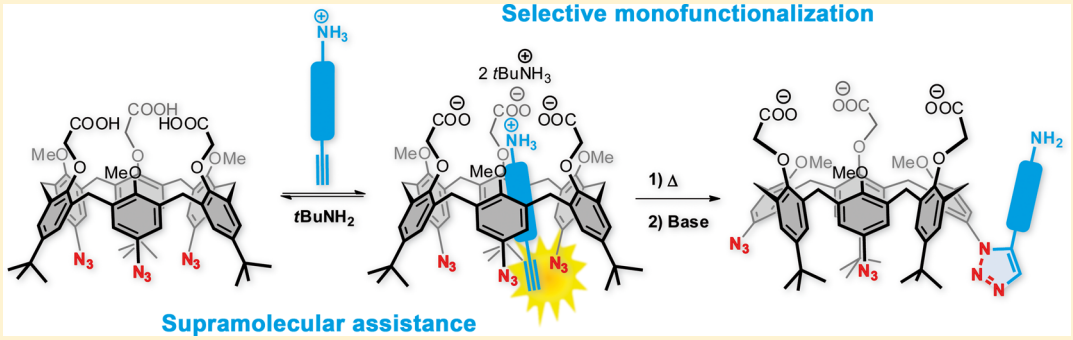
Alex Inthasot,[†,‡,§] Minh-Dung Dang Thy,[†,‡] Manuel Lejeune,[†] Luca Fusaro,[‡] Olivia Reinaud,[§] Michel Luhmer,*[,‡] Benoit Colasson,*[,§] and Ivan Jabin*[,†]

[†]Laboratoire de Chimie Organique, Université Libre de Bruxelles (U.L.B.), Avenue F.D. Roosevelt 50, CP160/06, B-1050 Brussels, Belgium

[‡]Laboratoire de Résonance Magnétique Nucléaire Haute Résolution, Université Libre de Bruxelles (U.L.B.), Avenue F.D. Roosevelt 50, CP160/08, B-1050 Brussels, Belgium

[§]Laboratoire de Chimie et de Biochimie Pharmacologiques et Toxicologiques (CNRS UMR 8601), Université Paris Descartes, 45 rue des Saints-Pères, 75006 Paris, France

Supporting Information



ABSTRACT: The selective functionalization of macrocyclic receptors remains extremely challenging because it generally requires the transformation of one and only one functional group among several identical groups. Recently, some of us described that the host–guest properties of a calix[6]arene-based Zn complex could be exploited for its selective monofunctionalization. Herein, we report on the extension of this synthetic strategy to a calix[6]arene-based receptor displaying a different recognition pattern with its guest. More precisely, a calix[6]arene tris-carboxylic acid-based receptor bearing three azido groups at the large rim was selectively monofunctionalized through an intramolecular thermal Huisgen reaction with a hexynNH$_3^+$ ion accommodated into the cavity. This work shows that the monofunctionalization methodology can also be performed efficiently with host–guest systems involving ionic/H-bonding interactions, and it is thus not limited only to the use of metal–ligand interactions. In other words, this supramolecular methodology can be used as a general tool for the selective functionalization of molecular receptors.

INTRODUCTION

The synthesis of sophisticated and functional molecules often requires the use of selective chemical transformations. A large part of the research in chemical science is devoted to the finding of such chemo-, regio-, or stereoselective reactions. These methodological studies often find a large echo in different fields such as medicinal chemistry, material science, or supramolecular chemistry. The repercussion of reactions such as olefin metathesis,[1] palladium-catalyzed carbon–carbon bond formation,[2] and more recently the cream of the crop click reaction Cu^I-catalyzed azide-alkyne cycloaddition[3] is undeniable.

Cyclodextrines,[4] cucurbiturils,[5] resorcinarenes,[6] pillararenes,[7] and calixarenes[8] are macrocyclic structures presenting a defined cavity, and for this reason, they are widely exploited in host–guest chemistry. Their selective functionalization with different functional groups is of high interest for molecular sensing, multivalent recognition,[9] supramolecular catalysis,[10] etc. However, for such large molecules, it remains extremely challenging to react one and only one functional group among several identical groups. This is due to the lack of electronic or spatial couplings, which are required to achieve selectivity.[11] If examples of highly selective functionalization have been described,[12] at this point, it seems that each macrocyclic platform needs a specific consideration, and thus, no general methods have been reported.

Recently, some of us have proposed a synthetic strategy for the monofunctionalization of a calix[6]arene receptor based on its recognition ability (Figure 1).[13] The calixarene receptor is a *funnel* Zn complex decorated at the large rim with 3 equivalent azido groups.[14] The encapsulation of an acetylene substrate is driven by the coordination of the amino or hydroxyl group to the Zn(II) center. In these host–guest complexes, the two reactive

Received: September 20, 2013
Published: November 13, 2013

   dx.doi.org/10.1021/jo402080d | J. Org. Chem. 2014, 79, 1913–1919

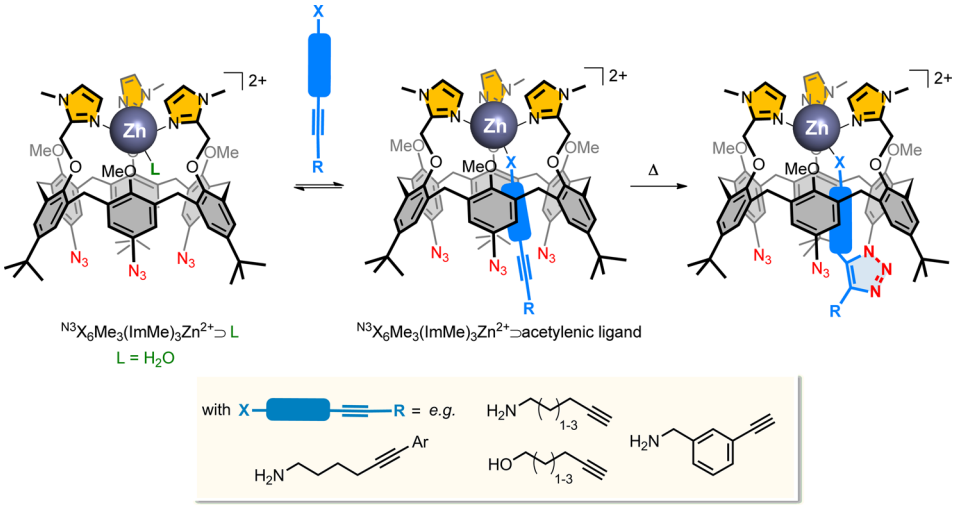


Figure 1. Selective monofunctionalization of a Zn^{II}-calix[6]arene-based funnel complex through thermal Huisgen cycloaddition in a noncoordinating solvent (toluene, THF).

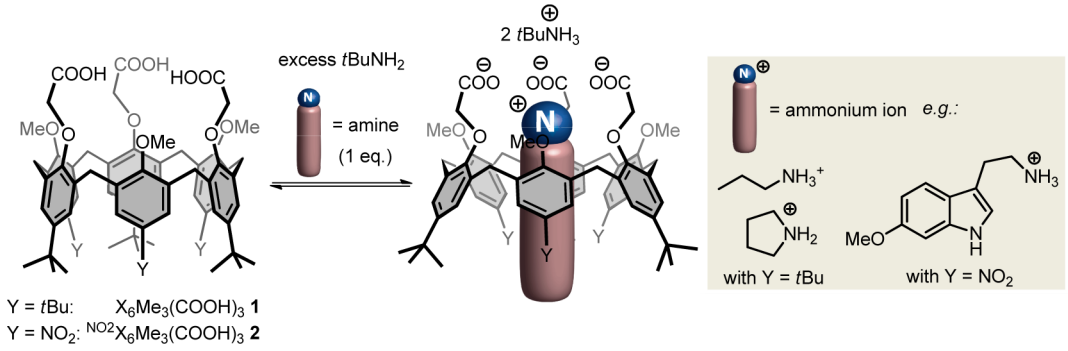


Figure 2. Recognition properties of calix[6]arene tris-carboxylic acid derivatives toward ammonium ions.

groups (azide and alkyne) face each other, and this preorganization dramatically increases the reaction rate of the intramolecular thermal Huisgen reaction.[15] After the formation of the first triazole ring, the intramolecular coordination of the arm is entropically favored and blocks the coordination of a second substrate. Hence, the reaction is inhibited after a monofunctionalization of the receptor. With this simple procedure, the pure monofunctionalized product is obtained in high yield.

We now want to further explore the potentiality of such a supramolecular methodology to be used as a general tool for the selective functionalization of molecular receptors. Hence, as a first step, we decided to evaluate whether this methodology could be applied to hosts displaying a different recognition pattern with their guest. In this regard, it was previously shown that calix[6]-arene tris-carboxylic acid derivatives such as **1** or **2** behave as selective receptors for ammonium ions (Figure 2).[16] Indeed, when an excess of a bulky amine such as tBuNH$_2$ is added to a solution of **1** or **2**, the acid−base reaction leads to the structuration of the calixarene into a cone conformation. The *exo*-binding of the bulky ammonium ions to the three adjacent carboxylate arms of the calix[6]arene occurs through ion pairing and H-bonding interactions. This closes the small rim, leaving a polarized cavity that can strongly bind, through ion pairing and H-bonding interactions, one equivalent of a primary or secondary ammonium ion of interest in *endo* position. With compound **2** deprived of three tBu substituents at its large rim, the selective inclusion of an ammonium guest as large as 6-methoxytryptammonium could be obtained. Given these host−guest properties, a calix[6]arene decorated with three carboxylic acid arms at the small rim and three azido groups at the large rim was considered as a possible actor for the monofunctionalization study.

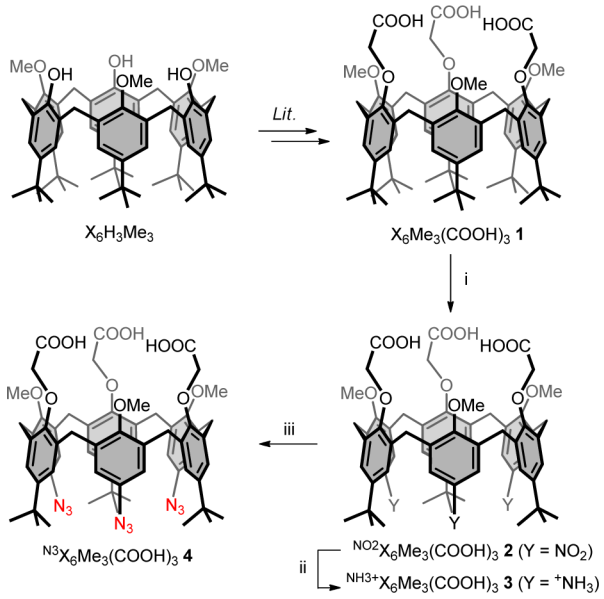
Herein, we report on the generalization of the host−guest assisted monofunctionalization to metal-free host−guest systems. The synthesis of a tris-azido tris-carboxylic acid calixarene is described, and we show that its monofunctionalization can be efficiently performed thanks to the assistance of ionic and H-bond interactions.

RESULTS AND DISCUSSION

Synthesis and Characterization of $^{N_3}X_6Me_3(COOH)_3$ 4. $X_6Me_3(COOH)_3$ **1** was prepared from 1,3,5-tris-methoxy-calix[6]arene ($X_6H_3Me_3$)[17] according to a previously reported procedure (Scheme 1).[18] For the selective introduction of the azido groups, the strategy relied on a highly selective *ipso*-nitration reaction as the key step.[19] Indeed, it was shown that phenolic units of 1,3,5-tris-methoxy-calix[6]arene derivatives bearing CH_2CH_2X groups (X = amino) or CH_2Y groups (Y = e.g. amido or carboxylate) are deactivated toward electrophilic reagents such as NO_2^+ in acidic media, allowing *ipso*-nitration to occur selectively on the anisole units. In the present case, a slightly modified procedure than the one previously reported afforded the 1,3,5-tris-nitrated $^{NO_2}X_6Me_3(COOH)_3$ **2** in quantitative yield. Reduction of the nitro groups with sodium dithionite and subsequent acidic treatment gave the corresponding

dx.doi.org/10.1021/jo402080d | J. Org. Chem. 2014, 79, 1913−1919

Scheme 1. Synthesis of $^{N_3}X_6Me_3(COOH)_3$ 4[a]



[a](i) HNO_3, AcOH, CH_2Cl_2, quant.; (ii) $Na_2S_2O_4$, K_2CO_3, EtOH/H_2O then HCl; (iii) $NaNO_2$, HCl (10% in water) then NaN_3, 91% overall yield from **2**.

1,3,5-tris-anilinium calix[6]arene, i.e., $^{NH_3^+}X_6Me_3(COOH)_3$ **3**, which was used without purification in the next step (Scheme 1). Diazotation followed by nucleophilic substitution with sodium azide gave the desired $^{N_3}X_6Me_3(COOH)_3$ **4** in 91% overall yield from **2**.

$^{N_3}X_6Me_3(COOH)_3$ **4** was unambiguously characterized by IR ($\nu_{(N_3)}$ = 2111 cm^{-1}), HRMS and NMR spectroscopy.[20] At 298 K in toluene-d_8, **4** exhibits ill-defined ^1H NMR signals (Figure 3a) whose broadness can be ascribed to the intramolecular self-association of the carboxylato groups through H-bonding interactions. However, a well-resolved NMR pattern that suggests a C_{3v}-symmetrical structure was observed at 363 K.[20] At this temperature, the signals of the calixarene core are characteristic of a flattened cone conformation ($\Delta\delta_{ArH}$ = 1.12 ppm) with the methoxy groups ejected from the cavity (δ_{OMe} = 3.75 ppm), and thus the carboxylato groups directed toward the inside of the cavity, confirming their self-association (see the structure schematized in Figure 3).

Formation and Characterization of the Precursor Host–Guest Complex. For the monofunctionalization study, hex-5-yn-1-ammonium ion ($hexynNH_3^+$) was chosen as the ammonium-acetylene guest. The alkyl chain length of this guest was indeed found optimal in the case of the parent Zn^{II}-calix[6]arene-based system,[13] while simple modeling studies showed that the same chain length would fit as well for the calix[6]arene tris-carboxylic derivative. Hence, the ability of $^{N_3}X_6Me_3(COOH)_3$ **4** to complex $hexynNH_3^+$ in presence of $tBuNH_2$ was evaluated by NMR spectroscopy. Upon the addition of an excess of $tBuNH_2$ (ca. 10 equiv) to a 3:1 mixture of hex-5-yn-1-amine hydrochloride and **4** in toluene-d_8,[21] a new C_{3v}-symmetrical calixarene species that displays sharp signals was formed quantitatively (Figure 3b).[22] All signals of this new species have been attributed through 2D NMR spectra (COSY, HSQC),[20] and the following points allowed us to conclude that it corresponds to the desired host–guest complex [$\mathbf{4}^{3-} \supset$ $\mathbf{hexynNH_3^+}$]·2$\mathbf{tBuNH_3^+}$ (Scheme 2):

(i) The intracavity complexation of the $hexynNH_3^+$ ion is clearly attested by the presence of high-field resonances (i.e., below 0 ppm) that belong to the included alkyl chain of this guest. Moreover, the *in–out* exchange of the $hexynNH_3^+$ ion is slow on the NMR time scale, and integration of appropriate

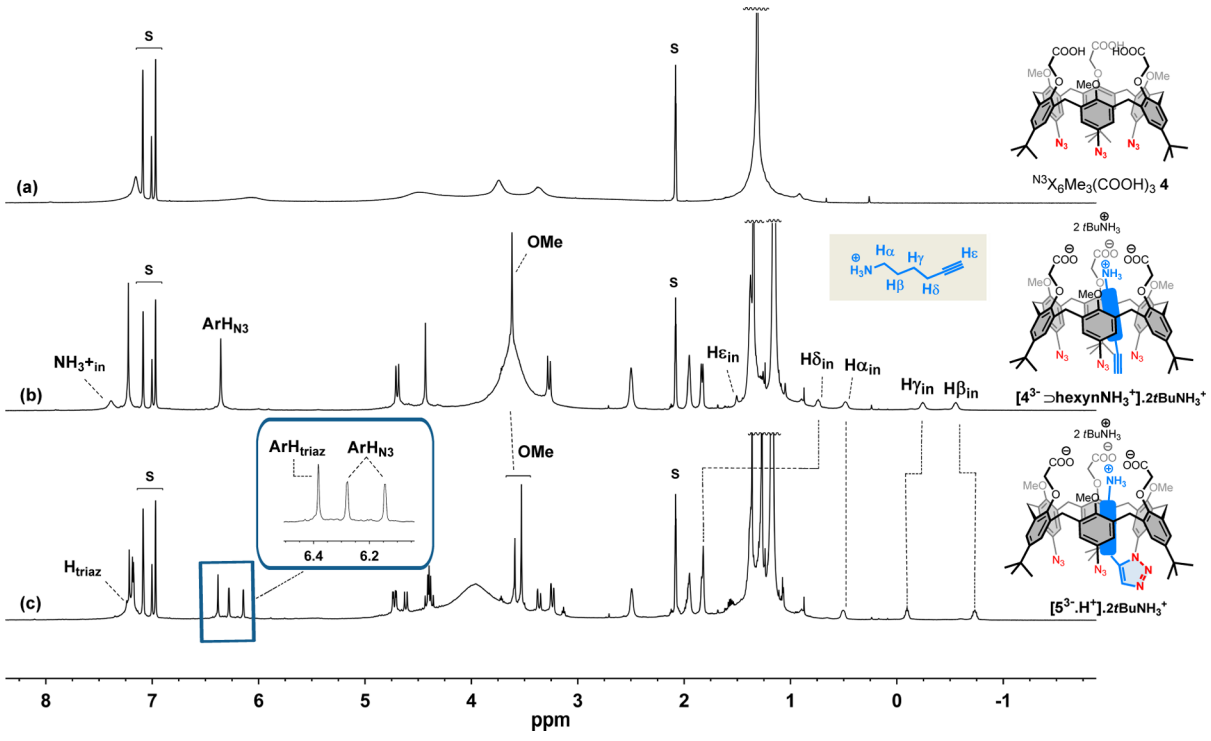
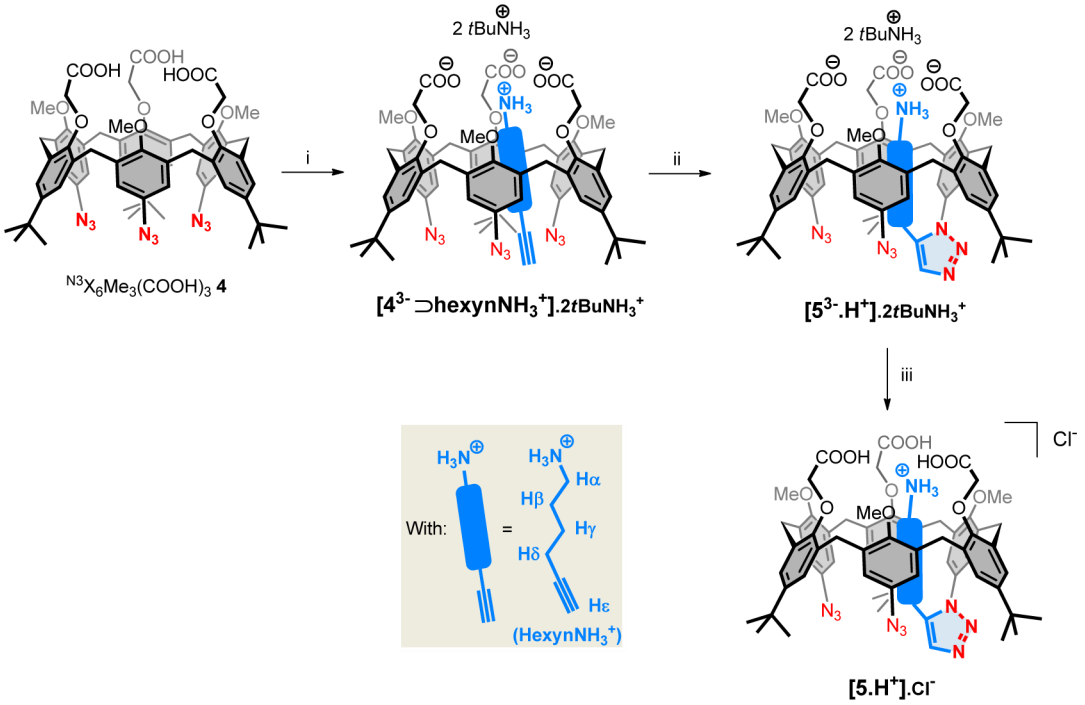


Figure 3. ^1H NMR spectra (298 K, toluene-d_8, 600 MHz) of (a) **4**; (b) **4** after the addition of 10 equiv of $tBuNH_2$ and 3 equiv of hex-5-yn-1-amine hydrochloride; (c) previous mixture after heating at 90 °C for 6 h. S: residual solvent. The methylene groups of the alkyl chain are denoted as Hα, Hβ, Hγ, Hδ, and Hε starting from the NH_3^+ group.

dx.doi.org/10.1021/jo402080d | J. Org. Chem. 2014, 79, 1913–1919

Scheme 2. Synthesis of Monofunctionalized Calix[6]arene [5·H$^+$]·Cl$^-$[a]



[a](i) tBuNH$_2$ (10 equiv), hex-5-yn-1-amine hydrochloride (3 equiv), toluene; (ii) 90 °C, 6 h; (iii) TMAOH (aq) (0.2 M) then HCl (aq) (1 M), 88% overall yield from **4**.

signals indicates a 1:1 host−guest stoichiometry. Similar to what was revealed by a XRD structure of the parent host−guest system (Figure 2),[16a] the hexynNH$_3^+$ ion is likely stabilized into the cavity through ion pairing and H-bonding interactions.

(ii) The signal corresponding to the protons of the included NH$_3^+$ group is observed at 7.39 ppm, which confirms that the guest is protonated when included in the calixarene host.

(iii) The complexation-induced shifts (CIS) indicate a positioning of the cationic guest in the heart of the cavity (see the values displayed in Table 1).

Table 1. ^{1}H NMR Complexation-Induced Shifts (CIS) Determined by ^{1}H NMR Spectroscopy in Toluene-d_8

	CIS[a] (ppm)				
host−guest complex	Hα_{in}	Hβ_{in}	Hγ_{in}	Hδ_{in}	Hε_{in}
[**4**$^{3-}$ ⊃ **hexynNH$_3^+$**]·2***t*BuNH$_3^+$	−2.02	−1.93	−1.62	−1.21	−0.33
[**5**$^{3-}$·**H**$^+$]·2***t*BuNH$_3^+$	−1.99	−2.11	−1.48	−0.13	—

[a]CIS defined as $\Delta\delta = \delta$(complexed amine or ammonium) − δ(free amine or ammonium). The methylene groups of the alkyl chain are denoted as Hα, Hβ, Hγ, Hδ, and Hε starting from the NH$_2$/NH$_3^+$ group. CIS are calculated from δ(free amine or ammonium) in the solution containing the host−guest complex.

(iv) Similar to the parent receptors, no inclusion of tBuNH$_3^+$ is observed even in absence of hexynNH$_3^+$,[20] confirming that this ammonium ion is too bulky to be included in the cavity of **4**.

(v) The resonances of the OMe (δ_{OMe} = 3.62 ppm) and tBu (δ_{tBu} = 1.35 ppm) groups indicate that these groups are pointing away from the cavity and, as a consequence, that the azido groups are oriented toward the inside of the host.

The structure of [**4**$^{3-}$ ⊃ **hexynNH$_3^+$**]·2***t*BuNH$_3^+$ was further corroborated by ROESY spectra recorded at different temperatures, which confirmed the inclusion of the hexynNH$_3^+$ ion and the *exo*-complexation of the tBuNH$_3^+$ ions at the level of the carboxylate arms.[20] The intermolecular NOE correlations also indicated a close proximity between all the methylene groups of the included hexynNH$_3^+$ and the ArH of the azido-substituted anisole units, confirming that the azido groups are directed toward the inside of the cavity. Moreover, no correlation between the included hexynNH$_3^+$ and tBu nor ArH$_{tBu}$ groups could be detected, suggesting that the complex indeed adopts a flattened cone conformation. Finally, the *in*−*out* exchange between the included and free hexynNH$_3^+$ ions was studied by 1D-EXSY experiments. The first-order dissociation rate constant of [**4**$^{3-}$ ⊃ **hexynNH$_3^+$**]·2***t*BuNH$_3^+$ was found to be 14.4 ± 0.8 s^{-1} at 298 K, which corresponds to a residence time of 70 ms.[20]

All these NMR data show the formation of the host−guest complex [**4**$^{3-}$ ⊃ **hexynNH$_3^+$**]·2***t*BuNH$_3^+$ with the tBuNH$_3^+$ ammonium ions shaping the calixarene in a flattened cone conformation and the alkyne function of the cationic guest facing the azido groups of the host. The preorganization of this host−guest precursor is thus ideal for a selective monofunctionalization through a thermal Huisgen cycloaddition.

Synthesis and Characterization of the Selectively Monofunctionalized Calix[6]arene [5·H$^+$]·Cl$^-$. A solution of the precursor [**4**$^{3-}$ ⊃ **hexynNH$_3^+$**]·2***t*BuNH$_3^+$ in toluene-d_8, obtained through the addition of tBuNH$_2$ (10 equiv) and hex-5-yn-1-amine hydrochloride (3 equiv) to **4**, was heated at 90 °C, and the thermal Huisgen cycloaddition reaction was monitored by ^{1}H NMR spectroscopy. About 55% of conversion was achieved after 1 h and 85% after 3 h. After 6 h, the complete disappearance of the signals belonging to the precursor [**4**$^{3-}$ ⊃ **hexynNH$_3^+$**]·2***t*BuNH$_3^+$ was observed together with a new NMR pattern corresponding to the expected calixarene [**5**$^{3-}$·**H**$^+$]·2***t*BuNH$_3^+$ (Figure 3c), which was fully characterized by NMR spectroscopy.[20] Electrospray mass spectroscopy (ESI-MS)

dx.doi.org/10.1021/jo402080d | J. Org. Chem. 2014, 79, 1913−1919

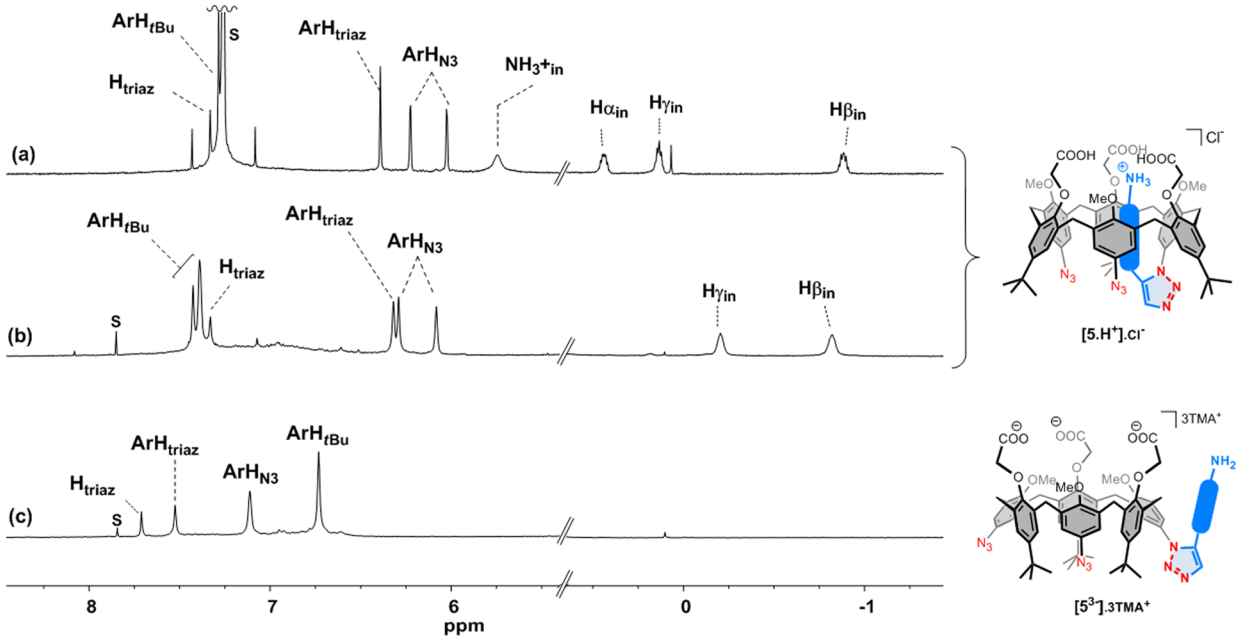


Figure 4. ^{1}H NMR spectra (600 MHz) (a) [**5**·**H**$^+$]·**Cl**$^-$ in $CDCl_3$ at 298 K; (b) [**5**·**H**$^+$]·**Cl**$^-$ in CD_3OD at 323 K; (c) [**5**·**H**$^+$]·**Cl**$^-$ in CD_3OD at 323 K after the addition of 10 equiv of TMAOH in CD_3OD (0.2 M). S: residual solvent. The methylene groups of the alkyl chain are denoted as H*α*, H*β*, H*γ*, H*δ*, and H*ε* starting from the NH_3^+ group.

of the crude reaction mixture showed the selective formation of the monofunctionalized calixarene with a peak (m/z = 1239.9) corresponding to [**5**$^{2-}$·**H**$^+$].[20] Moreover, no signal corresponding to **4** could be detected, confirming that the reaction was indeed complete. Interestingly, when the time of reaction was prolonged (10 h at 90 °C), the monofunctionalized compound [**5**$^{3-}$·**H**$^+$]·**2*t*BuNH$_3^+$** remained the sole product. Moreover, when reacting a sample containing only 3 equiv of *t*BuNH$_2$ and 2 equiv of hex-5-yn-1-amine hydrochloride, a single product (i.e., [**5**$^{3-}$·**H**$^+$]·**2*t*BuNH$_3^+$**) was still obtained in spite of the fact that the intracavity complexation of the hexynNH$_3^+$ ion was not quantitative at 90 °C. This remarkable selectivity is attributable to both the intramolecular nature of the reaction (the intermolecular cyclization is too slow to occur under these experimental conditions) and the "protecting" effect caused by the inclusion of the ammonium arm of the reaction product. Indeed, the favored intracavity complexation of the covalently linked ammonium chain prevents the inclusion of another hexynNH$_3^+$ guest and thus a second thermal Huisgen cycloaddition reaction.

The "ouroboros-like"[23] molecule was isolated under its acidic form [**5**·**H**$^+$]·**Cl**$^-$ in 88% overall yield from **4** (Scheme 2) and was characterized by IR, HRMS, and NMR spectroscopy.[20] First, the presence of an additional singlet (δ_{triaz} = 7.35 ppm) in the aromatic region attested to the formation of the triazole moiety (Figure 4a). New upfield signals corresponding to the methylenic protons of the included ammonium arm were also visible. The integration of these resonances indicated a 1:1 guest/calixarene ratio, which corroborates with a calixarene having a covalently grafted ammonium arm that is included into the cavity. Note that all the ^{1}H NMR signals are well-defined suggesting that the introverted arm rigidifies the calix[6]arene framework. The signal corresponding to the included ammonium group ($\delta_{NH_3^+in}$ = 5.75 ppm) was attributed thanks to a COSY experiment and confirmed the protonation of the arm.[24] The ^{1}H NMR spectrum of [**5**·**H**$^+$]·**Cl**$^-$ also displays a higher number of signals as compared to the starting complex [**4**$^{3-}$ ⊃ **hexynNH$_3^+$**]·**2*t*BuNH$_3^+$**. Indeed, although the OCH_3 and *t*Bu protons both resonate as one singlet in the precursor complex, they are differentiated into two singlets (with 2:1 integration ratios) after reaction. Likewise, the singlet corresponding to the ArH$_{N_3}$ of [**4**$^{3-}$ ⊃ **hexynNH$_3^+$**]·**2*t*BuNH$_3^+$** splits into three signals: one singlet for the ArH$_{triaz}$, and two doublets for the remaining ArH$_{N_3}$ (Figure 4a). These data are consistent with a symmetry decrease from C_{3v} to C_s: the σ_v plane of the C_s symmetrical calix[6]arene species passing through the ArH$_{triaz}$ unit. Again, the resonances of the OMe (δ_{OMe} = 3.89 and 3.79 ppm) and *t*Bu groups (δ_{tBu} = 1.35 and 1.40 ppm) suggest that the calixarene core of [**5**·**H**$^+$]·**Cl**$^-$ adopts a flattened cone conformation with the azido groups and the triazole unit oriented toward the inside of the cavity (see structure displayed in Figure 4). This conformation was confirmed through ROESY spectra, which also showed NOE intramolecular correlations between all the methylene groups of the introverted ammonium arm and the ArH of the azido/triazole-substituted anisole units (i.e., ArH$_{N_3}$ and ArH$_{triaz}$).[20] Interestingly, in contrast to [**4**$^{3-}$ ⊃ **hexynNH$_3^+$**]·**2*t*BuNH$_3^+$**, no EXSY correlation was observed for the upfield resonances of the covalently linked ammonium arm, indicating that its ejection from the cavity is both kinetically and thermodynamically unfavorable. In fact, the intramolecular binding of the ammonium arm is so strong that it also occurs in a protic solvent such as methanol, which usually competes for H-bonding interactions (Figure 4b).[20] Nevertheless, the expulsion of the introverted ammonium arm could be achieved through its deprotonation by a strong base such as tetramethylammonium hydroxide (TMAOH). The in situ addition of 10 equiv of TMAOH in a solution of [**5**·**H**$^+$]·**Cl**$^-$ in CD_3OD indeed led to the dissociation of the inclusion complex as attested by the disappearance of the ^{1}H NMR high-field signals (Figure 4c).[25] The resulting compound [**5**$^{3-}$]·**3TMA**$^+$ constitutes a monofunctionalized calix[6]arene-based receptor that can be further

dx.doi.org/10.1021/jo402080d | *J. Org. Chem.* 2014, 79, 1913−1919

functionalized at the level of the azido groups or easily grafted onto a surface via the amino arm.

CONCLUSION

The monofunctionalization methodology, which was initially developed on the *funnel* Zn complex system, has been successfully applied to the tris-carboxylic calix[6]arene host–guest system. This work shows that the methodology can be extended to a host–guest system involving another type of primary interactions (metal ligand vs ionic/H-bonding). Thus, we do believe that the methodology is very general and should be transferable to other kinds of recognition patterns and other cavitands (e.g., cyclodextrines, resorcinarenes, pillararenes, etc.). It is noteworthy that such covalent capture strategy has been recently applied in bioconjugation, using metal–ligand interactions for the synthesis of a carbonic anhydrase II mutant.[26] Finally, using the methodology several times with different alkyne substrates should ultimately lead to the synthesis of calix[6]arene tris-carboxylic acid-based receptors presenting an ABC pattern at the large rim, thus of inherent chirality.[27] This opens new perspectives in the recognition of chiral ammonium ions of biological interest (e.g., amino acids, neurotransmitters).

EXPERIMENTAL SECTION

General Experimental Methods. All the reactions were performed under an Ar atmosphere. Solvents were dried by conventional methods and distilled prior to use. All the organic layers were dried by filtration through a hydrophobic phase separation paper. ^{1}H spectra were recorded at 400 or 600 MHz. ^{13}C NMR spectra were recorded at 100 MHz. 2D NMR spectra (COSY, HSQC, HMBC, ROESY) were recorded to complete signal assignments. ^{1}H NMR spectra were referenced to residual protiated solvents (2.08 ppm (δ_{Me}) for toluene-d_8, 7.26 ppm for $CDCl_3$, 3.31 ppm (δ_{Me}) for CD_3OD). High resolution mass spectra (HRMS) were obtained with a QTOF spectrometer. Hex-5-yn-1-amine hydrochloride salt was prepared according to a literature procedure.[28]

^{NO_2}X$_6$Me$_3$(COOH)$_3$ 2. To a stirred solution of X$_6$Me$_3$(COOH)$_3$ **1** (0.902 g, 0.76 mmol) in dichloromethane (75 mL) at 0 °C was slowly added a mixture of HNO_3/AcOH (9 mL, 1:1, v/v). The reaction mixture turned to orange/red in color and was stirred for 1 h at 0 °C, after which time dichloromethane (90 mL) was added. The resulting mixture was washed with water (2 × 20 mL). The organic extracts were dried and concentrated under reduced pressure to give ^{NO_2}X$_6$Me$_3$(COOH)$_3$ **2** (0.876 g, 0.76 mmol, quant.) as a yellow solid whose ^{1}H NMR spectrum is identical to that reported in the literature.

^{N_3}X$_6$Me$_3$(COOH)$_3$ 4. K_2CO_3 (0.105 g, 0.76 mmol) and $Na_2S_2O_4$ (0.780 g, 4.48 mmol) were added to a suspension of ^{NO_2}X$_6$Me$_3$(COOH)$_3$ **2** (0.151 g, 0.13 mmol) in a mixture of EtOH (4 mL) and H_2O (2 mL). The reaction mixture was heated to reflux for 72 h. The solvents were evaporated under reduced pressure, and the resulting residue was taken up with water (100 mL). The aqueous layer was acidified with a 2 M HCl solution (until pH = 1) and was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were concentrated under reduced pressure to yield $^{NH_3^+}$X$_6$Me$_3$(COOH)$_3$ **3** (0.166 g), which was used in the next step without further purification. To a stirred solution of $^{NH_3^+}$X$_6$Me$_3$(COOH)$_3$ **3** (0.166 g) in 10% HCl (60 mL) at 0 °C was added $NaNO_2$ (0.038 g, 0.054 mmol). After 20 min, a solution of sodium azide (0.038 g, 0.059 mmol) in water (2 mL) was added dropwise. The reaction mixture was further stirred for 3 h at 0 °C. The aqueous layer was extracted with dichloromethane (3 × 50 mL), and the combined organic layers were washed with water (2 × 30 mL), dried, and evaporated, affording ^{N_3}X$_6$Me$_3$(COOH)$_3$ **4** (0.140 g, 0.12 mmol, 91% overall from **2**) as a beige solid: mp 140–141 °C (dec.); IR (KBr) ν = 3448, 2961, 2111, 1600 cm^{-1}; ^{1}H NMR (600 MHz, toluene-d_8, 363 K) δ 7.17 (s, 6H, ArH_{tBu}), 6.05 (s, 6H, ArH_{N_3}), 4.55 (bs, 6H, ArCH_2^{ax}), 3.98 (bs, 6H, OCH_2), 3.75 (s, 9H, OCH_3), 3.39 (bs, 6H, ArCH_2^{eq}), 1.32 (s, 27H, *t*Bu) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ 173.5, 153.4, 152.5, 147.8, 135.6, 135.5, 132.5, 128.4, 117.1, 70.0, 60.5, 34.4, 31.6, 30.7 ppm; HRMS (ESI–) calcd for $C_{63}H_{68}N_9O_{12}$ [**4**$^-$] 1142.4987, found 1149.4977.

[5·H$^+$]·Cl$^-$. *t*BuNH$_2$ (46 μL, 0.44 mmol) and hex-5-yn-1-amine hydrochloride (0.018 g, 0.13 mmol) were added to a solution of ^{N_3}X$_6$Me$_3$(COOH)$_3$ **4** (0.050 g, 0.044 mmol) in toluene (2.5 mL). The resulting mixture was heated to 90 °C for 6 h. The calixarene species was then extracted from the reaction mixture into a 0.2 M aqueous TMAOH solution (3 × 1.5 mL), and the combined alkaline aqueous phases were acidified with a 1 M HCl solution (until pH = 1). The acidified aqueous layer was extracted with $CHCl_3$ (3 × 3 mL), and the combined organic layers were dried and concentrated under reduced pressure yielding [**5**·**H**$^+$]·**Cl**$^-$ (0.048 g, 0.039 mmol, 88%) as an orange/brown solid: mp 156–158 °C (dec.); IR (KBr) ν = 2961, 2111, 1740, 1596 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.35 (s, 1H, H_{triaz}), 7.29 (s, 2H, ArH_{tBu}), 7.28/7.24 (m, 4H, ArH_{tBu}), 6.39 (s, 2H, ArH_{triaz}), 6.23 (d, 2H, ArH_{N_3}, J = 2.2 Hz), 6.03 (d, 2H, ArH_{N_3}, J = 2.2 Hz), 5.75 (bs, 3H, $[NH_3^+]_{in}$), 4.78 (d, 2H, OCH_2, J = 15.6 Hz), 4.66 (s, 2H, OCH_2), 4.61 (d, 2H, ArCH_2^{ax}, J = 16.2 Hz), 4.60 (d, 2H, ArCH_2^{ax}, J = 16.2 Hz), 4.54 (d, 2H, OCH_2, J = 15.6 Hz), 4.49 (d, 2H, ArCH_2^{ax}, J = 16.2 Hz), 3.89 (s, 3H, OCH_3), 3.79 (s, 6H, OCH_3), 3.60 (d, 2H, ArCH_2^{eq}, J = 16.2 Hz), 3.47 (d, 2H, ArCH_2^{eq}, J = 16.2 Hz), 3.45 (d, 2H, ArCH_2^{eq}, J = 16.2 Hz), 1.78 (t, 2H, $[CH_2(\delta)]_{in}$, J = 7.0 Hz), 1.40 (s, 9H, *t*Bu), 1.35 (s, 18H, *t*Bu), 0.48/0.40 (m, 2H, $[CH_2(\alpha)]_{in}$), 0.13 (q, 2H, J = 7.0 Hz, $[CH_2(\gamma)]_{in}$), −0.84/-0.91 (m, 2H, $[CH_2(\beta)]_{in}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 298 K) δ 173.3, 173.1, 156.5, 153.4, 152.8, 152.2, 148.4/147.0, 137.8, 136.2, 136.1, 135.6, 135.3, 132.5, 132.3, 132.2, 131.5, 129.5, 129.0, 123.9, 117.3, 116.3, 72.3/69.7, 61.6/60.0, 38.0, 34.5, 32.5/30.8, 29.4, 27.9, 25.8, 25.0, 22.8, 20.0, 14.3 ppm; HRMS (ESI+) calcd for $C_{69}H_{81}N_{10}O_{12}$ [**5**·**H**$^+$] 1241.6035, found 1241.6023.

ASSOCIATED CONTENT

Supporting Information

1D, 2D NMR and IR spectra of the new compounds as well as the procedure for the determination of the residence time of the hexynNH$_3^+$ ion. These materials are available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: mluhmer@ulb.ac.be.

*E-mail: benoit.colasson@parisdescartes.fr.

*E-mail: ijabin@ulb.ac.be.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

A. Inthasot is a Ph.D. student granted by the Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture (FRIA-FRS, Belgium). This research was supported by the Fonds de la recherche scientifique-FNRS (FRFC 2.4.617.10.F project), the COST Action 1005 "Supramolecular Chemistry in Water", the Agence Nationale de la Recherche (ANR10-BLAN-714 Cavity-zyme(Cu) project), and the Université Libre de Bruxelles (ULB).

REFERENCES

(1) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.

(2) (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821–1823. (b) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440. (c) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320–2322.

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

(4) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743–1753.

(5) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844−4870.
(6) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663−2704.
(7) (a) Ogoshi, T.; Yamagishi, T. *Eur. J. Org. Chem.* **2013**, *2013*, 2961−2975. (b) Ogoshi, T.; Kunai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5022−5023. (c) Xue, M.; Yang, Y.; Chi, X.; Zhang, Z.; Huang, F. *Acc. Chem. Res.* **2012**, *45*, 1294−1308.
(8) (a) Gutsche, C. D. In *Calixarenes: An Introduction, Monographs in Supramolecular Chemistry*, 2nd ed.; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 2008. (b) Gutsche, C. D. In *Calixarenes Revisited, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998.
(9) (a) Ornelas, C.; Pennell, R.; Liebes, L. F.; Weck, M. *Org. Lett.* **2011**, *13*, 976−979. (b) Ludden, M. J. W.; Reinhoudt, D. N.; Huskens, J. *Chem. Soc. Rev.* **2006**, *35*, 1122−1134. (c) Baldini, L.; Casnati, A.; Sansone, F.; Ungaro, R. *Chem. Soc. Rev.* **2007**, *36*, 254−266. (d) Badjic', J. D.; Nelson, A.; Cantrill, S. J.; Turnbull, W. B.; Stoddart, J. F. *Acc. Chem. Res.* **2005**, *38*, 723−732.
(10) (a) *Supramolecular Catalysis*; Van Leeuwen, P. W. N. M., Ed.; Wiley-VCH: Weinheim, 2008. (b) *Modern Supramolecular Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2008. (c) Vriezema, D. M.; Cormelass Aragonés, M.; Elemans, J. A. A. W.; Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105*, 1445−1489.
(11) (a) Gamez, P.; Reedijk, J. *Eur. J. Inorg. Chem.* **2006**, *2006*, 29−42. (b) Baker, M. B.; Ghiviriga, I.; Castellano, R. K. *Chem. Sci.* **2012**, *3*, 1095−1099. (c) Lehmann, M. *Chem.—Eur. J.* **2009**, *15*, 3638−3651. (d) Lehmann, M.; Jahr, M. *Chem. Mater.* **2008**, *20*, 5453−5456. (e) Rivera, D. G.; Wessjohann, L. A. *J. Am. Chem. Soc.* **2009**, *131*, 3721−3732.
(12) (a) Darbost, U.; Zeng, X.; Giorgi, M.; Jabin, I. *J. Org. Chem.* **2005**, *70*, 10552−10560. (b) Le Gac, S.; Marrot, J.; Jabin, I. *Chem.—Eur. J.* **2008**, *14*, 3316−3322. (c) Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Freriks, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R.; Nieto, P. M.; Carramolino, M.; Cuevas, F.; Prados, P.; De Mendoza, J. *Synthesis* **1993**, *1993*, 380−386. (d) Slavik, P.; Dudic, M.; Flidrova, K.; Sykora, J.; Cisarova, I.; Bohm, S.; Lhotak, P. *Org. Lett.* **2012**, *14*, 3628−3631. (e) Itzhak, N.; Biali, S. E. *J. Org. Chem.* **2010**, *75*, 3437−3442. (f) Jouffroy, M.; Armspach, D.; Matt, D.; Toupet, L. *Org. Biomol. Chem.* **2013**, *11*, 3699−3705. (g) Narumi, F.; Morohashi, N.; Matsumura, N.; Nobuhiko, I.; Kameyama, H.; Miyano, S. *Tetrahedron Lett.* **2002**, *43*, 621−625. (h) Galli, M.; Berrocal, J. A.; Di Stefano, S.; Cacciapaglia, R.; Mandolini, L.; Baldini, L.; Casnati, A.; Ugozzoli, F. *Org. Biomol. Chem.* **2012**, *10*, 5109−5112. (i) Gomez-Biagi, R.; Nitz, M. *Chem. Commun.* **2011**, *47*, 8614−8616. (j) Renslo, A.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 3281−3283. (k) Bistri, O.; Sinaÿ, P.; Sollogoub, M. *Chem. Commun.* **2006**, 1112−1114.
(13) (a) Colasson, B.; Reinaud, O. *J. Am. Chem. Soc.* **2008**, *130*, 15226−15227. (b) Menard, N.; Reinaud, O.; Colasson, B. *Chem.—Eur. J.* **2013**, *19*, 642−653. (c) Menard, N.; Hériot, Y.; Le Mest, Y.; Reinaud, O.; Le Poul, N.; Colasson, B. *Chem.—Eur. J.* **2013**, *19*, 10611−10618.
(14) Colasson, B.; Save, M.; Milko, P.; Roithová, J.; Schröder, D.; Reinaud, O. *Org. Lett.* **2007**, *9*, 4987−4990.
(15) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565−598.
(16) (a) Le Gac, S.; Giorgi, M.; Jabin, I. *Supramol. Chem.* **2007**, *19*, 185−197. (b) Le Gac, S.; Picron, J.-F.; Reinaud, O.; Jabin, I. *Org. Biomol. Chem.* **2011**, *9*, 2387−2396. (c) Le Gac, S.; Marrot, J.; Reinaud, O.; Jabin, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 3123−3126.
(17) Arduini, A.; Casnati, A. In *Macrocycle Synthesis: A Practical Approach, Pracical Approach in Chemistry*; Parker, D., Ed.; Oxford University Press: Oxford, 1996.
(18) Castani, A.; Minari, P.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1413−1414.
(19) (a) Redon, S.; Li, Y.; Reinaud, O. *J. Org. Chem.* **2003**, *68*, 7004−7008. (b) Lejeune, M.; Picron, J.-F.; Mattiuzzi, A.; Lascaux, A.; De Cesco, S.; Brugnara, A.; Thiabaud, G.; Darbost, U.; Coquière, D.; Colasson, B.; Reinaud, O.; Jabin, I. *J. Org. Chem.* **2012**, *77*, 3838−3845.
(20) See the Supporting Information.
(21) A 3:1 mixture of hex-5-yn-1-amine hydrochloride and **4** was used since this host−guest stoichiometry was reported as optimal in the case of the parent Zn^{II}-calixarene-based system.
(22) Note that quasi-exclusive formation of this new species was also observed with different stoichiometric amounts of tBuNH$_2$ and hex-5-yn-1-amine hydrochloride (e.g., 3 equiv of tBuNH$_2$ and 2 equiv of hex-5-yn-1-amine hydrochloride).
(23) Ouroboros ("tail-eater" in Greek) is an ancient symbol representing a serpent swallowing its own tail; see: (a) Durola, F.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2010**, *49*, 3189−3191. (b) Nygaard, S.; Liu, Y.; Stein, P. C.; Flood, A. H.; Jeppesen, J. O. *Adv. Funct. Mater.* **2007**, *17*, 751−762. (c) Enmi, Y.; Kobayashi, K.; Konishi, H.; Morimoto, M. *Tetrahedron Lett.* **2011**, *52*, 3367−3370.
(24) It is noteworthy that the recognition of ammonium ions by the parent tris-carboxylic calix[6]arene derivatives **1** or **2** under their acidic form was also observed. The corresponding host−guest complexes are however less stable because of the absence of ionic interactions.
(25) Note that this process is reversible since the subsequent addition of a strong acid (i.e., picric acid) restored the inclusion complex.
(26) Wischeler, J. S.; Sun, D.; Sandner, N. U.; Linne, U.; Heine, A.; Koert, U.; Klebe, G. *Chem.—Eur. J.* **2011**, *17*, 5842−5851.
(27) (a) Böhmer, V.; Kraft, D.; Tabatabai, M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 17−39. (b) Szumna, A. *Chem. Soc. Rev.* **2010**, *39*, 4274−4285.
(28) Saito, Y.; Matsumoto, K.; Bag, S. S.; Ogasawara, S.; Fujimoto, K.; Hanawa, K.; Saito, I. *Tetrahedron* **2008**, *64*, 3578−3588.