JOC The Journal of Organic Chemistry

Article

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Supramolecular Assistance for the Selective Demethylation of Calixarene-Based Receptors

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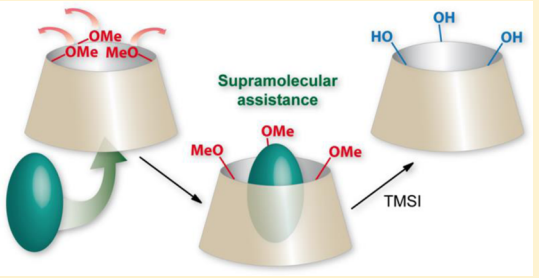
Supporting Information

ABSTRACT: The selective demethylation of methoxy groups of several multifunctionalized 1,3,5-trimethoxycalix[6]arene-based receptors has been achieved. It is shown in this study that the best reagent is trimethylsilyl iodide (TMSI) and that the conformation adopted by the calixarene core is crucial for both the selectivity and the efficiency of the process. A key feature appears to be the "in" or "out" orientation of the methoxy substituents relative to the macrocyclic cavity. If projected inward, the reaction is slow and not selective. If projected outward, the reaction is fast and selective. A strategy that consists of exploiting the host–guest properties of the receptors to change their conformation and to permit their selective demethylation has been developed. Four cases of such a supramolecular assistance are reported, demonstrating the efficiency of the strategy. Such an allosteric control is highly reminiscent of biological processes allowing selective transformation of multifunctional molecules.



INTRODUCTION

Concave macrocyclic scaffolds such as calixarenes,[1] cyclodextrins,[2] cucurbiturils,[3] resorcinarenes,[4] or pillararenes[5] are extensively exploited for the design of molecular receptors. Their selective functionalization is key either for appending a specific molecular recognition site, or the introduction of reporting, sensing, chiral, or water-soluble subunits, or for their grafting on solid materials. However, selective and efficient functionalization of macrocyclic multifunctional platforms is highly challenging.[6] Indeed, control of the chemo-, regio-, stereo-, and iteroselectivity[7] is required. Problems related to conformational behavior need also to be mastered as a reduced reactivity can be observed when a functional group is buried into a cavity.[8]

Among the various macrocyclic platforms that can be used for the construction of molecular receptors, calix[6]arenes are particularly attractive. Indeed, their cavity size is well adapted for the selective inclusion of organic molecules, and various synthetic strategies enabling their chemical modification have been described.[9] In this context, our groups have developed different families of C_{3v}-symmetrical receptors based on the calix[6]arene platform, where three out of the six phenolic functions have been protected by methyl groups in alternate positions[10] (Figure 1). These receptors display remarkably polyvalent host–guest properties and are capable of recognizing metal ions (**3**, **5**, and **6**), anions (**1**, **2**, and **3**), contact ion pairs (**1**, **2**, and **4**), or neutral molecules (**1**–**6**).[11] Recently, water-soluble or graftable derivatives of these receptors were obtained through their functionalization at the level of the large rim or of the trisaza cap.[12] However, these strategies require multistep syntheses. A simple alternative lies in the demethylation of the protecting methoxy groups of the anisole units and the subsequent introduction of functional arms on the resulting phenol moieties. However, such a strategy requires the demethylation reaction to proceed selectively, without cleavage of the ether bonds linking other groups at the small rim.

Several reagents are known to cleave methyl ethers of aromatic residues. Those most often used are BBr_3,[13] trimethylsilyl iodide (TMSI),[14] LiI,[15] $LiPPh_2$,[16] $BeCl_2$,[17] $AlBr_3$/NaI,[18] thiolates,[19] pyridine–HCl,[20] and HI.[21] Selective dealkylation of methoxy groups vs more sterically encumbered alkoxy substituents has been reported notably with $LiPPh_2$,[22] TMSI,[14] and sodium ethanethiolate.[23] Surprisingly, only one

Received: March 1, 2015
Published: April 15, 2015

DOI: 10.1021/acs.joc.5b00464
J. Org. Chem. 2015, 80, 5084–5091

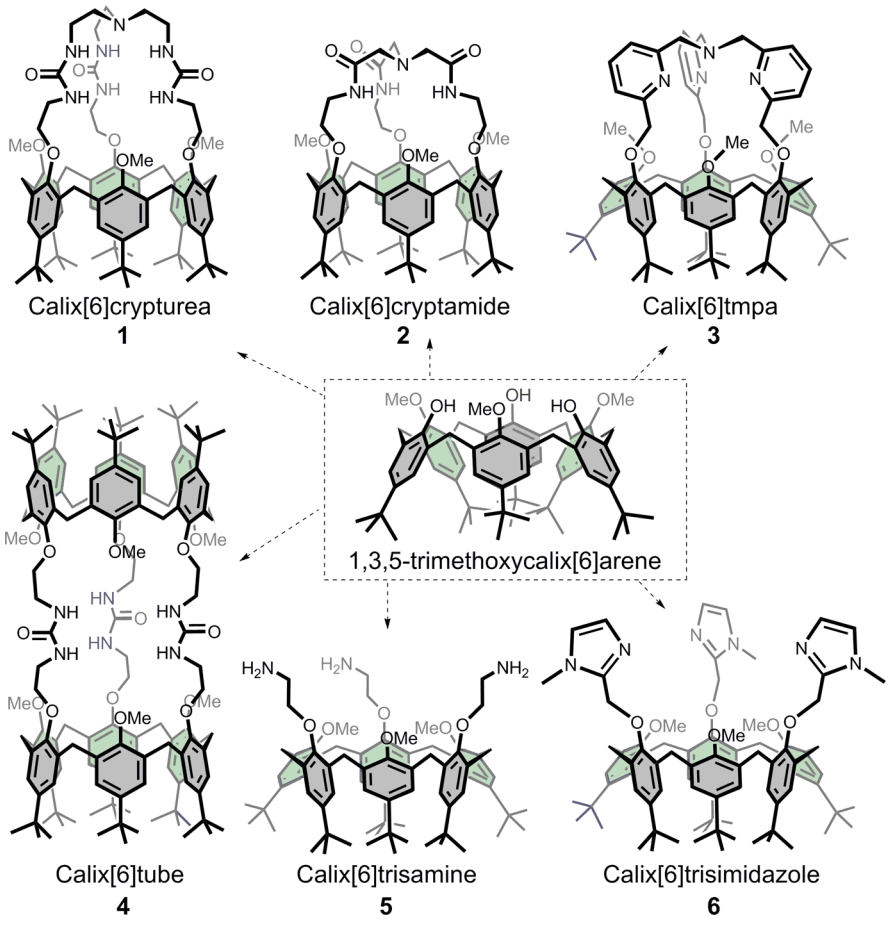


Figure 1. Various molecular receptors synthesized from the C_{3v} 1,3,5-trimethoxycalix[6]arene.

Table 1. Comparative Reactivity of Calix[6]crypturea 1 toward Various Dealkylating Reagents in View of the Selective Formation of Trisdemethylated Calix[6]crypturea 1^{-3Me} [a]

entry	demethylating agent	solvent	guest	$1{:}1^{-1Me}{:}1^{-2Me}{:}1^{-3Me}$ ratio[b]	byproduct[c]	yield[d] (%)
1	$LiPPh_2$	THF		100:0:0:0	nd[e]	
2	TMSI	$CHCl_3$		8:15:0:77	yes	
3	TMSCl, NaI	$CHCl_3/CH_3CN$ (1:1)		72:28:0:0	nd[e]	
4	TMSI	$CHCl_3$	Imi	0:0:0:100	trace	95[f]
5	TMSI	$CHCl_3$	Imi(cat)[g]	25:45:0:30	trace	
6	$LiPPh_2$	THF	Imi	100:0:0:0	nd[e]	
7	BBr_3	$CHCl_3$	Imi	50:21:19:0	nd[e]	
8	HI	$CHCl_3$	Imi	83:17:0:0	nd[e]	

[a]All reactions were run at 50 °C for 5 h except in the case of BBr_3, for which the reaction was run at −78 °C and then rt. The concentration of starting compound **1** was 3.7 mM. A 6 equiv portion of BBr_3, 15 equiv of the other demethylating agents [i.e., TMSI, $LiPPh_2$ (0.5 M in THF), or TMSCl/NaI], and 1.1 equiv of imidazolidin-2-one (Imi) were used. [b]Determined by ESI-MS analysis of the reaction mixture. [c]In some cases, the ESI-MS analyses displayed an ion (m/z = 1454) corresponding to the byproduct that results from the nucleophilic attack of iodide on the methylene linker of one urea arm of 1^{-3Me} (see the Supporting Information). [d]Calculated after flash chromatography purification. [e]Not detected. [f]This yield was obtained when the reaction was stopped after 2 h. [g]In this case, only 0.1 equiv of Imi was used.

example of selective demethylation of a calix[6]arene derivative was reported in the literature.[24] In this work, TMSI in chloroform was used to selectively remove all methyl groups out of a 1,3,5-trimethoxy-2,4,6-tris(alkylamido)calix[6]arene. Interestingly, the authors mentioned that the presence of Na^+ was mandatory for the reaction to be selective.

Here, we report a study aimed at developing a reliable procedure for the selective demethylation of calix[6]arene-based receptors. We show that supramolecular assistance (SA) using the recognition properties of the macrocyclic receptors is in all but one case necessary for the reaction to proceed selectively and with high yields.

RESULTS AND DISCUSSION

Calix[6]arenes **1**−**6** were synthesized from the 1,3,5-trimethoxy derivative according to previously published procedures (Figure 1).[25] As shown by ^{1}H NMR spectroscopy, these hosts display different conformational and recognition properties. In particular, the significantly high-field-shifted resonance of their OMe groups in $CDCl_3$ clearly shows that these groups

DOI: 10.1021/acs.joc.5b00464
J. Org. Chem. 2015, 80, 5084−5091

are either partially (in the case of **1**, **2**, **4**, and **5**, for which 2.69 ppm < δ_{OMe} < 3.07 ppm) or fully (in the case of **6**, for which δ_{OMe} = 2.14 ppm) self-included into the cavity.[26] In strong contrast, compound **3** adopts a conformation with the methoxy groups pointing toward the outside of the cavity, as shown by XRD and NMR analyses.[25c] Such a different behavior was attributed to the rigid 2-tris(pyridylmethyl)amino (tmpa) cap that forces the calixarene to adopt a conformation with introverted OCH_2 linkers (see the structure schematized in Figure 1). In this particular case, the high-field-shifted resonance of the OMe groups (δ_{OMe} = 2.53 ppm) is due to the anisotropic ring current from the pyridine units of the tmpa cap.

The reaction conditions for the demethylation reaction were first tested and optimized with calix[6]crypturea **1**. The reactions were run in $CHCl_3$, $CHCl_3/CH_3CN$ (1:1), or THF[27] at 50 °C, and the ratio of **1** and mono-, bis-, and trisdemethylated products (i.e., $\mathbf{1}^{-Me}$, $\mathbf{1}^{-2Me}$, and $\mathbf{1}^{-3Me}$, respectively) was monitored by ESI mass spectrometry (ESI-MS) analysis of the reaction mixture. First, no trace of demethylated products could be detected when $LiPPh_2$ was used (Table 1, entry 1). In contrast, the use of TMSI in $CHCl_3$ led to the expected trisdemethylated product $\mathbf{1}^{-3Me}$ after 5 h. However, the presence of starting material **1**, intermediate $\mathbf{1}^{-1Me}$, and a byproduct that results from the cleavage of one urea arm of $\mathbf{1}^{-3Me}$ was also detected (Table 1, entry 2) (see the Supporting Information). Prolonged reaction (16 h) led to a significant increase of byproduct formation. An attempt to produce TMSI in situ, i.e., through the addition of TMSCl and NaI, only led to partial demethylation of **1** after 5 h (Table 1, entry 3). Reasoning that the inefficiency of $LiPPh_2$ and the slow and nonselective reaction with TMSI are related to the steric hindrance around the methoxy groups, we thought of exploiting the host–guest properties of **1** to change its conformation. Indeed, we have reported previously that calix[6]crypturea **1** dissolved in chloroform binds residual water at the level of the crypturea cap through H-bonding interactions. It was shown by NMR spectroscopy that the corresponding complex $\mathbf{1}\supset H_2O$[28] has OMe groups oriented toward the inside of the cavity. An optimized structure of $\mathbf{1}\supset H_2O$ obtained through computer modeling[29] confirms the inclusion of these methoxy groups and clearly shows that such introverted groups cannot be reactive toward dealkylating agents (Figure 2, top). However, it was also shown that **1** strongly binds imidazolidin-2-one (Imi) in chloroform (log K > 3) through complementary H-bonding interactions, and as indicated by NMR spectroscopy, the resulting host–guest complex **1**⊃Imi adopts a flattened cone conformation with the OMe groups expelled from the cavity (δ_{OMe} = 3.84 ppm) (Scheme 1).[30] The optimized structure of **1**⊃Imi[29] shows that the methoxy groups are indeed projected away from the cone, hence now being accessible to a dealkylating reagent (Figure 2, bottom). Therefore, to facilitate the selective cleavage of the OMe groups, the impact of the presence of a guest that can fill the cavity (i.e., Imi) in the reaction mixture was evaluated. Quite remarkably, when Imi (1.1 equiv) and TMSI (15 equiv) were added consecutively, $\mathbf{1}^{-3Me}$ was produced quasi-exclusively (Table 1, entry 4). These optimized conditions allowed the efficient synthesis of $\mathbf{1}^{-3Me}$ in high yield (95%) after purification by flash chromatography (FC) on silica gel (Scheme 1). This remarkable result validates the strategy that consists of using supramolecular assistance:[31] the formation of a host–guest complex, which drives the substrate to adopt a specific conformation and orients the

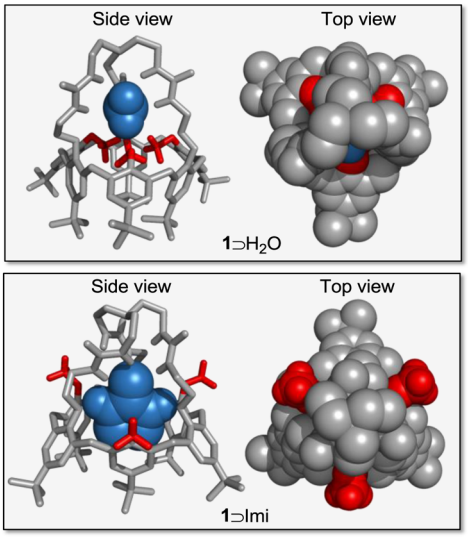
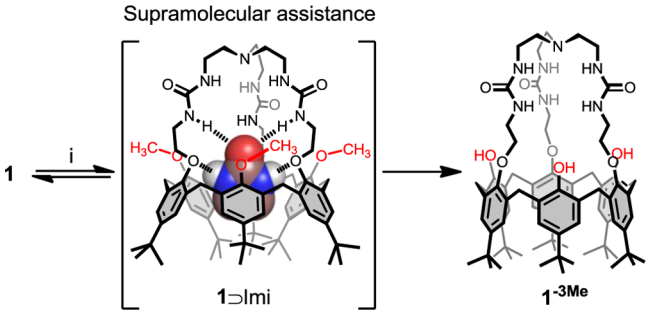


Figure 2. Energy-minimized structures in stick representation (side view) and space-filling representation (top view) of (top) $\mathbf{1}\supset H_2O$ and (bottom) **1**⊃Imi. Hydrogen atoms (except those of water, those of the urea, and those of the OMe groups) have been omitted for clarity.

Scheme 1. Synthesis of $\mathbf{1}^{-3Me}$ from 1 Thanks to Supramolecular Assistance[a]



[a]Reagents and conditions: (i) TMSI (15 equiv), Imi (1.1 equiv), $CHCl_3$(anhyd), 50 °C, 2 h, 95%. Dashed bonds represent H-bonding interactions between the host and its guest.

selectivity of the reaction. In other words, the guest can be considered as an allosteric activator that triggers the demethylation reaction of the calixarene-based receptor. It is noteworthy that, in good accordance with the above results, a much slower demethylation process was observed when the reaction was conducted in the presence of a catalytic amount of Imi (0.1 equiv) (Table 1, entry 5). Finally, the use of Imi in combination with other demethylating agents ($LiPPh_2$, BBr_3, HI) did not lead to the expected product $\mathbf{1}^{-3Me}$ (Table 1, entries 6–8), showing that TMSI is the reagent of choice for such a selective demethylation procedure.

The structure of $\mathbf{1}^{-3Me}$ was confirmed by 1D and 2D NMR analyses. In particular, the ^1H NMR spectrum of $\mathbf{1}^{-3Me}$ in $CDCl_3$ shows the absence of OCH_3 resonance and the presence of a broad signal at 7.14 ppm corresponding to the ArO*H* protons.[32] The overall NMR signature is characteristic of a C_{3v}-symmetrical calix[6]arene that adopts an averaged straight conformation ($\Delta\delta_{tBu}$ = 0.03 ppm) (Figure 3a). Quite remarkably, when 1.3 equiv of 3,4-*O*-dimethyldopammonium chloride ($Me_2DopaH^+Cl^-$) was added to a solution of $\mathbf{1}^{-3Me}$ in $CDCl_3$, the ternary host–guest complex $\mathbf{1}^{-3Me}\supset Me_2DopaH^+Cl^-$ was quantitatively obtained (Figure

DOI: 10.1021/acs.joc.5b00464
J. Org. Chem. 2015, 80, 5084–5091

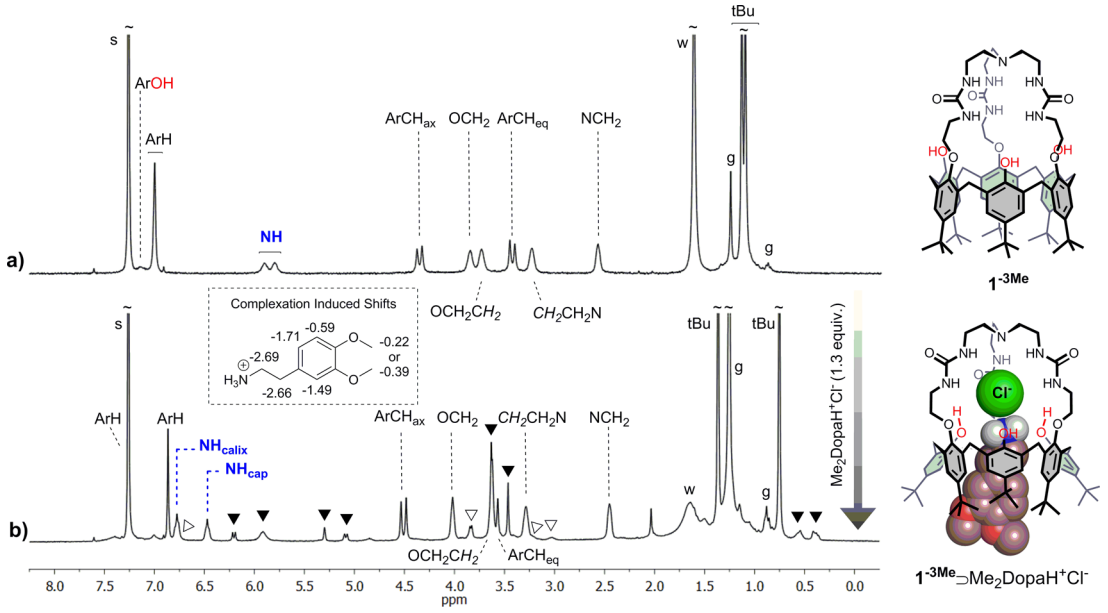
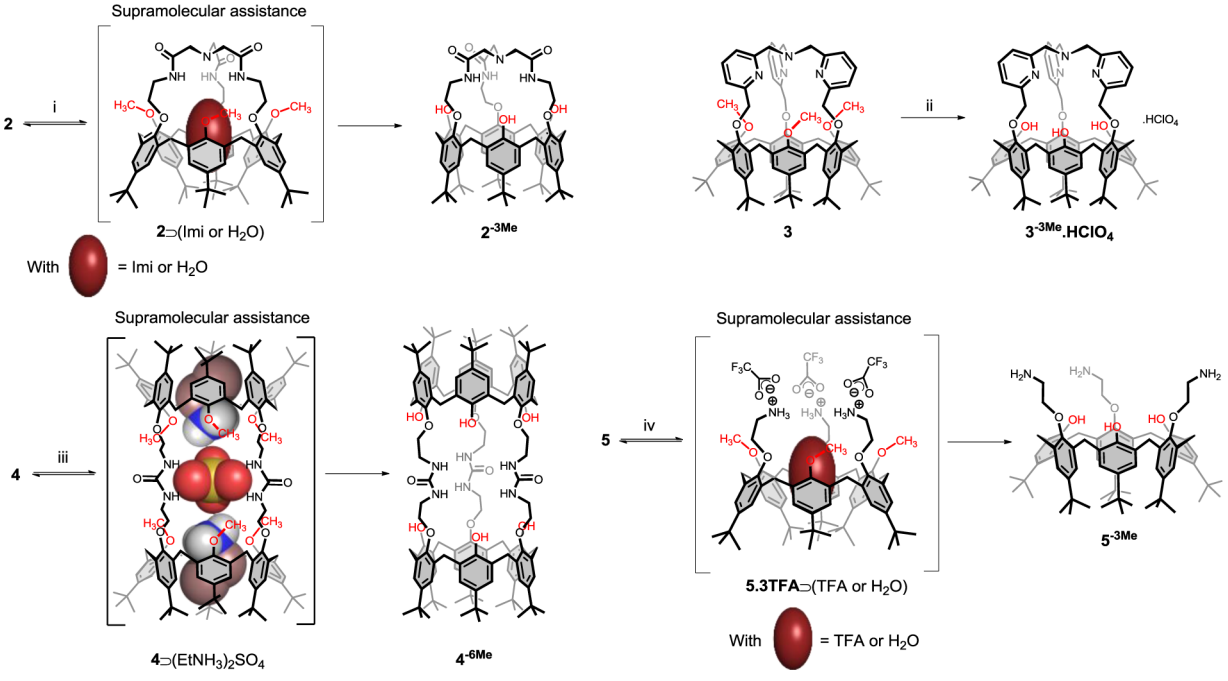


Figure 3. ^{1}H NMR spectra ($CDCl_3$, 298 K) of (a) $\mathbf{1}^{-3Me}$ and (b) $\mathbf{1}^{-3Me}$ after the addition of 1.3 equiv of Me_2DopaH^+: ▼, Me_2DopaH^+ (in); ▽, Me_2DopaH^+ (free); s, residual solvent; w, water; g, residual grease. Inset: CISs of the ammonium ion.

Scheme 2. Synthesis of $\mathbf{2}^{-3Me}$, $\mathbf{3}^{-3Me}$, $\mathbf{4}^{-6Me}$, and $\mathbf{5}^{-3Me}$ in $CHCl_3$(anhyd) at 50 °C[a]



[a]Reagents and conditions: (i) TMSI (15 equiv), Imi (1.1 equiv), $CHCl_3$(anhyd), 50 °C, 18 h, 61%; (ii) TMSI (15 equiv), $CHCl_3$(anhyd), 50 °C, 1 h, then $HClO_4$ (1 M), 81%; (iii) TMSI (27 equiv), $(EtNH_3)_2SO_4$ (1.25 equiv), $CHCl_3$(anhyd), 50 °C, 72 h, 89%; (iv) TMSI (15 equiv), TFA (10 equiv), $CHCl_3$(anhyd), 50 °C, 24 h, 63%.

3b). The association constant for this complex was too high to be determined accurately by NMR spectroscopy but was estimated to be log K > 4.4. The complexation-induced shifts (CISs) of the ammonium ion (Me_2DopaH^+) are indicative of its intracavity complexation (inset, Figure 3b), and the significant downfield shifts of the NH urea protons (δ_{NH} = 6.47 and 6.78 ppm) are characteristic of H-bonding interactions with the cobound anion.[30] This experiment shows that $\mathbf{1}^{-3Me}$ recognizes $Me_2DopaH^+Cl^-$ as a contact ion pair and thus behaves as a heteroditopic receptor. Such a property was reported for parent compound **1** with a variety of ammonium chloride salts. Interestingly, however, it was shown that **1** was unable to selectively bind $Me_2DopaH^+Cl^-$, the formation of the simple chloride complex ($\mathbf{1}\supset Cl^-$) being largely predominant in that case.[30] Hence, the preliminary result obtained with $\mathbf{1}^{-3Me}$ highlights its very promising binding properties, which appear enhanced in comparison with those of the methylated parent host **1**. The detailed recognition properties of $\mathbf{1}^{-3Me}$ as well as those of the other demethylated receptors (vide infra) will be described elsewhere.

DOI: 10.1021/acs.joc.5b00464
J. Org. Chem. 2015, 80, 5084−5091

Table 2. Reactions of Calix[6]arene-Based Receptors 2−6 with TMSI (ca. 4−5 equiv/OMe group) in $CHCl_3$ at 50 °C

entry	substrate (δ_{OMe}, ppm)[a]	SA (δ_{OMe}, ppm)[a]	product(s) without SA[b] (reaction time)	product(s) with SA[b] (reaction time)	yield[c] (%)
1	**2** (2.96)	Imi[d] (3.78)[e]	degrad	$\mathbf{2}^{-3Me}$ (18 h)	61
2	**3** (2.53)[f]		$\mathbf{3}^{-3Me}$ (1 h)		81
3	**4** (2.95)	$(EtNH_3)_2SO_4$[d] (4.12)	degrad	$\mathbf{4}^{-6Me}$ (73 h)	89
4	**5** (2.69)	TFA[d] (3.62)	degrad	$\mathbf{5}^{-3Me}$ (24 h)	63
5	**6** (2.14)	Zn^{2+} [d] (3.63)	degrad	degrad	

[a] δ_{OMe} determined in $CDCl_3$ by ^1H NMR spectroscopy. [b] Determined by ESI-MS analysis of the reaction mixture after 1 h and up to 120 h. The abbreviation "degrad" stands for "degradation" and means that a complex mixture of products resulting from the presence of partially demethylated intermediates and/or from a nonselective dealkylation was observed over the course of the reaction. [c] Yield of trisdemethylated product calculated after FC purification. $\mathbf{3}^{-3Me}$ was isolated under the corresponding protonated form $\mathbf{3}^{-3Me}\cdot HClO_4$ (see the Experimental Section). Note that all reactions were performed at least two times and consistent yields were obtained. [d] A 1.1 equiv portion of Imi, 1.25 equiv of $(EtNH_3)_2SO_4$, 10 equiv of TFA, and 2−20 equiv of $Zn(ClO_4)_2$ were used. [e] The addition of water (1.4 equiv) was necessary for the reaction to go to completion. [f] In this case, the OMe groups are directed toward the outside of the cavity, the high-field shifted resonance of the OMe groups being due to the anisotropic ring current from the pyridine units of the tmpa cap (see the text).

In a second set of experiments, we evaluated the possibility of extending the SA strategy to calix[6]arene-based receptors **2**−**6**. In all cases, the reactions were first attempted with an excess of TMSI (ca. 4−5 equiv/OMe group) in $CHCl_3$ at 50 °C. In the cases of compounds **2** and **4**−**6**, ESI-MS monitoring of the reaction (after 1 h and up to 120 h) showed the formation of a complex mixture of products resulting from partial demethylation and/or nonselective dealkylation. In strong contrast, the highly selective demethylation of the anisole units of calix[6]-tmpa **3** proceeded efficiently in only 1 h, affording the desired trisdemethylated product $\mathbf{3}^{-3Me}$ in 81% yield after FC purification (Scheme 2; Table 2, entry 2).[33] As mentioned above, such a different behavior may be explained in terms of conformational properties: in chloroform, the OMe groups of substrates **2** and **4**−**6** are either partially or completely self-included in the cavity (see the δ_{OMe} given in Table 2); in contrast, compound **3**, having a more rigid capping unit, adopts a well-defined cone structure as a major conformation in solution. In this cone conformation, nicely illustrated by an X-ray structure of its protonated derivative,[25c] calixarene **3** has its methyl substituents expelled from the cavity, which explains their fast reaction with TMSI (Scheme 2). Such a selectivity is particularly remarkable when considering that a benzylic position linked to a phenolic oxygen is classically highly reactive toward dealkylating agents such as TMSI.[14]

The SA approach was then attempted in the cases of compounds **2** and **4**−**6**, and the reaction conditions were chosen on the basis of the previously reported host−guest properties of these receptors. Various guests were screened, and the best results are displayed in Table 2 (entries 1 and 3−5).

First, calix[6]cryptamide **2** is known to strongly bind Imi in $CDCl_3$, leading to the ejection of the OMe groups from the cavity (δ_{OMe} = 3.78 ppm for complex **2**⊃Imi).[25b] Indeed, fast demethylation occurred when the reaction was conducted in the presence of this urea guest (1.1 equiv). However, the bisdemethylated intermediate $\mathbf{2}^{-2Me}$ was observed as the major compound after 1 h. Neither prolonged reaction time nor addition of more TMSI to the reaction medium allowed the reaction to go to completion. Quite remarkably, however, the subsequent addition of water (1.4 equiv), which is also bound by receptor **2** but more weakly than Imi, allowed the reaction to proceed further. It was actually found that the presence of both guests (Imi and water) is required for the reaction to give rise to the desired product $\mathbf{2}^{-3Me}$. A likely explanation is that Imi has much lower affinity for the phenol derivatives of receptor **2**, namely, intermediate $\mathbf{2}^{-2Me}$, whereas water still binds to them, thus stimulating the ejection of the remaining methoxy groups. This hypothesis is supported by a ^1H NMR study conducted in chloroform, which revealed the nonrecognition of Imi by product $\mathbf{2}^{-3Me}$. Under optimized conditions, $\mathbf{2}^{-3Me}$ was isolated in 61% yield after FC purification (Scheme 2; Table 2, entry 1).

In the case of biscalix[6]arene **4**, when the demethylation reaction was carried out in the absence of guest, degradation products resulting from cleavage of the urea arms were rapidly (i.e., after 1 h) and exclusively obtained (ESI-MS analysis). However, the addition of bis(ethylammonium) sulfate $(EtNH_3)_2SO_4$ (1.25 equiv) prior to TMSI led exclusively to the desired hexakisdemethylated product $\mathbf{4}^{-6Me}$ in high yield (Scheme 2; Table 2, entry 3).[34] This spectacular result is due to the strong affinity of **4** for ammonium sulfate salts and, thus, to the formation of the corresponding host−guest complex $\mathbf{4}\supset[(EtNH_3)_2SO_4]$ having an ideal conformation with OMe groups expelled from the cavity.[25d]

Reaction between calix[6]trisamine **5** and TMSI in chloroform without any SA led to incomplete conversion into the compound $\mathbf{5}^{-3Me}$ (even after 120 h) and to the formation of degradation products generated by the cleavage of the ethylamino arms. Knowing that this flexible compound can be structured in the cone conformation by self-assembly of its corresponding ammonium salt with counterions, we first reacted compound **5** with trifluoroacetic acid (TFA) to generate, in solution, the rigid supramolecular architecture **5**·3TFA that has OMe groups pointing outside of the cavity thanks to guest hosting (either a water molecule or TFA itself under these conditions).[35] This SA allowed the demethylation reaction to proceed faster (i.e., 24 h) and reduced drastically the ratio of degradation products. The corresponding tri-sphenolic product $\mathbf{5}^{-3Me}$ was thus isolated in 63% yield after FC purification (Scheme 2; Table 2, entry 4).

Finally, reaction of calix[6]trisimidazole **6** and TMSI led to a fast dealkylation of the *N*-methylimidazole arms. This result is explained by the high reactivity of the methylene groups linked to the *N*-methylimidazole residues and by the deep inclusion of the OMe groups in the cavity (δ_{OMe} = 2.14 ppm in $CDCl_3$). Therefore, the SA strategy was attempted with various guests and conditions, and notably, the addition of several metal salts (e.g., Zn^{2+}, K^+, Mg^{2+}) was tested. Indeed, the three *N*-methylimidazole arms of host **6** can complex various metal ions to yield "funnel complexes" where the OMe groups are oriented outside of the cavity.[36] Unfortunately, under all tested conditions, fast dealkylation of the *N*-methylimidazole arms was observed. This result is explainable by the demetalation of the calixarene ligand by iodides and/or traces of acid released by TMSI in the reaction medium.[37]

DOI: 10.1021/acs.joc.5b00464
J. Org. Chem. 2015, 80, 5084−5091

All new compounds (2^{-3Me}, 3^{-3Me}, 4^{-6Me}, and 5^{-3Me}) were characterized through 1D and 2D NMR analyses. In the cases of 4^{-6Me} and 5^{-3Me}, very broad ^{1}H NMR spectra were obtained whatever the solvent used and the temperature. These compounds were thus characterized in the presence of $(EtNH_3)_2SO_4$ and TfOH, respectively, the resulting rigidified complexes displaying sharp and well-defined NMR signals.

The efficacy of the demethylation procedure raises the question of the mechanism of the demethylation reaction itself. It is generally admitted that the backside attack of iodide onto the methyl groups (S_N2 mechanism) is preceded by the electrophilic activation of the methoxy group through the formation of a silylated oxonium.[38] Here, such a mechanism can be questioned since it appears that the oxygen lone pairs of the methoxy groups are directed toward the inside of the cavity and, as such, are not sterically available for the formation of a silylated intermediate. Hence, in these cases, it is likely that other oxygenated groups sitting next to the small rim interact first with TMSI. Indeed, the urea (in the cases of **1** and **4**), amido (in the case of **2**), OCH_2 (in the case of **3**), and carboxylate (in the case of **5**) groups, whose lone pairs are accessible, may well transiently react with TMSI. In an apolar solvent such as chloroform, this initial step would produce the nucleophilic iodide anion in close proximity of the anisole units, thus leading to their selective demethylation when well oriented.

Finally, it is worth mentioning that, in the cases of the hosts **1** and **3**, which possess a basic tertiary amino group, the demethylation reaction may well proceed, at least in part, through their protonated ammonium form.[39] Indeed, it is known that small amounts of HI are readily produced by reaction of TMSI with traces of water. In the case of substrate **1**, the supramolecular assistance would be reinforced since it has been shown that the hosting properties of **1** toward neutral guests such as Imi are strengthened upon protonation of its basic cap.[30] In the case of calix[6]tmpa **3**, the major conformation adopted by the calixarene core remains the same (i.e., cone) when the tmpa cap is protonated and when it is not protonated.[25c]

CONCLUSION

The successful selective polydemethylation was achieved on five different multifunctionalized calix[6]arene hosts (**1**−**5**). The procedure relies on two key points: (i) the nucleophilic attack of iodide using TMSI as a reagent and (ii) the correct orientation of the methoxy groups that must be projected away from the cone structure. For the rigid calix[6]azacryptand **3**, the conformation favorable to the reaction of the methoxy groups is spontaneously adopted and the reaction is fast and selective. In the cases of hosts **1**, **2**, **4**, and **5**, such a good orientation requires supramolecular assistance: the presence of a guest allows shaping of the calixarene, projecting the methyl groups subjected to the attack away from the macrocyclic hindering structure, thus exposing them to the demethylation reagent. The previously reported example of selective demethylation of a calix[6]arene derivative[24a] quite probably obeys the same rules: the sodium ion, which is required for the reaction, being bound to the calixarene small rim amido arms, shapes the calixarene core in a way that is similar to that of the cases reported herein.

The efficiency of the supramolecular assistance, best illustrated with compound **4**, is highly reminiscent of phenomena observed in biology. Indeed, it is, and has been for a long time, very well recognized that allosteric behaviors are keys in the control (on/off) and the selectivity of many biotransformations of exogenous as well as endogenous compounds. For example, a conformation change of DNA due to its interaction with a protein will expose specific bases for their selective methylation or demethylation.[40]

In terms of synthetic receptors, this procedure opens new routes for the chemical modification of highly functionalized calixarenes. Indeed, the deprotected phenol groups can easily be subsequently reacted in view of appending new functionalities to the receptors. Also noteworthy is that a preliminary study of the hosting properties of one of them (1^{-3Me}) evidenced the impact the replacement of three methoxy groups by phenol functions has on guest binding. These two points are currently under study in our groups.

EXPERIMENTAL SECTION

General Experimental Methods. Commercial anhydrous chloroform and copper-stabilized trimethylsilyl iodide (TMSI) were used. Other solvents and chemicals were of reagent grade and were used without purification. Silica gel (230−400 mesh) was used for flash chromatography separations. ^{1}H NMR spectra were recorded at 250, 300, 400, or 600 MHz. ^{13}C NMR spectra were recorded at 75, 100, or 126 MHz. Traces of residual solvents were used as the internal standard. $CDCl_3$ was filtered through a short column of basic alumina to remove traces of HCl. Most of the ^{1}H NMR spectral signals were assigned on the basis of 2D NMR analyses (COSY, HSQC, HMBC). NMR spectra were recorded at 298 K unless otherwise stated. Chemical shifts are quoted on the δ scale, coupling constants (J) are expressed in hertz, and "br" refers to "broad signal". ESI-MS and ESI-HRMS analyses were performed using methanol as the solvent. Low-resolution mass spectra were recorded with an ESI-MS spectrometer equipped with an ion trap using the following settings: flow rate, 8 μLmin^{-1}; spray voltage, 5 kV; capillary temperature, 160 °C; capillary voltage, −15 V; tube lens offset voltage, −30 V. High-resolution mass spectra were recorded with an ESI-MS spectrometer equipped with an orbitrap. Unless otherwise noted, IR analyses were performed with an FT-IR spectrometer using the ATR (attenuated total reflectance) method.

Calix[6]crypturea-tris-OH 1^{-3Me}. Calix[6]crypturea **1** (40 mg, 29 μmol) and imidazolidin-2-one (2.7 mg, 32 μmol) were dissolved in anhydrous $CHCl_3$ (8 mL). Trimethylsilyl iodide (63 μL, 440 μmol) was added, and the resulting solution was stirred at 50 °C under an argon atmosphere for 2 h (the reaction was monitored by ESI-MS). Water (8 mL) was added to the reaction mixture. Then the organic phase was extracted and evaporated under reduced pressure to afford a yellow solid which was purified by column chromatography (CH_2Cl_2 and then CH_2Cl_2/MeOH, 9:1) to give calix[6]crypturea-tris-OH 1^{-3Me} as a white powder (37 mg, 95%): mp > 250 °C; IR (solid) ν = 3361 (PhOH and NH), 2960, 1642, 1570, 1482, 1362, 1258, 1203, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD, 1:1, 298 K) δ (ppm) 0.99 (s, 27H, *t*Bu), 1.12 (s, 27H, *t*Bu), 2.62 (t, 6H, CH_2N, J = 5 Hz), 3.14 (t, 6H, CH_2NH, J = 4 Hz) 3.38 (d, 6H, $ArCH_2$, J = 15 Hz), 3.42 (br, 6H, CH_2NH), 3.53 (br, 6H, CH_2O), 4.42 (d, 6H, $ArCH_2$, J = 15 Hz), 6.90 (s, 6H, ArH), 6.99 (s, 6H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD, 1:1, 298 K) δ (ppm) 30.5, 31.6, 31.8, 34.4, 34.6, 38.8, 40.4, 55.2, 73.3, 126.0, 126.4, 127.4, 133.2, 143.0, 147.2, 149.2, 151.6, 161.0; HRMS (ESI-orbitrap) m/z $[M + H]^+$ calcd for $C_{81}H_{112}N_7O_9$ 1326.8516, found 1326.8502.

Calix[6]cryptamide-tris-OH 2^{-3Me}. Calix[6]cryptamide **2** (50 mg, 39 μmol) and imidazolidin-2-one (3.7 mg, 43 μmol) were dissolved in anhydrous chloroform (10 mL). Trimethylsilyl iodide (83 μL, 585 μmol) was added, and the resulting solution was stirred at 50 °C (the reaction was monitored by ESI-MS). After 1 h, 3 μL (1.4 equiv., 54 μmol) of distillated water was added, and the solution was stirred at 50 °C for an additional 17 h. The reaction mixture was washed with 10 mL of water, and the organic phase was concentrated under reduced pressure. The brown solid was purified by flash chromatography

DOI: 10.1021/acs.joc.5b00464
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(CH_2Cl_2/MeOH, 95:5) to yield calix[6]cryptamide-tris-OH $\mathbf{2}^{-3Me}$ as a white solid (30 mg, 61%): mp > 250 °C; IR (solid) ν = 3346 (PhOH), 2958, 1660 (C═O), 1544, 1482, 1362, 1276, 1202, 1119, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm) 1.12 (s, 27H, *t*Bu), 1.22 (s, 27H, *t*Bu), 3.34 (s, 6H, CH_2N), 3.50−3.60 (m, 12H, CH_2NH + $ArCH_2$), 3.84 (br, 6H, CH_2O), 4.23 (d, 6H, $ArCH_2$, J = 15 Hz), 6.84 (s, 3H, ArOH), 7.05 (s, 6H, ArH), 7.07 (s, 6H, ArH), 7.90 (br, 3H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ (ppm) 31.3, 31.4, 31.7, 34.1, 34.4, 39.7, 61.8, 73.6, 126.1, 126.8, 132.7, 143.0, 147.5, 149.5, 151.2, 170.5; HRMS (ESI-orbitrap) m/z $[M + H]^+$ calcd for $C_{78}H_{103}N_4O_9$ 1239.7720, found 1239.7694.

Calix[6]tmpa-tris-OH 3^{-3Me}·$HClO_4$. Calix[6]tmpa **3** (150 mg, 112 μmol) was suspended in 6 mL of freshly distilled anhydrous $CHCl_3$ in a Schlenk flask under an argon atmosphere. Trimethylsilyl iodide (180 μL, 1.26 mmol) was added, and the yellow mixture was stirred at 50 °C for 1 h (the reaction was monitored by ESI-MS). The reaction mixture was diluted with 20 mL of $CHCl_3$, and then 4 mL of a 1 M aqueous solution of $HClO_4$ was added. The mixture was vigorously stirred for 5 min, and the organic phase was washed with water (4 × 10 mL). The organic layer was evaporated to dryness, and the solid was purified by flash chromatography (CH_2Cl_2 and then CH_2Cl_2/MeOH, 9:1). The resulting solid was then dissolved in CH_2Cl_2 (10 mL) and washed with an aqueous solution of $HClO_4$ (10 mM, 10 mL) for 5 min. The organic phase was washed with water (4 × 10 mL, i.e., until the pH of the aqueous phase was 7) and evaporated under reduced pressure to obtain calix[6]tmpa-tris-OH·$HClO_4$ $\mathbf{3}^{-3Me}$·$HClO_4$ as a pale yellow solid (127 mg, 81%): mp 244 °C dec; IR (solid) ν = 3529 (PhOH), 2962, 1598, 1480, 1362, 1204, 1119 (ClO_4), 1052 cm^{-1}; ^1H NMR (250 MHz, CD_3CN, 300 K) δ (ppm) 0.93 (s, 27H, *t*Bu), 1.20 (s, 27H, *t*Bu), 3.41 (d, 6H, $ArCH_2$, J = 15 Hz), 4.23 (d, 6H, $ArCH_2$, J = 15 Hz), 4.49 (s, 6H, CH_2N), 5.10 (s, 3H, PhOH), 5.15 (s, 6H, CH_2O), 6.90 (s, 6H, ArH), 7.25 (s, 6H, ArH), 7.33 (d, 3H, H_{Py}, J = 5 Hz), 7.97 (m, 6H, H_{Py}); ^{13}C NMR (126 MHz, CD_3 CN, 300 K) δ (ppm) 31.6, 31.8, 58.2, 75.8, 118.3, 122.3, 122.6, 125.8, 126.1, 128.7, 139.7; HRMS (ESI-orbitrap) m/z $[M + H]^+$ calcd for $C_{87}H_{103}N_4O_6$ 1299.7878, found 1299.7892.

Calix[6]tube-hexakis-OH 4^{-6Me}. Calix[6]tube **4** (80 mg, 34 μmol) and $(EtNH_3^+)_2SO_4^{2-}$ (8 mg, 42 μmol) were stirred in anhydrous $CHCl_3$ (8 mL) for 1 h at 50 °C. Then trimethylsilyl iodide (87 μL, 610 μmol) was added, and the resulting solution was stirred at 50 °C under an inert atmosphere for 24 h. A second portion of trimethylsilyl iodide (58 μL, 405 μmol) was added, and the solution was stirred at 50 °C for an additional 48 h (the reaction was monitored by ESI-MS). Water (8 mL) was added to the reaction media. The organic phase was washed with water (2 × 10 mL) and dried under vacuum to afford a yellow solid which was purified by column chromatography (CH_2Cl_2 and then CH_2Cl_2/AcOEt, 9:1) to give calix[6]tube-hexakis-OH $\mathbf{4}^{-6Me}$ as a white powder (69 mg, 89%): mp 241 °C dec; IR (solid) ν = 3362 (PhOH and NH), 2960, 1640, 1563, 1482, 1393, 1362, 1257, 1202, 1120, 1047 cm^{-1}; HRMS (ESI-orbitrap) m/z $[M + H]^+$ calcd for $C_{147}H_{193}N_6O_{15}$ 2282.4524, found 2282.4478. Compound $\mathbf{4}^{-6Me}$ was characterized by NMR spectroscopy in the form of complex $\mathbf{4}^{-6Me}\supset(EtNH_3^+)_2SO_4^{2-}$ obtained by addition of $(EtNH_3^+)_2SO_4^{2-}$ (2 equiv) to a solution of $\mathbf{4}^{-6Me}$ (1.3×10^{-3} M in $CDCl_3$/CD_3OD, 10:1): ^1H NMR (600 MHz, $CDCl_3$/CD_3OD, 10:1, 298 K) δ (ppm) 1.65 (br, 6H, $CH_3CH_2NH_3^+$), 0.72 (s, 54H, *t*Bu), 1.28 (s, 54H, *t*Bu), 1.61 (br, 4H, $CH_3CH_2NH_3^+$), 3.38 (d, 12H, $ArCH_2$, J = 15 Hz), 3.57 (br, 12H, CH_2N), 3.98 (br, 12H, CH_2O), 4.44 (d, 12H, $ArCH_2$, J = 15 Hz), 6.54 (s, 12H, ArH), 7.12 (s, 12H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD, 10:1, 298 K) δ (ppm) 29.7, 31.0, 31.6, 33.9(6), 34.0(2), 40.4, 72.6, 123.8, 127.3, 127.6, 132.5, 143.3, 146.6, 148.8, 150.5, 159.5.

Calix[6]trisamine-tris-OH 5^{-3Me}. Calix[6]trisamine **5** (400 mg, 350 μmol) and trifluoroacetic acid (267 μL, 3.5 mmol) were placed in anhydrous $CHCl_3$ (80 mL). Trimethylsilyl iodide (750 μL, 5.24 mmol) was added, and the resulting solution was stirred at 50 °C for 24 h (the reaction was monitored by ESI-MS). The organic phase was washed with an aqueous solution of HCl (1 M, 80 mL) and water (4 × 20 mL). The organic layer was evaporated to dryness, and the solid was purified by flash chromatography (CH_2Cl_2 and then CH_2Cl_2/MeOH, 95:5). The residue was then triturated with MeCN (2 × 1 mL) and pentane (2 × 1 mL) to afford calix[6]trisamine-tris-OH $\mathbf{5}^{-3Me}$ as a white powder (243 mg, 63%): mp 223 °C dec; IR (solid) ν = 3600−3000 (PhOH and NH), 2967, 2901, 1680, 1483, 1408, 1393, 1275, 1259, 1203, 1056 cm^{-1}; HRMS (ESI-orbitrap) m/z $[M + H]^+$ calcd for $C_{72}H_{100}N_3O_6$ 1102.7607, found 1102.7592. Compound $\mathbf{5}^{-3Me}$ was characterized by NMR spectroscopy in the form of complex $\mathbf{5}^{-3Me}$·3TfOH obtained by addition of TfOH (3 equiv) to a CD_3CN solution of $\mathbf{5}^{-3Me}$: ^1H NMR (600 MHz, CD_3CN, 348 K) δ (ppm) 1.04 (s, 27H, *t*Bu), 1.21 (s, 27H, *t*Bu), 3.07 (m, 6H, CH_2N), 3.72 (t, 6H, CH_2O, J = 5 Hz), 3.94 (br, 12H, $ArCH_2$), 6.46 (s, 3H, ArOH), 6.73 (br, 6H, NH_3^+), 7.03 (s, 6H, ArH), 7.16 (s, 6H, ArH); ^{13}C NMR (75 MHz, CD_3CN, 298 K) δ (ppm) 30.8, 31.6, 31.7, 34.7, 35.0, 41.2, 69.4, 127.0, 127.1, 128.6, 133.6, 144.9, 148.5, 148.9, 151.4.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

1D and 2D NMR spectra of all new compounds and ESI-MS analyses of the demethylation reaction of calix[6]crypturea **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the ULB (D.C., S.Mo., and A.L. Ph.D. grants), the Fonds de la Recherche Scientifique-FNRS (FRFC 2.4.617.10.F Project and G.D.L. Ph.D. grant), and the Agence Nationale de la Recherche (ANR10-BLAN-714 Cavityzyme(Cu) Project) and was undertaken within the framework of COST Action CM-1005, Supramolecular Chemistry in Water. The modeling part of this work used resources of the Plateforme Technologique de Calcul Intensif (PTCI) (http://www.ptci.unamur.be) located at the University of Namur, Belgium, which is supported by the FRS-FNRS under Convention No. 2.4520.11. The PTCI is a member of the Consortium des Équipements de Calcul Intensif (CÉCI) (http://www.ceci-hpc.be).

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(27) Most of the calixarene-based receptors are poorly soluble in polar solvents, thus limiting the choice of demethylating agents that can be used. For example, sodium thiolates have to be used in polar solvents such as DMF.

(28) In chloroform, calixcrypturea **1** consists of a mixture of free host **1** and complex **1**⊃H_2O (obtained through complexation of residual water), the host−guest exchange being fast on the NMR time scale. The conformation of free host **1** was not characterized, but in strong analogy with a related receptor (see: Cornut, D.; Marrot, J.; Wouters, J.; Jabin, I. *Org. Biomol. Chem.* **2011**, *9*, 6373−6384), it is likely that **1** adopts a pinched cone conformation with a partial inclusion of the OMe groups.

(29) The starting conformations for both the **1**⊃H_2O and **1**⊃Imi structures have been manually built using Discovery Studio 3.5 (Accelrys). The geometries were further optimized using the PM6 Hamiltonian (Stewart, J. J. P. *J. Mol. Model.* **2007**, *13*, 1173−1213) via the semiempirical MOPAC2012 software (Stewart Computational Chemistry). MM corrections were applied to the CONH barrier (MMOK). The convergence gradient criterion was fixed to 0.1 (GNORM = 0,1).

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(33) Note that a ^1H NMR study in $CDCl_3$ revealed that $\mathbf{3}^{-3Me}$ is unstable in solution. Thus, this compound was isolated and characterized under the corresponding protonated form $\mathbf{3}^{-3Me}$.$HClO_4$ (see the Experimental Section).

(34) $(EtNH_3)_2SO_4$ being weakly soluble in chloroform, heating at 50 °C for 1 h was necessary to form the host−guest complex **4**⊃$(EtNH_3)_2SO_4$, prior to the addition of TMSI.

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DOI: 10.1021/acs.joc.5b00464
J. Org. Chem. 2015, 80, 5084−5091