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Intramolecularly Bridged Calix[4]arenes with Pronounced Complexation Ability toward Neutral Compounds

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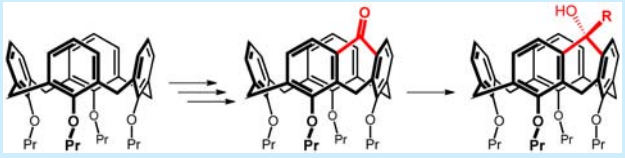
Supporting Information

ABSTRACT: Regioselective derivatization via an organomercury intermediate allowed for the introduction of carboxylic acid functionality into the *meta* position of the calix[4]arene skeleton. Intramolecular Friedel–Crafts cyclization led to a novel type of calixarene containing a ketone bridging moiety. Subsequent attack of the ketone by organometallic compounds occurred selectively from outside providing tertiary alcohols with the OH group oriented inside the cavity. These compounds can complex neutral molecules both in the solid state (X-ray) and in solution (NMR) using the cooperative effect of hydrogen bonding (OH) and CH–π interactions from within the cavity.

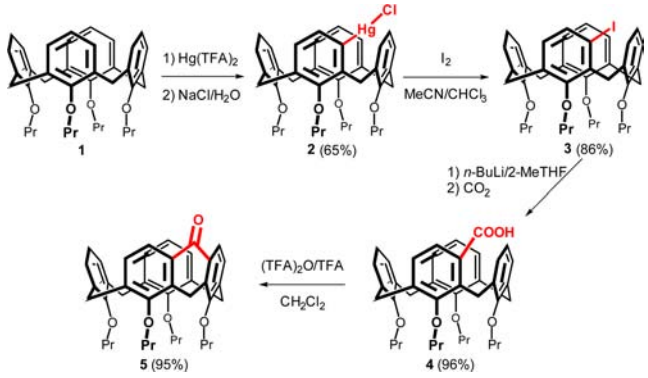


Macrocyclic molecules of calix[*n*]arenes[1] are very popular building blocks in supramolecular chemistry. Specifically, calix[4]arene provides us with a unique opportunity to work on well-defined and tunable 3D shapes of the molecule. Consequently, it represents an ideal starting platform for the design of novel receptors and/or more sophisticated supramolecular systems.[2] Moreover, the chemistry of calix[4]arene is well established and offers a plethora of possibilities for derivatization of the basic skeleton.[1,3]

Electrophilic substitution of calix[4]arene (either directly or through *ipso* substitution) represents the most common way for introducing substituents into the upper rim of the parent macrocycle. The limitation of this approach can be seen in the fact that only the *para*-substituted isomers (with respect to the phenolic functionality) are formed.[1,3] Very recently, we reported[4] the reaction of calix[4]arene **1** with mercury trifluoroacetate ($Hg(TFA)_2$) leading to *meta*-substituted organomercurial product **2**. This unexpected regioselectivity thus paved the way toward derivatization of calixarenes at this unusual position.[5] Although organomercury derivatives are usually avoided in synthesis due to their alleged toxicity, in this case they mediate direct access to an otherwise inaccessible substitution pattern. In this paper we report on bridging calix[4]arene **1** with the keto functional group and subsequent formation of tertiary alcohols that can serve as receptors for catching selected neutral molecules.

As recently reported,[4a] direct mercuration of tetrapropoxycalix[4]arene **1** with 1 equiv of $Hg(TFA)_2$ led to *meta*-substituted product **2** in good yield (65%). This organomercury compound is accessible on a multigram scale and can be easily transformed into corresponding iodo derivative **3** (86% yield) by reaction with I_2.[6] Iodine–lithium exchange was achieved via treatment with *n*-BuLi/hexane in 2-MeTHF at −78 °C. Direct lithiation by transmetalation of **2** would also be possible, but we wanted to avoid introduction of unwanted alkyl mercury byproducts. Subsequent quenching with gaseous CO_2 (generated in a separate flask from dry ice) provided the corresponding carboxylic acid **4** in almost quantitative yield (96% after column chromatography on a silica gel); see Scheme 1. Interestingly, the crystalline product possessed a strong

Scheme 1. Preparation of Ketone-Bridged Calix[4]arene



distinctive odor, a phenomenon which is exceptionally rare in calixarene chemistry. Unfortunately, reflux of **4** with $POCl_3$ (5 equiv) in nitromethane did not lead to the expected Friedel–Crafts intramolecular acylation product, possibly due to very poor solubility of the reactant. Luckily this could be overcome by stirring **4** in a trifluoroacetic anhydride–TFA mixture which provided ketone-bridged calixarene **5** in very high yield (95%).

The structure of the product was confirmed by a combination of MS and NMR techniques. Thus, HRMS ESI+

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analysis of **5** showed signals at m/z = 641.32416 and 657.29671, which was in perfect accordance with the proposed structure ($[M + Na]^+$ and $[M + K]^+$, respectively). The ^1H NMR spectra of **5** showed three doublets indicating equatorial C−H bonds from the methylene Ar−CH_2−Ar bridges (3.08, 3.33, and 3.51 ppm in a 1:2:1 ratio) and three similar doublets suggesting axial bonds (4.32, 4.56, and 4.73 ppm), all with typical geminal coupling constants (J = 12.3 to 15.7 Hz), corresponding to the expected C_S symmetry of the product **5**. Finally, the signal at 191 ppm in the ^{13}C NMR spectrum confirmed the presence of a ketone group.

The X-ray crystallography of **5** (monoclinic, space group $C2/c$) revealed a distorted shape of the cavity as a consequence of the ketone bridge (Figure 1a). Thus, the length of the short

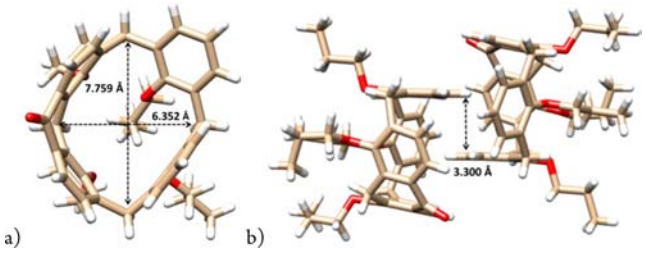


Figure 1. X-ray structure of **5**: (a) distorted cavity of calix[4]arene, (b) dimer formation via $\pi-\pi$ interactions.

diagonal (i.e., the C···C distance between opposing methylene bridges) was 6.352 Å, while the other diagonal was much longer (7.759 Å). Both values substantially differ from the typical distance found in common calix[4]arene derivatives (~7.0−7.2 Å) devoid of ketone bridging. Moreover, two molecules of **5** formed a dimer held together by $\pi-\pi$ interactions between two nearly perfectly coplanar phenolic subunits (Figure 2b). Finally, the unusually short distance (3.300 Å) between the aromatics in the "parallel displaced" mutual position[7] also indicated very strong interactions.

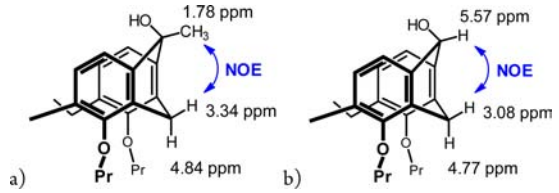
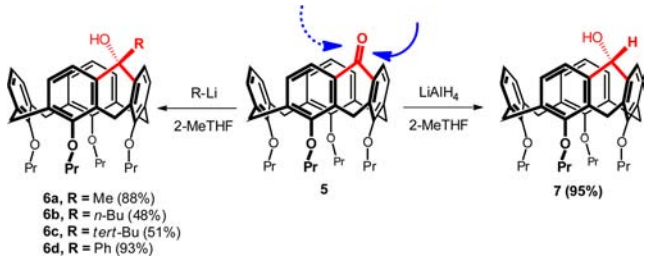


Figure 2. NOE contacts observed in the ^1H NMR spectra ($CDCl_3$, 298 K, 400 MHz) of **6a** (a) and **7** (b).

Derivative **5** represents a previously undescribed substitution pattern in calix[4]arene chemistry. The presence of the additional carbonyl bridge not only rigidifies the skeleton but also offers a new reactive center for subsequent derivatization. We decided to study the reactivity of this carbonyl group toward nucleophilic addition of RLi compounds. Theoretically, two different products could be formed depending on the direction of nucleophilic attack (Scheme 2). The reaction with MeLi carried out in 2-MeTHF at −78 °C led smoothly to product **6a** that was isolated in 88% yield as a single stereoisomer. To evaluate the influence of steric hindrance on the course of the reaction, nucleophilic addition using *n*-Buli, *tert*-BuLi, and PhLi were carried out under identical conditions to those for MeLi. In all cases, isolation of only a single

Scheme 2. R−Li Addition to Ketone 5



stereoisomer of products **6b**, **6c**, and **6d** occurred in 48%, 51%, and 93% yields, respectively. Interestingly, compound **7** was isolated in 21% yield as a byproduct in the reaction with *n*-BuLi. This phenomenon has been described for the reaction of diaryl ketones: benzophenone was reduced with *n*-BuLi to the analogous product in 23−26% yield.[8] As expected, tertiary alcohol **7** could also be obtained by direct reduction of the carbonyl group using $LiAlH_4$ in nearly quantitative yield.

The splitting pattern and multiplicity of signals in the ^1H NMR spectra of **6a−d** and **7** corresponded to the expected C_S symmetry of the products. Again, two series of three doublets (1:2:1 intensity) indicating the equatorial and axial methylene Ar−CH_2−Ar bridges were the most striking feature of all these compounds. The stereochemistry of the addition reaction was assigned using NOE experiments. Thus, irradiation of the CH_3 signal at 1.78 ppm in **6a** (Figure 2a) led to through space interactions with the doublet at 3.34 ppm belonging to the equatorial C−H bond of the Ar−CH_2−Ar group.[9] Similarly, the C−H bond from the tertiary alcohol group (5.57 ppm) of compound **7** exhibited (Figure 2b) a clear interaction with the equatorial C−H bond of the bridging methylene moiety at 3.08 ppm. These findings strongly supported that all nucleophiles, including the smallest hydride anion, attacked from the outward face, probably because the steric hindrance prevented the correct trajectory for attack from inside of the cavity.

Final unequivocal structural evidence was obtained by single crystal X-ray crystallography (Figure 3). Compound **6b**

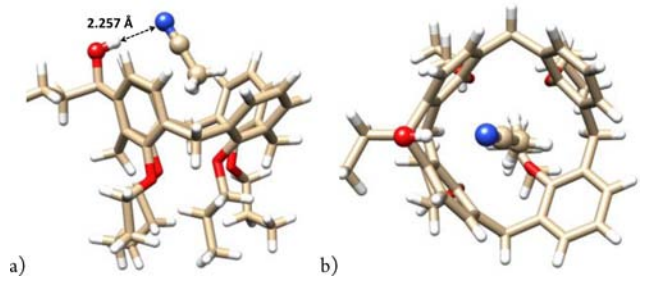


Figure 3. X-ray structure of **6b**·MeCN complex: (a) Hydrogen bonding interaction with MeCN - side view, (b) the same complex - from above; butyl group partly cutoff for clarity.

crystallized in the orthorhombic system, space group $Pn2_1a$, with three independent molecules in the asymmetric unit. The introduction of an (*n*-butyl)hydroxymethylene bridge between the two neighboring *meta* positions led to a similar distortion as mentioned above for ketone derivative **5** (long versus short diagonals of a basic skeleton = 7.639−7.702 Å vs 6.441−6.500 Å). Addition of the butyl group from the outside forced the OH group to an almost vertical position toward the main plain of the calixarene (defined by the C atoms of the four methylene

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bridges). As a result, the OH group points toward the opening of the cavity and can serve as a potential catcher unit as a result of hydrogen bonding (HB) interactions.

This was nicely demonstrated by the complex formed with MeCN. As can be seen in Figure 3a, the acetonitrile molecule was held by HB interactions from the OH group (O···N distance = 3.025 Å). This interaction routed the methyl group of MeCN directly to the cavity, where the C−H···π interactions occurred (Figure 3b). The whole cooperative system behaved as a two-point lock, and the overall complexation performance was strengthened.

Very similar results were obtained for **6d** that crystallized from methanol as a 2**6d**·3MeOH complex (monoclinic, space group $P2_1$). Figure 4a and 4b show the complexation of the

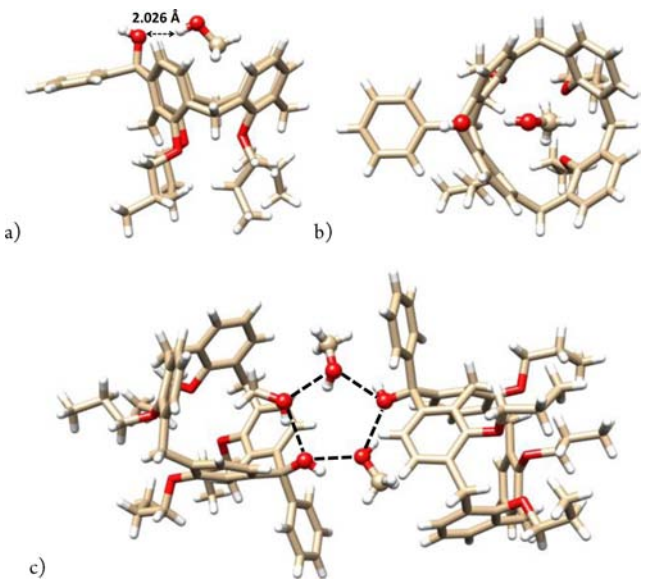


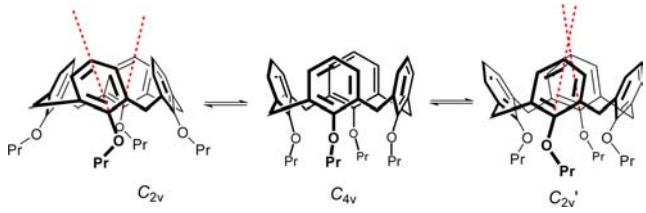
Figure 4. X-ray structure of **6d**·MeOH complex: (a) Hydrogen bonding interaction with MeOH - side view, (b) the same complex - from above, (c) circular hydrogen bond array in dimer with indicated O···O short distances.

methanol molecule with a binding mode very similar to the one described for MeCN. A very interesting supramolecular motif was found in the crystal packing of this complex. Two calixarene cavities interacted via a circular hydrogen bond array of three MeOH and two OH groups from the calixarenes to form a dimeric structure (Figure 4c).

It is well-known that the recognition ability of calix[4]arenes toward neutral molecules in solution depends on the rigidity and shape of the cavity.[11] Although the calix[4]arenes in the *cone* conformation are usually drawn as a structure with C_{4v} symmetry, this is in fact only the time averaged result of the fast equilibrium between two so-called *pinched cone* conformations with lower C_{2v} symmetries (Scheme 3). In solution, this equilibrium hinders efficient complexation of neutral guest molecules inside the cavity.

Since the rigidity of the calixarene ligand in the *cone* conformation is an essential prerequisite for binding efficiency, several strategies have been developed to rigidify the basic *cone* skeleton. Probably the most successful approach is based on the introduction of short oligoethylene bridges into the lower rim of calixarene, leading to a conformationally very rigid system.[10,11]

Scheme 3. Pinched *Cone*-Pinched *Cone* Equilibrium in the *Cone* Conformation of Calix[4]arene



Data from the X-ray analysis suggested that calixarenes **6a**−**6d** and **7** can be very efficient receptors for neutral molecules. Obviously, the rigidity of the *cone* skeleton is highly increased by the presence of the additional hydroxymethylene (−CH(R)OH−) bridge. Thus, bridging of the neighboring aromatic subunits via the upper rim of calix[4]arene represents a previously inaccessible approach toward skeleton rigidification.

The complexation ability of the novel bridged derivatives in solution was screened against selected neutral guests. Thus, 1.0 equiv of calixarene was added to a $CDCl_3$ solution of the guest, and the corresponding complexation induced chemical shift (CIS) of methyl group[12] was measured. As shown in Figure 5a,

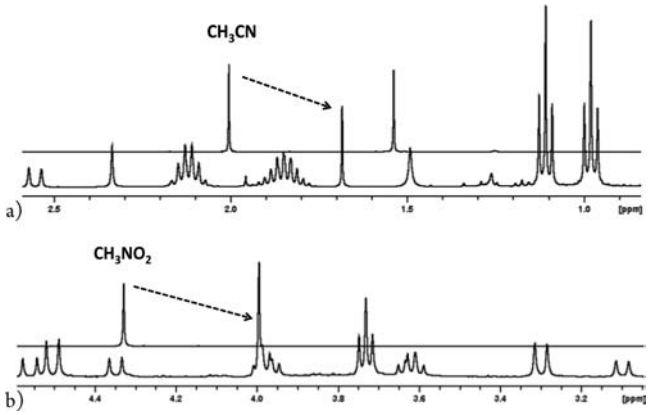


Figure 5. Partial ^{1}H NMR spectra of (a) MeCN and (b) $MeNO_2$ in the absence (upper part) and in the presence (lower part) of calixarene **6d** (1.0 equiv). All spectra: $CDCl_3$, 298 K, 400 MHz.

the addition of **6d** to MeCN in $CDCl_3$ led to a dramatic upfield shift of the methyl signal (0.33 ppm). This strongly suggested that the methyl group was shielded by magnetic anisotropy resulting from the aromatic units surrounding the methyl group in the cavity. In other words, the binding mode in solution was basically the same as that obtained by the X-ray data. Similar features can be seen for $MeNO_2$ (Figure 5b, CIS = 0.33 ppm) as well as for MeOH (CIS = 0.05 ppm), albeit slightly less pronounced.

The key role of the upper rim bridging OH− group from the calixarene moiety can be demonstrated by comparing ketone **5** with alcohol **7**. While **7** shows essentially the same CIS of MeCN as **6d** (0.26 ppm), the presence of the C═O bond instead of the C−OH bond of compound **5** prevented any measurable complexation of MeCN (see Supporting Information). This indicates that the existence of a rigid bridged cavity itself is not the only prerequisite for efficient binding and that the additional presence of an OH group is crucial for the whole binding phenomenon.

To gain deeper insight into the binding phenomenon we carried out a preliminary complexation study of selected guests

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molecules. The complexation occurred under fast-exchange conditions, and the ^{1}H NMR titration experiments were performed using a constant concentration of **6d** and an increasing concentration of the appropriate guest to obtain different host/guest ratios (1:1−25). The addition of guest molecules resulted in a significant downfield shift of the OH signal (CIS up to 400 Hz) indicating its participation in hydrogen bonding interactions. The titration curves obtained suggested the formation of complexes with 1:1 stoichiometry (see Supporting Information). The results (Table 1) show that

Table 1. Complexation Constants of Compound 6d toward Selected Neutral Guests (^{1}H NMR Titration, 400 MHz, $CDCl_3$, 298 K)

compd	guest	solvent	K [M^{-1}]
6d	MeCN	CD_2Cl_2	4 ± 0.3
6d	MeCN	$CDCl_3$	5 ± 0.4
6d	MeCN	CCl_4	40 ± 8
6d	$MeNO_2$	$CDCl_3$	5 ± 0.2
6d	$MeNO_2$	CCl_4	44 ± 2
8[a]	$MeNO_2$	$CDCl_3$	5 ± 2[b]
8[a]	$MeNO_2$	CCl_4	28 ± 7[b]

[a]For structure of **8**, see the Supporting Information. [b]For comparison from ref 10a.

calixarene **6d** possesses a higher complexation constant for $MeNO_2$ in CCl_4 than the rigidified *cone* derivative **8** bearing short diethylene glycol bridges on the lower rim.[11]

In conclusion, introducing carboxylic acid functionality into the *meta* position allowed for the preparation of a novel type of calix[4]arene with a ketone bridging moiety. Subsequent attack of the ketone by organolithium compounds occurred selectively from the outward face of the calixarene and led to tertiary alcohols with the OH group being oriented toward the entrance of the cavity. These compounds not only represent a previously unknown substitution pattern in calixarene chemistry but also can complex neutral molecules in both the solid state (X-ray) and in solution (NMR) using the cooperative effect of hydrogen bonding (OH) and CH−π interactions (cavity).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of compounds **4**, **5**, **6a−d**, and **7**, complexation study, and the X-ray structures of **5**, **6b**, and **6d**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01200.

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Notes

The authors declare no competing financial interest.

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(9) The doublets of the Ar−CH_2−Ar moiety close to the additional bridge (ketone or alcohol) can be easily recognized using the geminal interaction constants J which are in the range of 14−15.5 Hz, while the other −CH_2− bridges exhibit visibly lower values (J = 12.3−12.9 Hz).

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(12) CIS was calculated as the difference between the chemical shift of the free guest and the chemical shift of the guest after addition of 1.0 equiv of calixarene (in ppm).

(13) Our preliminary binding experiments with calixarenes **6a−d** and **7** indicated that these compounds can interact with residual water in $CDCl_3$ or CCl_4. However, we were unable to measure the corresponding binding constants, as we could not achieve rigorous anhydrous conditions necessary for the quantification. Thus, the complexation constants given in Table 1 are for illustration purposes only, and the exact role of water has yet to be determined.

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