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Inherently Chiral Upper-Rim-Bridged Calix[4]arenes Possessing a Seven Membered Ring

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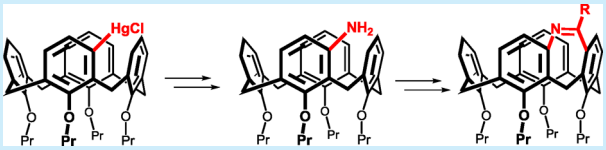
Supporting Information

ABSTRACT: The mercuration of calix[4]arene immobilized in the *cone* conformation allowed the introduction of an amino group at the *meta* position of the basic skeleton. Acylation and subsequent intramolecular Bischler−Napieralski-type cyclization led to a novel type of bridged calixarene containing a seven-membered ring. These compounds with an enlarged and rigidified cavity represent a unique and inherently chiral system that may potentially be applicable for the design of chiral receptors. The absolute configuration of one enantiomer, obtained by resolution of the racemate using chiral HPLC, was assigned by single-crystal structure determination.



Calix[*n*]arenes,[1] and more recently thiacalix[*n*]arenes,[2] are macrocyclic families frequently used as building blocks in supramolecular chemistry. As one can simply select not only the size of their cavity (from four to eight phenolic moieties) but also their three-dimensional shape (in the case of calix[4]arene), they have become popular starting points in the design and synthesis of various receptors and/or supramolecular functional systems.[3]

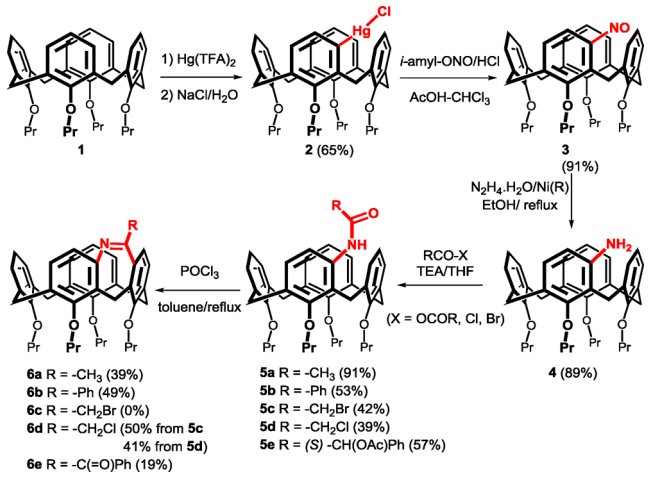
The chemistry of calix[4]arenes is currently well-established, offering many general derivatization methods for the basic macrocyclic skeleton.[1] Nevertheless, electrophilic aromatic substitution commonly used for derivatization of the aromatic region of the molecule (usually called the "upper rim") suffers from some limitations in terms of regioselectivity. Indeed, when using common direct or *ipso* substitutions (halogenation, nitration, sulfonation, Friedel−Crafts reactions, chloromethylation, etc.) only the *para* positions of the phenolic moieties (with respect to the phenolic oxygen) are accessible.[1]

We recently discovered[4] direct mercuration in the calix[4]-arene series with unprecedented regioselectivity. Thus, the *meta*-substituted chloromercurio derivative **2** can be obtained selectively in high yield by simple reaction of the starting calix[4]arene **1** with mercury(II) trifluoroacetate ($Hg(TFA)_2$) and subsequent reaction with NaCl. Although organomercury derivatives tend to be avoided because of their toxicity (*all organomercury derivatives are considered potentially hazardous and require special consideration*), in this case, *meta*-mercuration represents an irreplaceable tool for the derivatization[5] of calix[4]arenes in this rarely accessible position.[6] The synthetic usefulness of this approach was demonstrated inter alia by the formation of highly rigidified systems bearing single-bond[7] or carbonyl bridges[8] within the calix[4]arene skeleton.

In this paper we report on the very straightforward synthesis of calix[4]arenes rigidified by an additional bridge on the upper rim connecting two neighboring aromatic subunits. These compounds, which possess a seven-membered ring within their macrocyclic structure, represent inherently chiral systems[9] with an as yet unknown substitution pattern in calixarene chemistry that may potentially be applicable for the design of chiral receptors.

The starting tetrapropoxycalix[4]arene **1**, immobilized in the *cone* conformation, was transformed into *meta*-substituted chloromercurio derivative **2** in 65% yield (on a multigram scale) using a recently described procedure[4] (Scheme 1). The corresponding nitroso derivative **3** was obtained in 91% yield

Scheme 1. Preparation of the Upper-Rim-Bridged Calix[4]arenes



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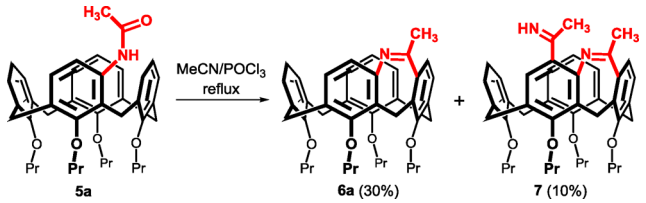
via reaction with nitrosyl chloride generated in situ from isoamyl nitrite and aqueous HCl at 0 °C.[10] Reduction of the nitroso group was accomplished using Raney nickel and hydrazine hydrate in refluxing EtOH to provide the key intermediate, *meta*-amine **4**, in 89% yield. The corresponding acylation was carried out using various carboxylic acid derivatives. Thus, compound **5a** was smoothly prepared in 91% yield by reaction with acetic anhydride in THF in the presence of triethylamine (TEA) as a base (Scheme 1). A similar reaction with benzoyl chloride led to **5b** in 53% yield. To obtain intermediates possessing a reactive functional group that is potentially capable of further derivatization, compounds **5c** and **5d** were prepared using $BrCH_2COBr$ and $ClCH_2COCl$ in 42% and 39% yield, respectively.

(*S*)-*O*-Acetylmandelic acid was reacted with amine **4** using standard DCC coupling conditions to provide amide **5e** in 41% yield. The same product **5e** was obtained in slightly higher yield (57%) using the chloride of the above-mentioned acid. Amide **5e** combines the inherent chirality of the *meta*-substituted skeleton with the stereogenic center of the mandelic acid moiety, thus leading to a mixture of diastereomeric products. Unfortunately, all of our attempts to separate this mixture were unsuccessful.

The Bischler−Napieralski reaction[11] is a well-known method to access 3,4-dihydroisoquinolines from the *β*-ethylamides. Initially we used the traditional condensation agent, $POCl_3$ in refluxing MeCN. The reaction of amide **5a** led to a mixture of two main products: the expected bridged compound **6a** isolated in 30% yield and the byproduct **7** with an additional acetylimino group in 10% yield (Scheme 2). The latter is

Scheme 2. Unusual Course of the Bischler−Napieralski Reaction



probably formed by initial direct acylation of **5a** with MeCN under the reaction conditions and subsequent bridging of the intermediate. The structure of **7** was supported by the presence of two methyl singlets in the ^{1}H NMR spectrum ($CDCl_3$) at 2.83 and 2.91 ppm, together with a singlet from the aromatic region of the molecule (7.73 ppm). The HRMS ESI$^+$ analysis of **7** revealed signals at m/z = 673.40042 and 695.38144, which were in agreement with the predicted values for the $[M + H]^+$ (673.39998) and $[M + Na]^+$ (695.38193) cations.

As benzoyl amide **5b** under identical reaction conditions yielded no cyclization product, we used higher-boiling toluene instead of MeCN. Under these conditions, the corresponding cyclic products **6a** and **6b** were isolated in 39% and 49% yield, respectively, after purification of the crude reaction mixture by preparative TLC on silica gel. Similar cyclization of **5d** gave the chloromethyl-substituted derivative **6d** in 41% yield. Interestingly, the same chloromethyl derivative **6d** was obtained in even higher yield (50%) by the reaction of bromoacetylamide **5c**, showing the lower stability of the bromine atom in the presence of $POCl_3$. The cyclization of a diastereomeric mixture of **5e** led to deprotection of the acetyl group and subsequent oxidation of the free OH group to the ketone moiety, resulting in the formation of **6e** in 19% yield.

The structures of the products were confirmed by a combination of NMR and MS techniques. The HRMS ESI$^+$ analysis of **6a** showed signals at m/z = 632.37399 and 654.35502, which were in good agreement with the $[M + H]^+$ (632.37344) and $[M + Na]^+$ (654.35538) cations predicted for the bridged product. The ^{1}H NMR spectrum of **6a** ($CDCl_3$) revealed the presence of four doublets at 2.79, 3.19, 3.24, and 3.28 ppm with appropriate geminal coupling constants ($J \approx 12.1-12.5$ Hz), consistent with the equatorial C−H bonds from the methylene bridges. Similarly, four doublets corresponding to axial C−H bonds could be found between 4.41 and 4.60 ppm. This clearly supported the absence of any symmetry elements in the product (inherent chirality).

The racemic compound **6a** was subsequently separated into enantiomers **6a_1** and **6a_2** on a chiral polysaccharide column. The method was developed on an analytical scale (see Figure 1a), allowing for efficient preparative enantioseparation (see the

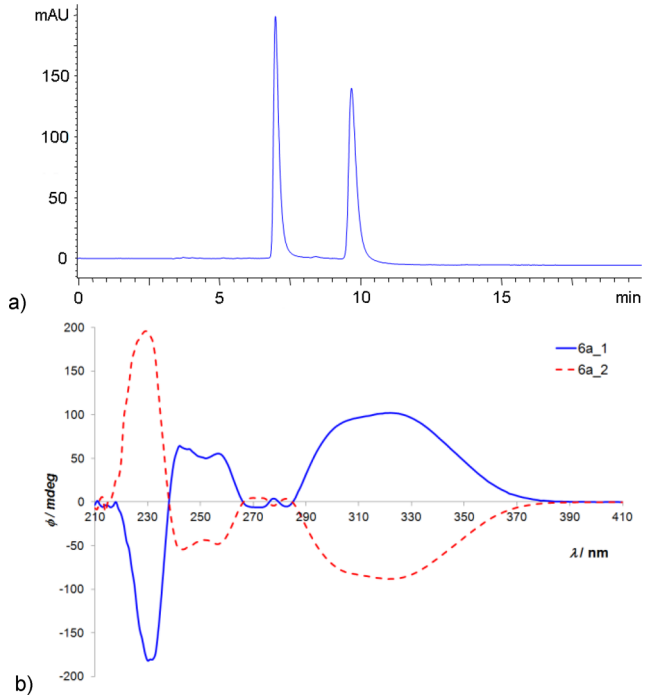


Figure 1. (a) Chromatographic resolution of racemic compound **6a** on a chiral column (Chiral Art Amylose-SA; mobile phase: heptane/propan-2-ol (95/5 v/v); flow rate: 1 mL/min; rt). (b) ECD spectra of the separated enantiomers of **6a** in MeOH: the first-eluting enantiomer **6a_1**, solid blue line; the second-eluting enantiomer **6a_2**, dashed red line.

Supporting Information (SI)). The enantiomeric character of the separated substances **6a_1** and **6a_2** was verified with electronic CD (ECD) spectroscopy, which showed the typical mirror images (Figure 1b). The optical purities of both enantiomers were found to be >99.5% ee (see the SI).

Final unambiguous proof of the structure of the upper-rim-bridged derivatives was obtained by single-crystal X-ray structure determination[12] of enantiomer **6a_1** (the first-eluting isomer from the above-described racemate resolution) obtained by slow evaporation from an $EtOH/CH_2Cl_2$ mixture. This revealed that the enantiomer **6a_1** crystal belonged to the monoclinic system, space group $P2_1$. As follows from the X-ray

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structure (Figure 2), the absolute configuration of inherently chiral **6a_1** could be assigned as *cS* (or *M*).[9] The asymmetric

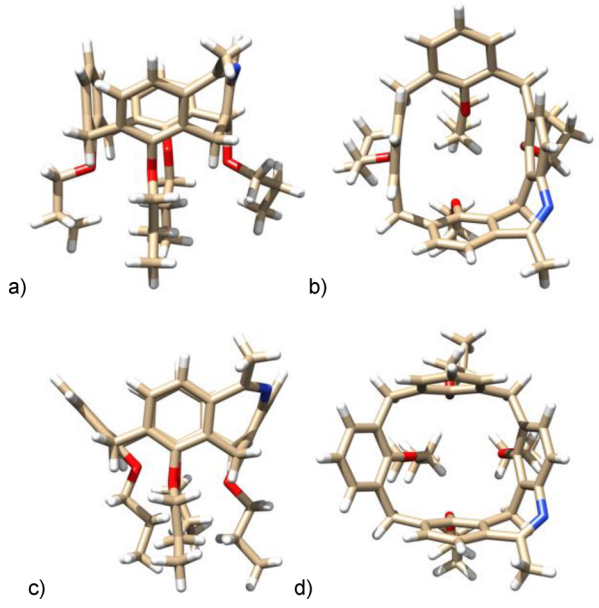

Figure 2. Single crystal X-ray structures of the two *pinched cone* conformations **PC1** and **PC2** of enantiomer **6a_1**: (a) **PC1** side view; (b) **PC1** top view; (c) **PC2** side view; (d) **PC2** top view.

unit consists of two independent molecules showing two different *pinched cone* conformations **PC1** and **PC2**. If we define the main plane of the molecule by the four C atoms of the CH_2 bridges, the corresponding interplanar angles Φ with aromatic subunits are 97.96°, 117.82°, 90.09°, and 137.83° for **PC1** starting from the moiety bearing the nitrogen atom and continuing clockwise from the top view (see Figure 2a,b). The same angles for **PC2** were Φ = 113.44°, 101.87°, 135.75°, and 101.02°. The existence of two different conformations **PC1** and **PC2** was rather unexpected as it indicated that the two-atom bridge is still long enough that it cannot stop the interconversion between the two *pinched cone* conformers.

Our preliminary binding experiments with (*rac*)-**6a** indicated that this bridged compound can interact with neutral molecules bearing an acidic CH_3 group. Thus, ^{1}H NMR titration experiments ($CDCl_3$) carried out with MeCN and $MeNO_2$ yielded the corresponding complexation constants 5.5 ± 1.2 and 20 ± 12 M^{-1}, respectively. The complexation constants were determined by analyzing the binding isotherms (obtained from NMR data) using the application Bindfit,[12] which is designed to work with classical supramolecular titration data obtained from NMR, UV, fluorescence, and other methods.[13] On the basis of these results, we attempted the enantioselective resolution of the chiral guest molecule. Natural (*S*)-nicotine was reacted with methyl iodide in AcOH to achieve methylation of the pyridinium moiety,[14] and the resulting *N*-methylnicotinium salt **8** was used for the titration experiments. As shown in Figure 3a, the addition of 1 equiv of receptor **6a_1** to a solution of **8** in $CDCl_3$ led to the complexation-induced shift (CIS) of the singlet of methyl group A (from the pyridinium moiety) toward higher magnetic field (CIS = −101 Hz). Similar shielding effects were demonstrated for the neighboring hydrogen atom at position 2 (CIS = −60 Hz), especially that at position 6 (CIS = −143 Hz), and also that at position 5 (CIS = −56 Hz). This indicated the immersion of

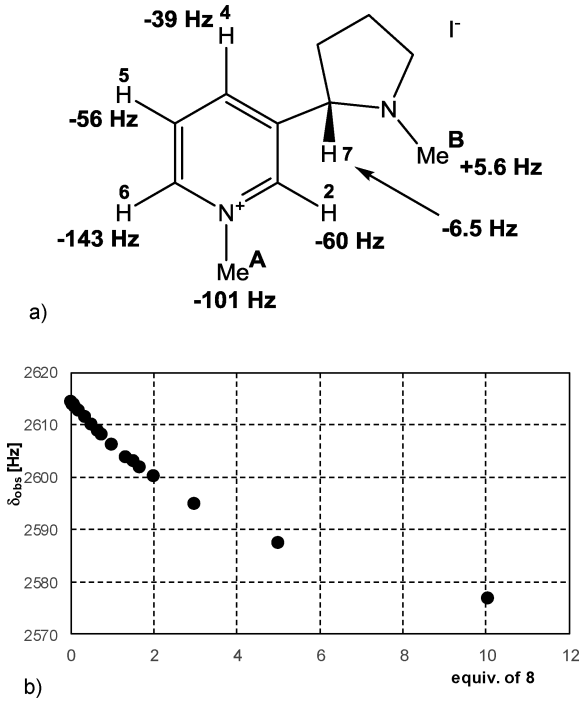

Figure 3. (a) ^{1}H NMR CIS values (+, upfield shift; −, downfield shift) for compound **8** induced by the addition of 1 equiv of **6a_1** (400 MHz, $CDCl_3$, $c = 3 \times 10^{-3}$ mol·dm^{-3}, 298 K). (b) ^{1}H NMR titration curve for **6a_1** with **8** (400 MHz, $CDCl_3$, $c = 3 \times 10^{-3}$ mol·dm^{-3}, 298 K).

this part of the pyridinium moiety into the aromatic cavity of the receptor using a combination of CH−π, π−π, and/or cation−π interactions[15] with surrounding aromatic subunits. Methyl group A was obviously shielded by the magnetic anisotropy of the aromatic cavity (CIS = −101), while the *N*-methyl group B on the pyrrolidine part of the molecule showed a small downfield shift (CIS = +5.6 Hz) at the same time. Together with the very small shift for position 7 (CIS = −6.5 Hz), this confirmed that the pyrrolidine part of nicotine was localized outside the cavity of the receptor.

As shown in Figure 3b, the addition of **8** to the solution of **6a_1** in $CDCl_3$ also led to distinct upfield shifts of the aromatic signals on the receptor that could be easily used for the construction of the corresponding titration curve. The resulting complexation constant for receptor **6a_1** was 81 ± 2 M^{-1}. The same titration experiments with enantiomer **6a_2** led to a higher value (94 ± 5 M^{-1}), indicating only modest enantioresolution ability of the receptors in this particular case, probably as a consequence of the relatively large distance between the chiral center and the point of immersion into the cavity. Further research on chiral recognition is currently in a progress.

In conclusion, mercuration of calix[4]arene immobilized in the *cone* conformation allowed the introduction of an amino group at the *meta* position of the basic skeleton. Acylation and subsequent intramolecular Bischler−Napieralski-type cyclization led to a novel class of bridged calixarenes containing a seven-membered ring. These compounds with an enlarged and rigidified cavity represent a unique inherently chiral system that may potentially be applicable for the design of receptors. This can be documented by the complexation of neutral compounds bearing an acidic CH_3 group (MeCN, $MeNO_2$) or by the inclusion of *N*-methylpyridinium derivatives into the cavity

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through the combination of CH−π and/or cation−π interactions. The absolute configuration of one enantiomer, obtained by resolution of the racemate using chiral HPLC, was assigned by single-crystal structure determination.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01170.

Experimental procedures, full characterization of compounds **3**, **4**, **5a−e**, **6a−d**, **7**, and **8**, and results of the complexation study (PDF)

X-ray crystallographic data for **6a_1** (CIF)

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Notes

The authors declare no competing financial interest.

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