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Dimercuration of Calix[4]arenes: Novel Substitution Pattern in Calixarene Chemistry

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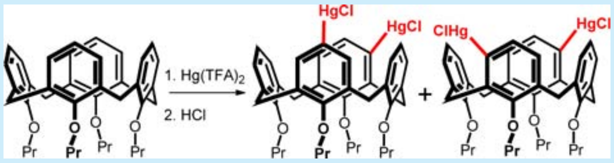
Supporting Information

ABSTRACT: A mercuration reaction of tetrapropoxycalix[4]arene immobilized in the *cone* conformation gave a mixture of two dimercurated products (*meta,meta* and *meta,para*) in approximately a 1:1 ratio. Both regioisomers represent inherently chiral compounds, which makes them very attractive for design of novel receptors. As demonstrated by Pd-catalyzed arylation, the different reactivity of HgCl functions in the *meta,para*-disubstituted isomer opens the door for regioselective introductions of two different functional groups to achieve a substitution pattern so far unknown in calixarene chemistry.



Electrophilic substitution of classical calix[*n*]arenes[1] represents a straightforward way for the modification of aromatic subunits (the so-called upper rim) of the parent macrocyclic skeleton. All direct electrophilic substitutions of the upper-rim-unsubstituted calixarenes known so far in calixarene chemistry[1,2] lead exclusively to the *para*-substituted (with respect to phenolic function) products. These compounds are then used as valuable intermediates in the design and preparation of more sophisticated supramolecular systems.

Very recently, we described[3] an unprecedented reaction of classical calix[4]arene **1** with mercury(II) trifluoroacetate leading exclusively to the *meta*-substituted organomercurial product **2**. This unexpected regioselectivity thus enables a direct derivatization of calixarenes in this unusual position as demonstrated by *meta*-arylation[4] or by the formation of *meta*-bridged calixarenes.[5] As the *meta*-substituted[6] calixarenes represent inherently chiral compounds, these macrocyclic systems are very attractive potential building blocks for the construction of chiral receptors. In this paper we report on the dimercuration reaction of calix[4]arene **1**, which leads regioselectively to a mixture of two isomers, **3** and **4**. Although organomercurial compounds are not very popular due to their alleged toxicity, in this case they enable a direct way to inherently chiral unique substitution pattern (*meta,para*) inaccessible[7] by other synthetic methods.

The regioselectivity of the dimercuration reaction was studied using the *cone* conformer **1**, which was reacted with 2 equiv of Hg(TFA)$_2$ in CHCl$_3$ at room temperature. As depicted in Scheme 1, theoretically up to 10 different regioisomers **A**–**J** could be obtained if we consider only monomercuration of aromatic subsunits. It is known[3] that monomercuration leads to the *meta*-substituted compound **2**, while the corresponding *para*-isomer was never observed in the reaction mixture. This excludes the formation of isomers **I** and **J**, which can be formed only from a *para*-substituted intermediate. As the mercury trifluoroacetates cannot be purified on silica gel, the crude reaction mixture was transformed into the chloromercurio derivatives by reaction with brine. This transformation allowed us to remove the unreacted starting compound **1** (4%) and monoderivative **2** (10%) by column chromatography. Surprisingly, the fraction containing dimercurated compounds consists of only two main products, which were separated by repeated chromatography and crystallization. As a result, compounds **3b** and **4b** were isolated in 13% and 14% yields, respectively. Low yields are caused by the affinity of the mercurated calixarenes to sorbent during chromatographic separation. On the other hand, the reaction is easily scalable up to a gram scale.

The assignment of structures is not a trivial task. Thus, the splitting pattern and multiplicity of signals in the ^{1}H NMR spectrum of **3b** (CDCl$_3$) indicates a highly symmetrical structure with both HgCl groups in the *meta* positions (**A**–**E**). Two pairs of doublets at 4.70, 4.46, 3.22, and 3.03 ppm for methylene bridges with typical geminal coupling constants (14 Hz), together with the signals of only two different propyl groups, indicate the C_2 symmetry of molecule corresponding to structure **B**.

On the other hand, the ^{1}H NMR spectrum of **4b** exhibits lower symmetry as demonstrated by four doublets for equatorial C–H bonds. This excludes structures **A**, **B**, **D**, and **E** and indicates that an unknown isomer possesses both *meta* and *para* substitution. This assumption was further corroborated by ^{199}Hg NMR spectra of both isomers (Figure 1). The spectrum of **3b** shows a doublet (J = 154 Hz) at −1029 ppm (referenced to HgPh$_2$, which was reported[8] to have δ = −745 ppm toward HgMe$_2$ as a standard). The spectrum of **4b** shows a similar doublet at −1031 ppm corresponding to the *meta*-substitution) and a triplet at −1065 ppm (J = 188 Hz)

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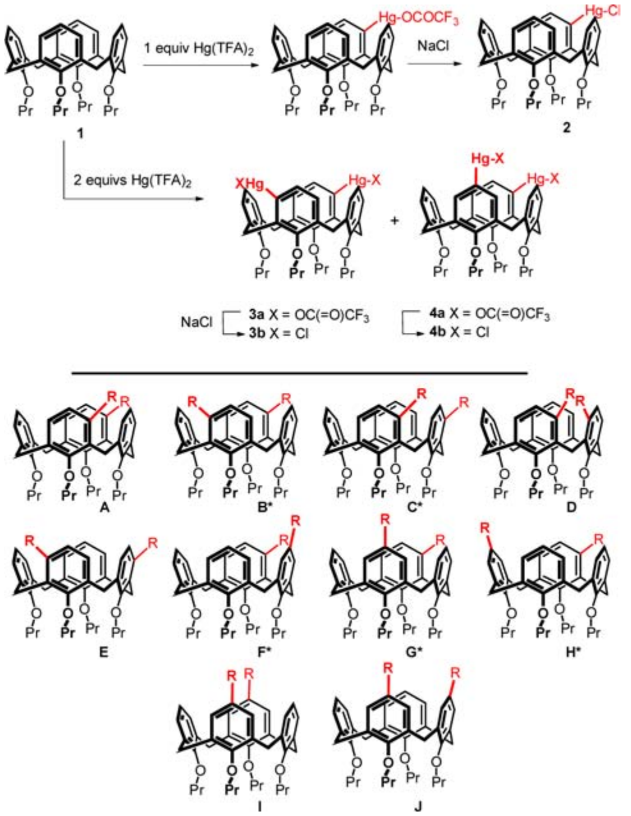
Scheme 1. Dimercuration of Calix[4]arenes and Theoretically Possible Regisomers (Asterisk Denotes Inherent Chirality)



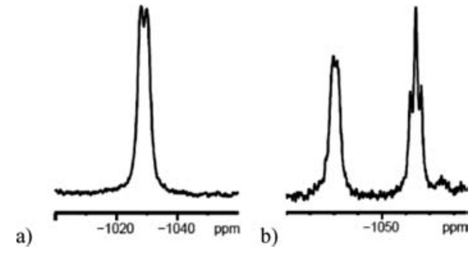


Figure 1. ^{199}Hg NMR spectra of (a) **3b** and (b) **4b** ($CDCl_3$, 298 K, 89 MHz, $HgPh_2$ as standard).

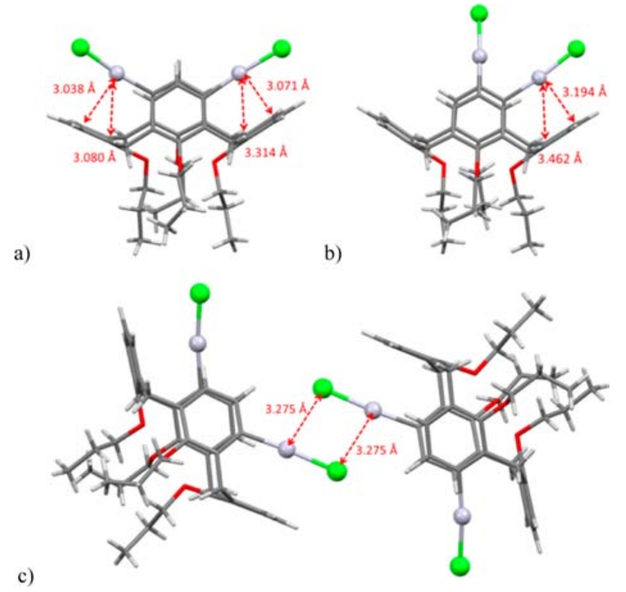


Figure 2. (a) X-ray structure of **3b** showing the Hg···aromatic interactions and (b) the same for isomer **4b**. (c) Packing motif of **3b**.

indicating the *para*-substitution pattern. The above results clearly showed for the isomers **F**, **G**, or **H**, nevertheless, the final assignment of this structure was enabled only by a single crystal X-ray analysis.

Compound **4b** crystallizes in the space group *P*-1 with both enantiomers in the asymmetric unit. The calixarene moiety adopts the *pinched cone* conformation (Figure 2b) with chloromercurio groups in *meta* and *para* positions on the opposite phenolic rings (isomer **G**) oriented inside (the interplanar angle ~27.15°). The unsubstituted phenolic units are oriented outside the cavity with interplanar angle ~112.3°. Chloromercurio group in the *meta* position shows intramolecular Hg···π interactions with two neighbor aromatic carbons (η^2 interaction). The Hg···C distances are 3.194 and 3.462 Å, respectively. Similar Hg···π interactions can be also seen in the X-ray structure of **3b** (Figure 2a). The corresponding Hg···C distances 3.072, 3.314 Å (for one aromatic moiety) and 3.038, 3.080 Å (for the second one) indicate that these interactions are much stronger if compared with isomer **4b**. An interesting motif can be found in crystal packing of **3b** where the intermolecular Hg···Cl interactions (3.275 Å) lead to the formation of dimers (Figure 2c). This kind of interaction is encountered also in **4b** where the dimer is formed via the intermolecular interactions between two -HgCl groups in the *meta* positions (3.270 and 3.272 Å).

The formation of *meta,para* isomer **G** is rather unexpected as we have never observed direct *para*-substitution during the monomercuration of compound **1**. To gain deeper insight into the regioselectivity of dimercuration, we have carried out a quantum-chemical calculation of the correspoding isomers **A**–**H**. The combination of methods PBEPBE/LANL2DZ, which was successfully applied in our previous paper,[3] was used for the evaluation of the thermodynamic stability of the dimercuration products.

Calix[4]arene immobilized in the *cone* conformation is known to exhibit so-called *pinched cone-pinched cone* equilibrium.[1] That is why we took into consideration two frontier conformations with the Hg-substituted rings pointing outside the cavity ("ring out") or inside the cavity ("ring in"). As can be seen from Table 1, the *meta,para* substitution in isomer **G** is thermodynamically the most favored arrangement. This is in good agreement with our experiments and indicates that regioselectivity can be thermodynamically driven. On the other hand, the energy of second isolated isomer **B** (11.26 kcal·mol^{-1}) is visibly higher than that of product **A** (8.11 kcal·mol^{-1}) and **C** (3.04 kcal·mol^{-1}), which were never observed in the reaction mixture.

In this context, a dimercuration reaction was carried out at three different temperatures to evaluate the influence of reaction temperature on the regioselectivity. Reaction carried out at 0 and 30 °C gave the identical mixture of isomers **3b** and **4b** as the main products.[9] The same reaction conditions at 60 °C led to a very small amount of dimercurated products, while probably higher mercurated compounds were formed (as deduced from their TLC behavior).

To demonstrate the synthetic usefulness of dimercurio derivatives, we have carried out an arylation reaction using

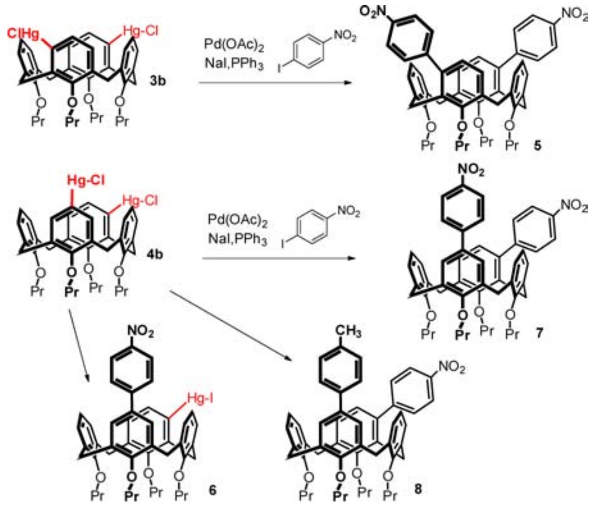
Table 1. Comparison of Total and Relative Energies of the Corresponding Dimercurated Isomers A−H (X = $-OC(=O)CF_3$)

structure[a]	total energy[b]	relative energy[c]
A (Hg in)	−2987.0679636	8.11
A (Hg out)	−2987.0467116	21.45
B (Hg in)	−2987.0629571	11.26
B (Hg out)	−2987.0475791	20.91
C	−2987.0601964	3.04
D	−2987.0703280	21.53
E	−2987.0547837	16.38
F (*para* Hg in)	−2987.0502192	19.25
F (*para* Hg out)	−2987.0601779	13.00
G (*para* Hg in)	−2987.0808945	0.00
G (*para* Hg out)	−2987.0467544	21.42
H (*para* Hg in)	−2987.0487432	20.18
H (*para* Hg out)	−2987.0543193	16.68

[a] PBEPBE/LANL2DZ method. [b] In au. [c] In kcal·mol^{-1}.

conditions[4] developed for monoderivative **2**. Thus, the reaction of **3b**/**4b** with 2 equiv of *p*-nitrophenyl iodide using a $Pd(OAc)_2/PPh_3/NaI$ catalytic system in acetone/THF mixture gave smoothly the corresponding diarylated compounds **5** or **7** in approximately 50% yields (Scheme 2). Both products represent completely novel substitution pattern in calixarene chemistry.

Scheme 2. Arylation of Dimercurycalix[4]arenes 3b and 4b



Interestingly, when reacted with only 1 equiv of *p*-nitrophenyl iodide, isomer **4b** yielded monosubstituted product **6** (40%), indicating the higher reactivity of the HgCl group in the *para* position. The structure of this intermediate was unambiguously confirmed by X-ray crystallography. As shown in Figure 3, the calixarene moiety adopts the *pinched cone* conformation with Hg···π interactions between the iodomercurio group in *meta* position and neighbor aromatic unit (η^2 interaction). The corresponding Hg···C distances are 3.253 and 3.081 Å, respectively. The formation of compound **6** even extends the synthetic possibilities, offered by organomercurial chemistry of calix[4]arene, as it enables the introduction of two different functional groups into the *meta* and *para* positions. To validate this assumption, we have carried out a one-pot double-arylation procedure of **4b**. The first arylation with 1 equiv of *p*-tolyl iodide was accomplished under standard conditions, and then another equivalent of *p*-nitrophenyl iodide was added to the same flask without any isolation of intermediate. The expected derivative **8** bearing two different aryl moieties was isolated in 26% yield after column chromatography.

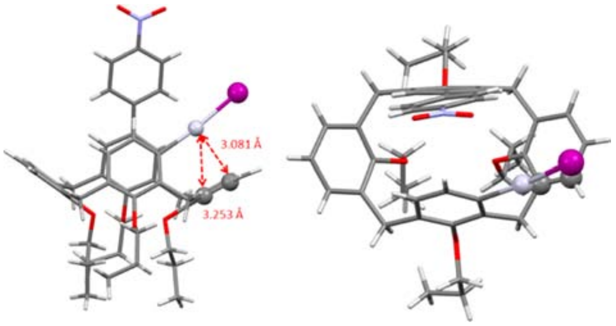


Figure 3. X-ray structure of **6** showing the Hg···aromatic interactions.

In conclusion, a highly regioselective dimercuration of the calix[4]arene skeleton leads to two different products **3b** and **4b** with distal *meta*,*meta* and *meta*,*para* arrangement of functional groups, respectively. Both compounds represent a unique substitution pattern in calixarene chemistry so far inaccessible by other synthetic methods. As demonstrated by Pd-catalyzed arylation reactions, different reactivity of *meta* and *para* mercury groups open the way for the synthesis of completely novel type of inherently chiral calixarenes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, full characterization of compounds, and the X-ray structures of **3b**, **4b**, and **6**. 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.

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