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## Mercuration of calix[4]arenes immobilized in the 1,2- and 1,3-alternate conformations

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### ABSTRACT

Calix[4]arenes immobilized in the 1,2-alternate and 1,3-alternate conformations were directly mercured using Hg(TFA)<sub>2</sub>. The reaction regioselectivity was compared with the thermodynamic stability of the corresponding products obtained by theoretical calculations (wB97XD/def2tzvp method). Both experimental and theoretical data suggest that *para* substitution is slightly preferred over *meta* attack for the 1,2-alternate conformer, while in the case of the 1,3-alternate conformation the situation is reversed. The usefulness of the mercury intermediates was demonstrated by the synthesis of a rigid upper-rim-bridged calixarene in the 1,2-alternate conformation possessing a highly distorted cavity. A simple transformation of the organomercury compounds afforded the corresponding iodo derivatives, which are potentially applicable as building blocks for further synthesis. Moreover, many products are inherently chiral representing unique substitution patterns inaccessible by common “mercury-free” chemistry.

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### Introduction

Calix[*n*]arenes, a well-known family of macrocyclic oligophenols, have attracted the attention of supramolecular chemists for many years because of their easy synthesis and derivatization.<sup>1</sup> They can not only be prepared on a large scale with well-defined cavity diameters, but moreover, in the case of calix[4]arenes, conformations (atropisomers) with unique 3D shapes of the cavity (*cone*, *partial cone*, *1,2-alternate*, and *1,3-alternate* conformations) are readily available. Unsurprisingly, calix[4]arenes have become popular building blocks and molecular scaffolds in the design of novel ligands and receptors.<sup>2</sup>

The *para*-position (with respect to the phenolic hydroxyl group) of calix[4]arenes could be easily modified by direct electrophilic aromatic substitution using halogenation, chloromethylation, nitration, sulfonation, and Friedel-Crafts reactions.<sup>1</sup> Obviously, the regioselectivity of these reactions is governed by the overall electronic effects of the substituents introduced onto the aromatic macrocycle (–OH/–OR, versus CH<sub>2</sub> groups) leading exclusively to a *para*-substitution pattern. On the other hand, the introduction of substituents at the *meta* position<sup>3</sup> requires specific approaches and time-consuming synthetic strategies.<sup>4</sup>

Recently, we discovered an unprecedented method for direct *meta*-substitution of the basic skeleton *via* the mercuration of calix[4]arenes.<sup>5</sup> As indicated by theoretical calculations (PBEP-BE/LANL2DZ), the electrophilic species <sup>+</sup>Hg(TFA) (soft acid) is highly stabilized by interactions inside the π aromatic cavity (soft base) leading preferentially to *meta*-substitution. The thermodynamic stability of the *meta*-products is favored over the *para*-derivative by more than 3.5 kcal mol<sup>–1</sup>. The X-ray structures of the *meta*-mercured intermediates also revealed strong Hg···π interactions of the –HgCl groups with the neighboring aromatic subunits,<sup>6</sup> a phenomenon which is only enabled for *meta*-substitution. All of these data suggest that the unexpected regioselectivity is thermodynamically driven and the most stable isomer is formed.

Organomercurial intermediates represent valuable synthetic tools, as their subsequent transformation can lead to unique substitution patterns in calixarene chemistry (Fig. 1).<sup>7</sup> As all the mercurations carried out so far have only been applied to the *cone* or *partial cone* conformers, we were curious if the same regioselectivity could be achieved using the 1,2-alternate or 1,3-alternate conformations where the stabilizing effect of a neighboring aromatic unit is either partly or entirely missing. Herein, we report the direct mercuration<sup>8</sup> of the above-mentioned unexplored conformers, and the synthesis of novel substitution patterns using organomercury intermediates.

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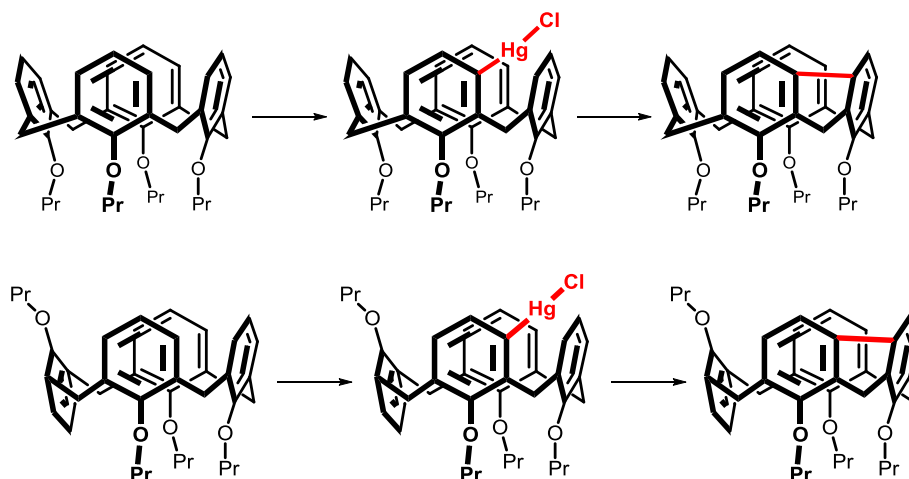


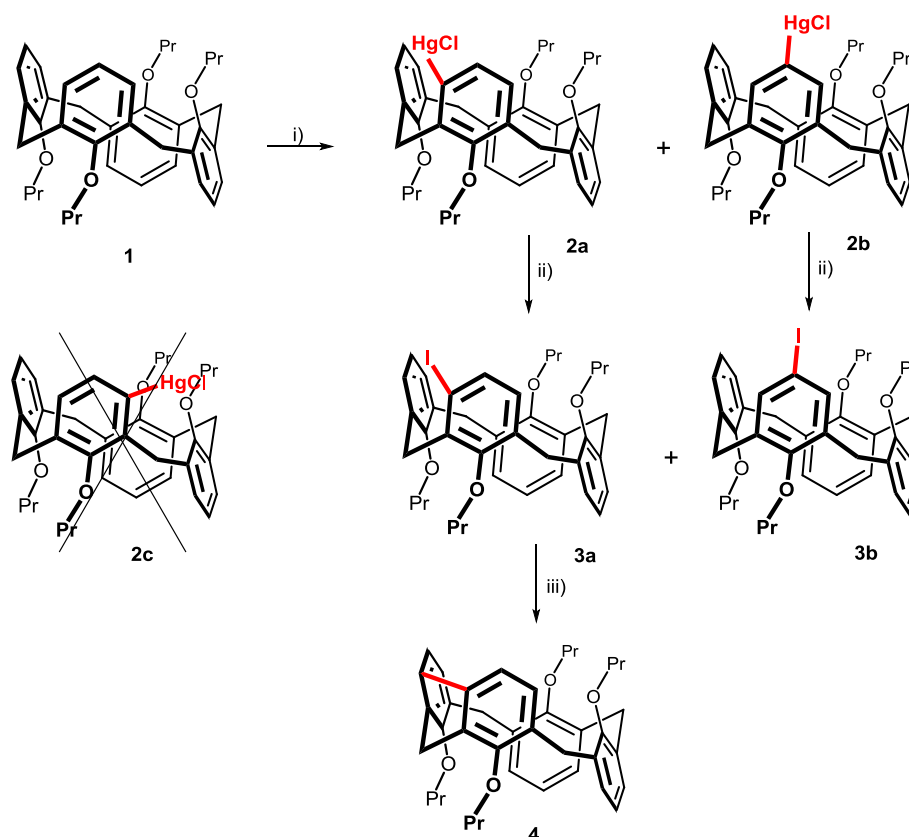
Fig. 1. Direct mercuration of the *cone* and *partial cone* conformations of calix[4]arenes and the synthesis of bridged calixarenes.

## Results and discussion

Direct mercuration of 1,2-*alternate* conformer **1** was carried out using the procedure as previously reported by our group for the *cone* conformation.<sup>5</sup> Thus, a solution of compound **1** in  $\text{CHCl}_3$  was stirred with  $\text{Hg}(\text{TFA})_2$  (1.0 equiv.) at room temperature overnight. The mercury trifluoroacetate intermediates were then transformed into the corresponding chloromercurio compounds by the addition of NaCl (Scheme 1). The evaporated reaction mixture was then subjected to column chromatography on silica gel to provide the unreacted starting material in 26% recovery and an inseparable

mixture of monomercured isomers (as determined by HRMS).<sup>9</sup> As shown in Scheme 1, up to three different monomercured regioisomers **2a–c** can be theoretically prepared. However,  $^1\text{H}$  NMR spectroscopic analysis of the crude fraction confirmed the presence of only two main products in an approximately 60:40 ratio.

To gain deeper insight into the regioselectivity of the mercuration reaction, the thermodynamic stability of the corresponding regioisomers **2a–c** was evaluated using the wB97XD/def2tzvp method, which was previously applied to the *cone* and *partial cone* conformations.<sup>5,6b</sup> The structures were calculated in their trifluo-



Scheme 1. Reagents and conditions: (i) (a)  $\text{Hg}(\text{TFA})_2/\text{CHCl}_3$ , rt, overnight, (b) NaCl (56% **2a** + **2b**, 40:60 mixture); (ii)  $\text{I}_2/\text{MeCN} + \text{CHCl}_3$ , rt, overnight (99% **3a** + **3b** mixture); (iii)  $\text{Pd}(\text{OAc})_2/\text{PCy}_3\text{BF}_4/\text{K}_2\text{CO}_3/\text{DMA}$ , 140 °C, overnight. (13% **4**, based on **1**).

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