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Unprecedented *Meta*-Substitution of Calixarenes: Direct Way to Inherently Chiral Derivatives

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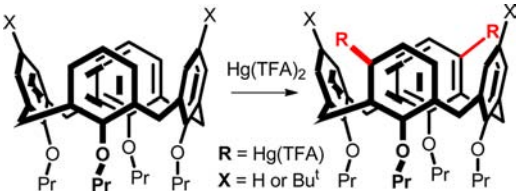
ABSTRACT



Electrophilic aromatic substitution in the calix[*n*]arene series is a well-established procedure leading exclusively to *para*-substituted derivatives. An unprecedented regioselectivity of the mercuration reaction leading to the *meta*-substituted calix[4]arenes is described. These compounds represent a new type of substitution pattern in classical calixarene chemistry and open the door for the straightforward synthesis of inherently chiral receptors based on calixarenes.

Calixarenes[1] and more recently thiacalixarenes[2] are frequently used as molecular scaffolds or building blocks in supramolecular chemistry. The unique 3D shapes of these molecules together with well-established derivatization procedures make these compounds good candidates for the design and construction of various molecular receptors. A general strategy usually consists of (i) immobilization of calixarene in a specific conformation (the *cone* conformer is mostly used due to the precisely defined cavity) and (ii) subsequent introduction of functional groups into the upper rim of a calixarene.

Electrophilic aromatic substitution represents a straightforward strategy for the modification of classical calixarenes. Many reactions known from the chemistry of aromatic compounds (nitration, halogenation, sulfonation, alkylation, acylation, etc.) were optimized for calix[*n*]arenes[1,3] and gave high yields of the *para*-substituted products (Figure 1). In this context, we have recently described unexpected regioselectivity during the nitration and formylation of the thiacalix[4]arene skeleton, surprisingly leading to the *meta* substitution.[4] Obviously, this phenomenon can be ascribed to the electronic effects of two sulfur atoms which can override the influence of the

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(1) For books on calixarenes, see: (a) Gutsche, C. D. *Calixarenes: An introduction*, 2nd ed.; The Royal Society of Chemistry; Thomas Graham House: Cambridge, 2008. (b) Vicens, J., Harrowfield, J., Backlouti, L., Eds. *Calixarenes in the Nanoworld*; Springer: Dordrecht, 2007. (c) Mandolini, L.; Ungaro, R. *Calixarenes in Action*; Imperial College Press: London, 2000.

(2) For recent reviews on thiacalixarenes, see: (a) Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291. (b) Lhotak, P. *Eur. J. Org. Chem.* **2004**, 1675.

(3) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.

(4) (a) Kundrat, O.; Kroupa, J.; Böhm, S.; Budka, J.; Eigner, V.; Lhotak, P. *J. Org. Chem.* **2010**, *75*, 8372. (b) Kundrat, O.; Cisarova, I.; Böhm, S.; Pojarova, M.; Lhotak, P. *J. Org. Chem.* **2009**, *74*, 4592. (c) Kundrat, O.; Dvorakova, H.; Eigner, V.; Lhotak, P. *J. Org. Chem.* **2010**, *75*, 407. (d) Kundrat, O.; Dvorakova, H.; Cisarova, I.; Pojarova, M.; Lhotak, P. *Org. Lett.* **2009**, *11*, 4188.

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alkoxy group otherwise known as a textbook example of the *ortho*/*para* strongly orienting group (Figure 1).

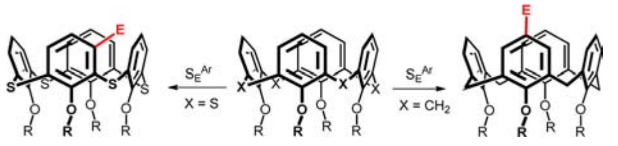
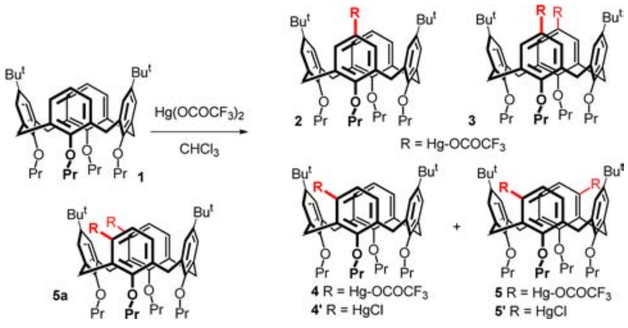


Figure 1. Regioselectivity of electrophilic substitution in the thiacalixarene and classical calixarene series.

The *meta*-substituted derivatives represent attractive inherently chiral systems, and their application in classical calix[*n*]arene chemistry would enable the construction of chiral receptors.[5,6] Unfortunately, no such direct substitution has been described so far as the influence of OR or OH groups on the lower rim always direct the electrophile exclusively to the para position of the calixarene skeleton.

Scheme 1. Electrophilic Substitution of **1** with Hg(TFA)$_2$



During our ongoing research on calixarene derivatization we discovered an unprecedented regioselective substitution of classical calixarenes using a very simple experimental procedure. Derivative **1** immobilized in the *cone* conformation was treated with mercury(II) trifluoroacetate in CHCl$_3$ at rt to achieve the mercuration of unsubstituted phenolic rings. Depending on the stoichiometry, either mono- or disubstituted derivatives were easily obtained in good yields (Scheme 1). The structures of organomercurial products were assigned by MS. Thus, MS ESI$^+$ analysis of a monosubstituted compound showed a signal at m/z = 1041.5, which is in agreement with the [M + Na]$^+$ cation, also the exact mass obtained by HRMS (m/z = 1041.41845) perfectly agreed with a proposed structure.

On the other hand, the splitting pattern and multiplicity of signals in the ^{1}H NMR spectra of crude products did not correspond with those expected for *para*-substituted derivatives **2** and **3**. Thus, two pairs of doublets at 2.99, 3.24, 4.46, and 4.69 ppm for methylene bridges with typical geminal coupling constants ($J \approx 14$ Hz) suggested the cone conformation with C_2 symmetry. The presence of two doublets at 6.03 and 6.33 ppm with an *ortho*-coupling constant ($J \approx 7.8$ Hz) showed the presence of two neighboring H-atoms in the aromatic part of the product. This evidence clearly supported the introduction of Hg(TFA) groups into the *meta* position of the calix[4]arene skeleton leading to inherently chiral structure **5**. Surprisingly, the formation of achiral regioisomer **5a** was not observed.

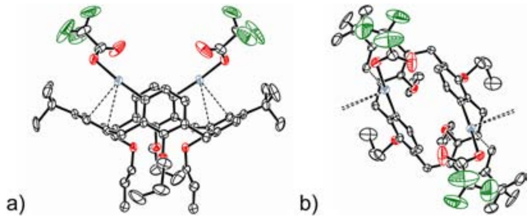


Figure 2. X-ray structure of **5** (H-atoms were omitted for better clarity): (a) intramolecular and (b) intermolecular Hg–π interactions.

The final unequivocal structural evidence was obtained by single crystal X-ray crystallography (Figure 2). Compound **5** crystallizes in the centrosymmetric space group $C2/c$ with the half of the molecule in the independent part of the lattice cell. The molecule keeps the C_2 symmetry, and both enantiomers are present in the crystal. The calixarene moiety adopts the *pinched cone* conformation (with the interplanar angle between two *tert*-butyl phenolic units ~125° and with ~37° between two *meta* substituted/mercuriated aromatic rings). The linear coordination sphere of mercury (the C–Hg–O bond angle is 174° with distances 2.038 and 2.092 Å) is supported by Hg–π interaction of the adjacent phenolic unit bearing a *tert*-butyl group (Figure 2a) and by Hg–π intermolecular interaction with the proximate calixarene molecule in the crystal lattice (Figure 2b). The distance of the mercury atom from the plane defined by the aromatic ring in the intramolecular Hg–π interaction is 2.98 and 3.21 Å in the intermolecular one. The stronger intramolecular interaction draws the Hg-atom into the calixarene cavity causing the distortion of the mercuriated aromatic ring and its deviation from the parallel direction (~7°).

Presuming a similar interaction as a general feature of the *meta* mercuriated calix[4]arenes, the presence of the first Hg-atom in **4** probably deactivates the nucleophilicity of the neighboring aromatic unit which excludes the formation of achiral regioisomer **5a**. Another explanation lies

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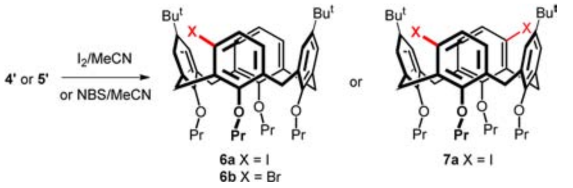
(5) *Meta*-substituted calix[4]arene derivatives were recently prepared by the rearrangement of *p*-bromodienone derivatives: (a) Gatea, C.; Troisi, F.; Talotta, C.; Pierro, T.; Neri, P. *J. Org. Chem.* **2012**, *77*, 3634. (b) Troisi, F.; Pierro, T.; Gaeta, C.; Neri, P. *Tetrahedron Lett.* **2009**, *50*, 4416. Nevertheless, this approach needs the lower rim unsubstituted starting calixarenes.

(6) Several *meta*-substituted calixarenes were prepared using *ortho*-directing groups introduced into the *para* position of the calixarene moiety; see e.g.: (a) Miao, R.; Zheng, Q. Y.; Chen, C. F. *J. Org. Chem.* **2005**, *70*, 7662. (b) Xu, Z. X.; Zhang, C.; Chen, C. F.; Huang, Z. T. *Org. Lett.* **2007**, *9*, 4447. (c) Herbert, S. A.; Arnott, G. E. *Org. Lett.* **2010**, *12*, 4600. (d) Herbert, S. A.; Arnott, G. E. *Org. Lett.* **2009**, *11*, 4986. (e) Mascal, M.; Warmuth, R.; Naven, R. T.; Edwards, R. A.; Hursthouse, M. B.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3435.

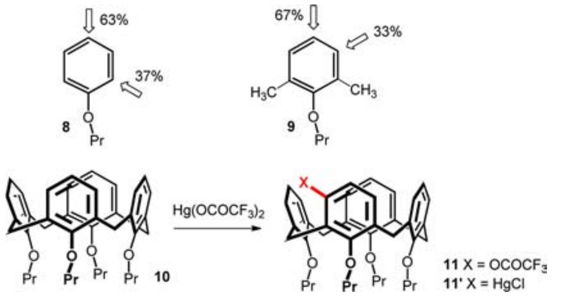
Scheme 2. Synthesis of Inherently Chiral Calixarenes



in the severe interference between two Hg-atom van der Waals radii[7] in the corresponding σ-complex leading to the formation of **5a**.

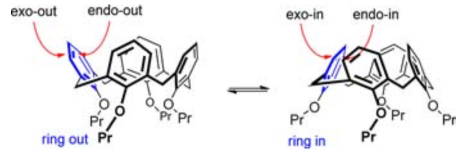
As this unusual regioselectivity of electrophilic substitution has never been observed in the classical calixarene series we attempted to use organomercurial **4** and **5** as intermediates in the preparation of synthetically useful calix[4]arene-based derivatives. Trifluoroacetates **4** and **5** could not be purified on silica gel; hence, we transformed them into the chloromercurio derivatives **4′** and **5′** by reaction with aqueous HCl in acetone.[8] These intermediates were then purified using column chromatography[9] and converted (Scheme 2) into the corresponding halogen derivatives.[10] Thus, calixarene **1** was stirred overnight with 2 equiv of Hg(TFA)$_2$, the crude reaction mixture (containing mainly **5**) was evaporated, and the remaining solid was treated overnight with I$_2$ (rt, MeCN) to yield the corresponding diiodo derivative **7a**. A similar strategy using only 1 equiv of Hg(TFA)$_2$ gave monosubstituted **6a** or **6b**.

Scheme 3. Synthesis of Inherently Chiral Calixarenes



The electrophilic aromatic substitution in the calixarene series is a well-established procedure leading exclusively to the *para*-substituted calixarenes. This indicates that the unusual regioselectivity must be a consequence of either using Hg(TFA)$_2$ as an electrophile or choosing an uncommon calixarene derivative **1**[11] (two *t*-Bu groups) as the starting compound. We have carried out an extensive literature survey focused on the reactivity[12] of Hg^{2+} derivatives in S_E^{Ar}, but we could not find any reaction with similar unexpected results.[13]

Table 1. Comparison of Total and Relative Energies of the Corresponding *Meta*- and *Para*-Substitution with Hg(TFA)$_2$



calculation[a]	total energy[b]	relative energy[c]
***σ*-complexes**		
meta-exo-in	−2563.3265643	13.73
meta-exo-out	−2563.3224481	16.31
para-exo-in	−2563.3263886	13.84
para-exo-out	−2563.3230609	15.93
meta-endo-in	−2563.3484429	0.00
meta-endo-out	−2563.3483226	0.08
para-endo-in	−2563.3482551	0.12
para-endo-out	−2563.3484095	0.02
products		
meta-in (**11**)	−2562.9595952	0.00
meta-out (**11**)	−2562.9580536	0.97
para-in	−2562.9540017	3.51
para-out	−2562.9517125	4.95

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

To shed light on this situation, we have carried out the mercuration of model compounds **8** and **9**. The results are depicted in Scheme 3. As expected, simple propoxy derivative **8** gave only *ortho*- and *para*-substituted products in a 67:33 ratio, and no isolable amount of *meta*-substituted product was formed. Surprisingly, 2,6-dimethyl-1-propoxybenzene **9** gave a high yield of *meta* substitution (33%) which is rather unexpected. Due to the strong *ortho*/*para* orienting effect of the alkoxy group together with possible steric repulsion with large electrophile $^+$Hg(TFA) in position 3, one should expect the regioselective formation of a 4-substituted derivative.[14] Based on these model reactions, we have selected simple tetrapropoxycalix[4]arene **10** to test the general applicability of this reaction in calixarene

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(7) Canty, A. J.; Deacon, G. B. *Inorg. Chim. Acta* **1980**, *45*, L225.

(8) Patel, A.; Liebner, F.; Mereiter, K.; Netscherc, T.; Rosenau, T. *Tetrahedron* **2007**, *63*, 4067.

(9) Albeit they are formed in very high yields (NMR), compounds **4′** and **5′** were obtained only in 45% yields after column chromatography on silica gel. A substantial part of the compound (~50% of original mass) “disappeared” during chromatography as it is irreversibly adsorbed by sorbent.

(10) Brown, M. A.; Kerr, M. A. *Tetrahedron Lett.* **2001**, *42*, 983.

(11) Frank, M.; Maas, G.; Schatz, J. *Eur. J. Org. Chem.* **2004**, *3*, 607.

(12) Gabbai, F. P.; Burress, C. N.; Melaimi, M.-A.; Taylor, T. J. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H. D., Mingos, M. P., Eds.; Elsevier Science: 2006; Vol. 2, p 419.

(13) The formation of a substantial amount of *meta* isomer in the mercuration of toluene with Hg(TFA)$_2$ in TFA was reported: Olah, G. A.; Hashimoto, I.; Lin, H. C. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 4121. The content of the *meta* isomer increased with increasing reaction temperature which indicates the thermodynamic control of the reaction. Based on this reference, we have carried out the monomercuration reaction of **1** at −20 °C to show the regioselectivity under kinetic control. Only the formation of *meta*-substituted derivative **4** was observed.

(14) Surprisingly, the benzylation of 2,6-dimethylanisol proceeds with almost identical regioselectivity: Laali, K. *J. Org. Chem.* **1985**, *50*, 3638 as suggested by one of the referees.

chemistry. Using 1 equiv of $Hg(TFA)_2$ and subsequent reaction with HCl gave only *meta*-substituted product **11′** in 70% yield. This experiment indicates that the unexpected regioselectivity of mercuration is a general phenomenon in the calixarene series irrespective of the upper rim substitution.[15,16]

To gain deeper insight into the regioselectivity we have carried out a quantum-chemical calculation of the reaction of **10** with $Hg(TFA)_2$. The study of the interactions of mercury compounds with an organic substrate is not a trivial task, as there is no reliable critical evaluation of the applicability of the existing bases. Therefore, we tested some selected methods included in the Gaussian03 software package[17] (LANL2DZ and CEP) in the combination with DFT methods B3LYP and PBEPBE. As a criterion for assessing the appropriateness of the corresponding method, the agreement of computed geometrical parameters with a known X-ray structure of mercury(I) trifluoroacetate[18] was evaluated. The best fit was achieved using the combination PBEPBE/LANL2DZ, and the energies of the corresponding σ-complexes were evaluated using this method. Similarly, the thermodynamic stability of *meta*- and *para*-substituted products was obtained.

Generally, the attack of electrophilic species $^{+}Hg(TFA)$ is possible from two basic directions: (i) inside the cavity (endo-σ-complex) and (ii) outside the cavity (exo-σ-complex). What is more, calix[4]arenes in the *cone* conformation are also known to exhibit so-called *pinched cone–pinched cone* interconversion.[1] As a result, we took into consideration two boundary conformations with the substituted ring pointing into the cavity ("ring in") or outside the cavity ("ring out") (Table 1).

As can be seen from Table 1, all *endo* attacks of the electrophile represent the lower energy state if compared with the *exo* σ-complexes. The huge energy gap (13.7 $kcal \cdot mol^{-1}$ for the most stable meta-*endo*-in arrangement) clearly indicates that electrophile is highly stabilized by the interactions with the π aromatic cavity. On the other hand, the differences between the appropriate *endo* attacks are negligible (less than 0.12 $kcal \cdot mol^{-1}$) and cannot be used for the evaluation of the regioselectivity. The explanation could be based on the energy of the products. Obviously, the *meta* substitution is favored over the *para* attack by more than 3.5 $kcal \cdot mol^{-1}$. This indicates that regioselectivity is thermodynamically driven and the most stable isomer is finally formed.

To conclude, we have discovered an unprecedented regioselectivity of the mercuration reaction leading to the *meta*-substituted calix[4]arenes. These compounds represent a very unique substitution pattern in classical calixarene chemistry and open the door for the synthesis of inherently chiral receptors based on calixarenes. The application of organomercury derivatives as synthetically useful intermediates is currently underway.

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Supporting Information Available. Experimental procedures, full characterizations, results of computational chemistry, and the X-ray structure of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(15) Dimercuration of dialkoxycalixarene with $Hg(TFA)_2$ was described in: van Loon, J. D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639. In this case, the strong directing effect of free OH groups directs substitution regioselectively into the *para* positions of the unsubstituted rings.

(16) Tetramercuration of calixarene was described by: Markowitz, M. A.; Janout, V.; Castner, D. G.; Regen, S. L. *Am. Chem. Soc.* **1989**, *111*, 8192. The *cone* conformer of the tetrabutoxy derivative was reacted with 4 equiv of $Hg(TFA)_2$ and directly treated with Br_2. The formation of the *para*-substituted tetrabromo derivative in the *partial cone* conformation (71% yield) is clearly incorrect, as the starting compound is conformationally immobilized. Most likely, the authors prepared a *meta*-substituted *cone* compound which was misinterpreted as the *para*-substituted *partial cone*.

(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, B. Johnson, P. M. W.; Chen, W.; Wong, M. W.; Gonzalez, C. Pople, J. A. *Gaussian03*; Gaussian, Inc.: Wallingford, CT, 2004.

(18) Sikirica, M.; Grdenic, D. *Acta Crystallogr., Sect. B* **1974**, *30*, 144.