Organic LETTERS

Letter

pubs.acs.org/OrgLett

Regioselective Halogenation of Thiacalix[4]arenes in the *Cone* and *1,3-Alternate* Conformations

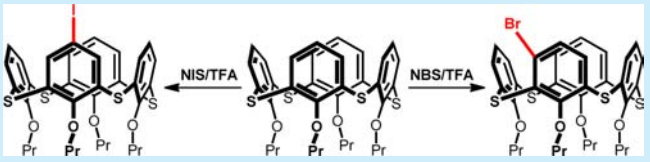
Jan Lukášek,[†] Stanislav Böhm,[†] Hana Dvořáková,[‡] Václav Eigner,[§,∥] and Pavel Lhoták*[,†]

[†]Department of Organic Chemistry, [‡]Laboratory of NMR Spectroscopy, and [§]Department of Solid State Chemistry, Institute of Chemical Technology, Prague (ICTP), Technicka 6, 166 28 Prague 6, Czech Republic

[∥]Institute of Physics AS CR, v.v.i., Na Slovance 2, 182 21 Prague 8, Czech Republic

Supporting Information

ABSTRACT: Monohalogenation of thiacalix[4]arene in the *cone* conformation gave either the *meta*- or *para*-substituted isomers depending on the halogen and reaction conditions used. Surprisingly, the same reaction with the *1,3-alternate* conformer led only to the *meta* isomer. This is the first example of such a conformation-dependent regioselectivity in calixarene/thiacalixarene chemistry. As the halogen-substituted calixarenes are useful synthetic intermediates, this provided the unique opportunity to functionalize the basic skeleton at two different positions.

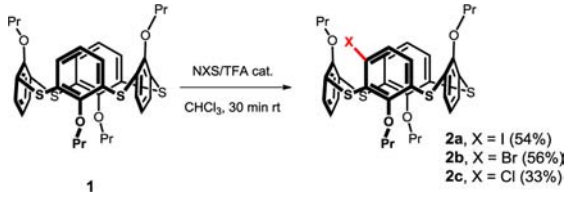


Thiacalix[4]arene emerged[1] in 1997 as a new member of the calix[n]arene family.[2] Substitution of the methylene bridging units with sulfur atoms leads to many novel features that are not present in the chemistry of common calixarenes.[3] Thus, thiacalix[4]arenes can be highly regio- and stereoselectively *S*-alkylated to form sulfonium salts[4] or *S*-oxidized to provide various sulfoxides or sulfones.[5] Moreover, the presence of sulfur significantly modifies the chemical behavior of thiacalixarenes as documented by the altered regioselectivity of electrophilic aromatic substitution. Contrary to classical calixarenes where only *para*-isomers are formed (with respect to phenolic oxygen), formylation[6] or nitration[7] of tetraalkylated thiacalix[4]arenes results in *meta*-substitution of the macrocycle. Consequently, thiacalixarenes represent very attractive building blocks as they allow for a direct approach to unique substitution patterns that are still very rare in calixarene chemistry.

Until recently, a broader application of thiacalixarenes was hindered by our limited knowledge of their chemical properties and a lack of general derivatization methods. Halogen-substituted calixarenes are considered to be important intermediates in the synthesis of more sophisticated molecules,[3] but very little is known about the halogenation of thiacalixarenes.[8] In this paper, we report on the first monohalogenation of thiacalix[4]arenes immobilized in the *cone* or *1,3-alternate* conformations. To the best of our knowledge, this is the first example of conformation-dependent regioselectivity in calixarene/thiacalixarene chemistry where the result (*meta* or *para* substitution) is dramatically influenced by the conformation of the starting compound, halogen source, and the reaction conditions used.

As iodo-substituted thiacalix[4]arenes are expected to be useful synthetic intermediates, known iodination agents were selected first and screened against the *1,3-alternate* conformer **1** (Scheme 1). Treatment of **1** overnight with I_2, I_2/HNO_3, or NIS in $CHCl_3$ at rt gave no reaction. On the other hand, ICl gave

Scheme 1. Halogenation of Thiacalix[4]arene in the *1,3-Alternate* Conformation



monosubstituted compound **2a** in 22% yield, while I_2/CF_3COOAg provided the same product in 48% yield. Finally, we found that NIS in the presence of acidic catalyst (AcOH or TFA) afforded the monosubstituted product in 28% and 54% yield, respectively. In all cases, the monosubstituted product **2a**, separated by column chromatography on silica gel, was accompanied by a fraction of disubstituted products (as shown by MS) as an inseparable mixture of various regioisomers. The choice of solvent was shown to be very important as the same reaction carried out in acetone or 2-butanone resulted in no product formation. The best reaction conditions (NIS/cat. TFA in $CHCl_3$, 30 min at rt) were then applied without further optimization for bromination (NBS) and chlorination (NCS) reactions. The corresponding products[9] **2b** and **2c** were isolated on a gram scale in 56 and 33% yield, respectively, albeit with some amount of disubstituted byproducts.

The structures of the products were assigned by a combination of NMR and MS techniques. Thus, HRMS analysis of **2a** showed signal at m/z = 813.06681, which exactly matched the monoiodinated structure ($[M + Na]^+$). The complex splitting pattern and multiplicity of signals in ^1H NMR spectrum of **2a** suggested the expected inherently chiral structure. The presence

Received: August 19, 2014
Published: September 16, 2014

dx.doi.org/10.1021/ol5024536 | *Org. Lett.* 2014, 16, 5100−5103

of two well-resolved doublets in the aromatic region of the ^{1}H NMR spectrum (7.46 and 7.02 ppm) with a typical *ortho*-interaction constant (J = 8.2 Hz) confirmed the *meta* substitution pattern (see Figure 1).

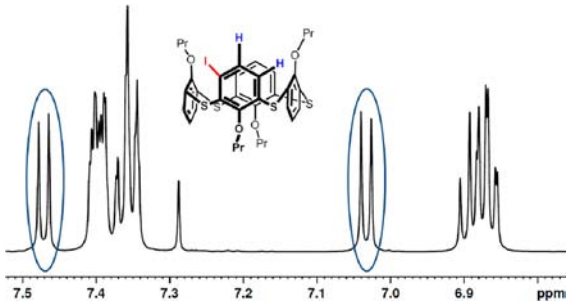


Figure 1. Partial ^{1}H NMR spectrum of **2a** ($CDCl_3$, 298 K, 300 MHz).

The *meta* regioselectivity was also confirmed by X-ray crystallography using monocrystals of **2b** and **2c** (see the Supporting Information). As shown in Figure 2, the *meta*-

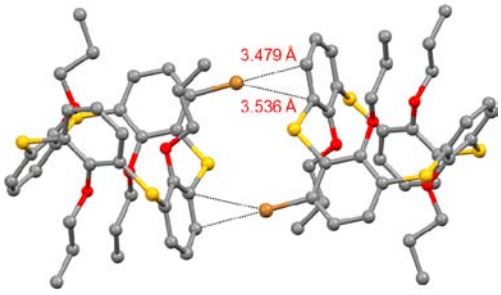


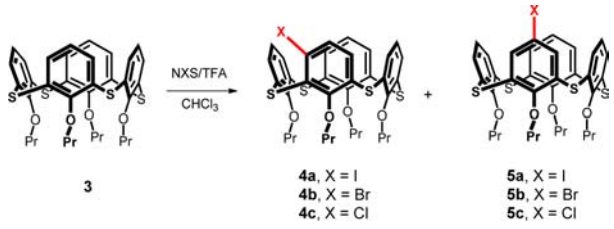
Figure 2. (a) X-ray structure of **2b** confirming a dimer formation via halogen−π interactions (hydrogen atoms omitted for clarity).

bromine atom in **2b** forms a unique dimeric structure via halogen bonding[10] with the aromatic subunit of the neighboring thiacalixarene molecule. The bromine atom is oriented almost exactly to the middle of the aromatic bond with C···Br distances of 3.479 and 3.536 Å. The resulting supramolecular structure could be described as a T-shaped halogen−π interaction with η^2 binding mode, recently studied for bromobenzene−benzene dimer formation.[11]

Conversely, the *cone* conformer **3** did not react under the optimized reaction conditions (NIS/cat. TFA). Even use of an excess of NIS, higher temperature, or longer reaction time did not lead to iodination, thus showing a substantial difference in reactivity between the conformers. Fortunately, using a stoichimetric excess of TFA (instead of catalytic amount) led smoothly to monoiodination after stirring for 24 h, and two regioisomers **4a** (*meta*) and **5a** (*para*) could be isolated in 6 and 64% yields, respectively (Scheme 2). The 10:1 selectivity with a dominating *para* isomer was very surprising as to date *meta* substitution has always prevailed[6,7] in tetraalkylated thiacalixarenes. As the corresponding *para*-substituted derivatives are inaccessible by a direct electrophilic substitution, this unexpected regioselectivity paves the way toward this kind of substitution in thiacalixarene chemistry.[12]

Interestingly, bromination of the *cone* conformer with NBS gave a mixture of **4b** and **5b** in a 23:49 ratio, while the same reaction with NCS gave *meta* isomer **4c** as the major product (33%) accompanied by only a minor amount of *para* isomer **5c**

Scheme 2. Halogenation of Thiacalix[4]arene in the *Cone* Conformation



(<1%). Obviously, the regioselectivity toward the *para* position is directly proportional to the size of halogen used. While the bulky iodine atom prefers *para* substitution, the much smaller chlorine atom attacks preferentially at the *meta* position. To the best of our knowledge, this kind of interdependence is unprecedented in calixarene chemistry and gave us the unexpected opportunity to tune the regioselectivity using different halogens. Moreover, the regioselectivity of bromination could be tuned using various reaction conditions. Thus, the same reaction with NBS added at −78 °C and then warmed to room temperature over 30 min gave the reversed ratio of isomers **4b**:**5b** = 47:26. This indicated that the *meta* bromination could be under kinetic control.

The assignment of the corresponding *meta* and *para* isomers of the *cone* conformation was not trivial due to the *pinched cone*−*pinched cone* interconversion that strongly influences the NMR spectra of these compounds. As a consequence, all signals in the ^{1}H NMR spectra of **4** and **5** were extremely broadened and gave us almost no structural information at room temperature (see the Supporting Information). Fortunately, the same spectra at low temperature were relatively well resolved and reflected a higher symmetry for the *para* isomers. Thus, the spectrum of **4b** (CD_2Cl_2, 213 K, 500 MHz) exhibited two aromatic doublets[13] at 7.35 and 7.47 ppm characteristic of *meta* substitution. Furthermore, the spectrum of **5b** showed a singlet[13] at 6.53 ppm (aromatic C−H bonds next to Br atom) supporting the *para* substitution of this isomer.

The conformational behavior of **4a** and **5a** in solution was studied using dynamic NMR measurements. The ^{1}H NMR spectra revealed that the *pinched cone*−*pinched cone* interconversion was heavily influenced by the substitution pattern of thiacalixarene. As shown in Figure 3, the temperature-dependent ^{1}H NMR spectra (CD_2Cl_2, 500 MHz) of *para*-substituted isomer **5a** exhibited typical features for a *pinched cone*−*pinched cone*

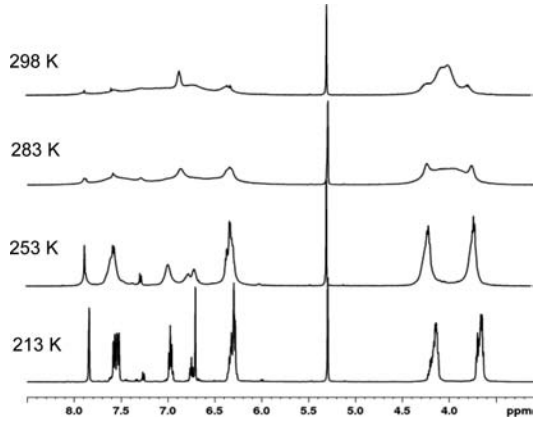


Figure 3. Partial ^{1}H NMR spectra of **5a** (CD_2Cl_2, 500 MHz) in the range of 213−298 K.

dx.doi.org/10.1021/ol5024536 | *Org. Lett.* 2014, 16, 5100−5103

equilibrium. Very broad spectra at 298 K due to the time-averaging of signals were gradually (with decreasing temperature) changed into the well resolved signals of individual *pinched cone* conformers under slow exchange conditions. The integral intensity of the corresponding singlets at 6.81 and 7.84 ppm indicated that both *pinched cone* conformers were present at 213 K in a ~1:1 ratio (Figure 3).

On the other hand, a similar dynamic study of *meta*-substituted isomer **4a** revealed that the equilibrium was shifted toward one specific *pinched cone* conformer as the ratio under slow exchange conditions was approximately 10:1 (Figure 4).

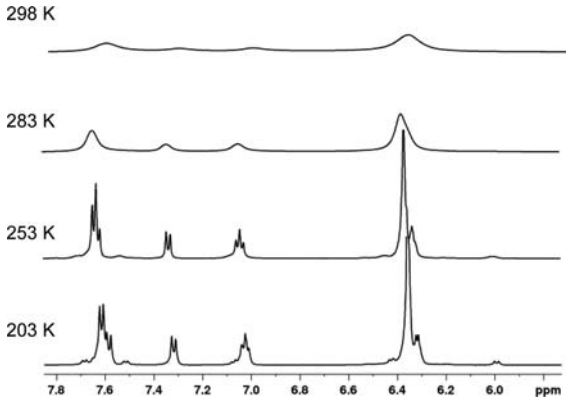
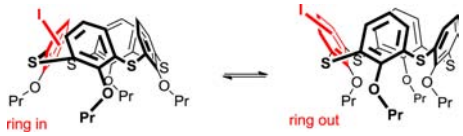


Figure 4. Aromatic region in the ^{1}H NMR spectra of **4a** (CD_2Cl_2, 500 MHz) in the range of 203−298 K.

As the ^{1}H NMR spectra of both **4a** and **5a** suffered from severe overlap in the corresponding *pinched cone* resonances, well-resolved, low-temperature, ^{13}C-decoupled spectra were necessitated to assign all signals of both individual *pinched cone* conformers (see the Supporting Information). These results indicated that the installation of iodine atom at the *meta* position exhibited much more dramatic consequences to the equilibrium than the same substituent at the *para* position.

To explain these differences in conformational behavior between the *meta* and *para* substitution we carried out quantum-chemical calculations of the corresponding *pinched cone* conformers of iodo derivatives **4a** and **5a** using a B3LYP/6-311G(d,p) method. The results are shown in Table 1. The energy difference between in−out conformers was almost negligible (0.22 kcal·mol^{-1}) for the *para* isomer **5a**, which perfectly agreed with the ~1:1 ratio of conformations in solution. On the other hand, the in−out difference for *meta* isomer **4a** was almost 2 kcal·mol^{-1}. Obviously, as a consequence of the introduction of iodine at the *meta* position, the molecule prefers a specific *pinched cone* conformation in solution, with a bulky group on the flattened aromatic ring (ring out). Similar trends can be observed also for the respective bromo isomers (see Table 2).

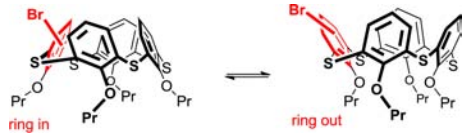
Table 1. Comparison of Total and Relative Energies of the Pinched Cone Conformers of 4a and 5a



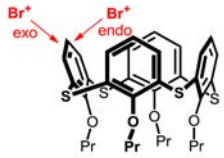
structure[a]	total energy[b]	relative energy[c]	in−out difference[c]
4a (in)	−10208.962001	5.17	1.99
4a (out)	−10208.965170	3.18	
5a (in)	−10208.970243	0.00	0.22
5a (out)	−10208.969895	0.22	

[a]B3LYP/6-311G(d,p) method. [b]In au. [c]In kcal·mol^{-1}.

Table 2. Comparison of Total and Relative Energies of Bromo Isomers 4b and 5b (Upper Part) And the Corresponding σ Complexes (Lower Part)



run	structure[a]	total energy[b]	relat. energy[c]
1	**4b** (in)	-5863.583072	4.49
2	**4b** (out)	-5863.585155	3.18
3	**5b** (in)	-5863.590224	0.00
4	**5b** (out)	-5863.589465	0.48



5	**4b** (in-endo)	-5863.920512	10.06
6	**4b** (in-exo)	-5863.936550	0.00
7	**4b** (out-endo)	-5863.928638	4.96
8	**4b** (out-exo)	-5863.928673	4.94
9	**5b** (in-endo)	-5863.920657	9.97
10	**5b** (in-exo)	-5863.928136	5.28
11	**5b** (out-endo)	-5863.925542	6.91
12	**5b** (out-exo)	-5863.926401	6.37

[a]B3LYP/6-311G(d,p) method. [b]In au. [c]In kcal·mol^{-1}.

The opportunity to control the formation of either *meta* or *para* isomers is so far unprecedented in calixarene chemistry. Hence, to gain deeper insight into the regioselectivity of bromination, we carried out a quantum-chemical calculation of the corresponding *meta* and *para* products **4b** and **5b**. The B3LYP/6-311G(d,p) method was used for the evaluation of the thermodynamic stability of the monobrominated products. As mentioned previously, the *cone* conformations of thiacalix[4]-arenes exhibit so-called *pinched cone*−*pinched cone* interconversion.[3] Consequently, we had to consider both frontier conformations with the Br-substituted rings being pointed inside ("ring in") or outside the cavity ("ring out"). As shown in Table 2, *para* substitution (runs 3 and 4) of the *cone* isomer was thermodynamically favored by more than 3 kcal·mol^{-1} when compared to *meta* substitution (runs 1 and 2). This was in a good accord with our observations that the *para* isomer was formed at room temperature (as the thermodynamic product). On the other hand, the relative stability of the σ complexes indicate the most stable structure for the σ complex formed by exo *meta* attack of Br^+ to the phenolic units oriented inside the cavity (run 6). This arrangement was more stable than any other σ complex by ca. 5 kcal·mol^{-1} (see Table 2) and indicated kinetic control of *meta* substitution, which was once again in perfect agreement with our experimental data.

In conclusion, the halogenation of thiacalix[4]arenes immobilized in the *cone* and in the *1,3-alternate* conformations revealed substantially different reactivity of these conformations. While

dx.doi.org/10.1021/ol5024536 | *Org. Lett.* 2014, 16, 5100−5103

the *1,3-alternate* afforded only *meta* substitution, the halogenation of the *cone* conformation yielded a mixture of two regioisomers located at the *meta* or *para* positions. Quantum chemical calculations support our finding that the regioselectivity can be controlled by utilizing kinetic or thermodynamic conditions, which is unprecedented in calixarene chemistry. As halogen-substituted thiacalix[4]arenes are potentially useful synthetic intermediates, this gave us the unique opportunity to functionalize the basic thiacalix[4]arene skeleton at two different positions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of compounds **2a**−**c**, **4a**−**c**, and **5a**−**c**, and X-ray structures of **2b** and **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lhotakp@vscht.cz.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Czech Science Foundation (Grant P207/12/2027) and by a grant from Praemium Academiae of the Academy of Sciences of the Czech Republic.

■ REFERENCES

(1) Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, *38*, 3971.

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

(3) For recent reviews on thiacalixarenes, see: (a) Kumar, R.; Lee, Y. O.; Bhalla, V.; Kumar, M.; Kim, J. S. *Chem. Soc. Rev.* **2014**, *43*, 4824. (b) Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291. (c) Lhotak, P. *Eur. J. Org. Chem.* **2004**, 1675.

(4) (a) Kundrat, O.; Eigner, V.; Dvorakova, H.; Lhotak, P. *Org. Lett.* **2011**, *13*, 4032. (b) Kundrat, O.; Dvorakova, H.; Böhm, S.; Eigner, V.; Lhotak, P. *J. Org. Chem.* **2012**, *77*, 2272.

(5) (a) Morohashi, N.; Iki, N.; Sugawara, A.; Miyano, S. *Tetrahedron* **2001**, *57*, 5557. (b) Katagiri, H.; Hattori, T.; Morohashi, N.; Iki, N.; Miyano, S. *J. Org. Chem.* **2007**, *72*, 8327.

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

(7) (a) Kundrat, O.; Kroupa, J.; Böhm, S.; Budka, J.; Eigner, V.; Lhotak, P. *J. Org. Chem.* **2010**, *75*, 8372. (b) Kundrat, O.; Dvorakova, H.; Böhm, S.; Eigner, V.; Lhotak, P. *J. Org. Chem.* **2012**, *77*, 2272.

(8) For bromination of lower rim-unsubstituted or partly substituted thiacalixarenes, see, e.g.: (a) Kasyan, O.; Swierczynski, D.; Drapailo, A.; Suwinska, K.; Lipkowski, J.; Kalchenko, V. *Tetrahedron Lett.* **2003**, *44*, 7167. (b) Desroches, C.; Lopes, C.; Kessler, V.; Parola, S. *Dalton Trans.* **2003**, 2085. (c) Lhotak, P.; Himl, M.; Stibor, I.; Sykora, J.; Cisarova, I. *Tetrahedron Lett.* **2001**, *42*, 7107.

(9) Compounds **2a** and **2b** were recently prepared using the reaction of organomercury calixarene derivative with I_2 or Br_2, albeit in low overall yields: Botha, F.; Böhm, S.; Dvorakova, H.; Eigner, V.; Lhotak, P. *Org. Biomol. Chem.* **2014**, *12*, 5136−5143.

(10) For recent review on halogen bonding, see: Metrangolo, P.; Meyer, F.; Pilati, T.; Resnati, G.; Terraneo, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6114.

(11) Reid, S. A.; Nyambo, S.; Muzangwa, L.; Uhler, B. *J. Phys. Chem. A* **2013**, *117*, 13556.

(12) So far, the only precedence is direct mercuration of thiacalix[4]arenes where a small amount of *para* isomer is formed as a byproduct; see ref 9.

(13) Both bromo-substituted *cone* isomers (**4b** and **5b**) exhibit the *pinched cone*−*pinched cone* interconversion resulting in the two sets of signals in the ^{1}H NMR spectrum. Consequently, only the signals of the major conformers are discussed here.