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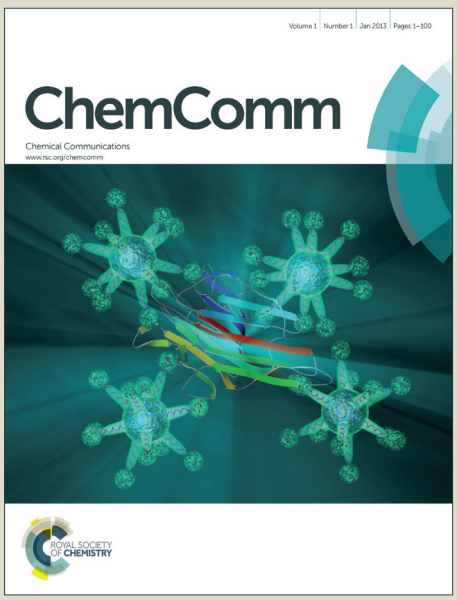

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Selective functionalization of methylene bridges of calix[6]arenes. Isolation and identification of stable conformers of methyl ether of *p-tert*-butylcalix[6]arene

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Shafali Arora,[a] Shivali Sharma,[a] Venus S. Mithu,[a] Chang Hee-Lee[b] and Kamaljit Singh*[,]

Abstract. Direct disubstitution at the methylene bridges of *p-tert*-butylcalix[6]arenemethyl ether has been achieved for the first time using a lithiation-substitution protocol. Two stable conformers have been isolated using column chromatography, and their structures have been unambiguously confirmed from 1D, 2D and variable temperature NMR studies and single crystal X-ray structure analysis.

Ever since the seminal work of Gutsche[1] on the rational and large scale synthesis of calix[n]arenes with n = 4, 6 and 8, a lot of attention has been invested in the functionalization of both upper and the lower rims of calix[4]- as well as calix[6]arenes and their conformational analysis.[2] These systems have recently been intensively studied due to their diverse applications in biomedical research,[3] supramolecular chemistry,[4] recognition[5] and material science applications[6] and are thus much sought-after targets even today. Although a number of mono-, di- and tetramethylene-substituted calix[4]arenes have been previously synthesized,[7] a direct route for the methylene bridge (Figure 1) substitution of calix[6]arenes is unprecedented.

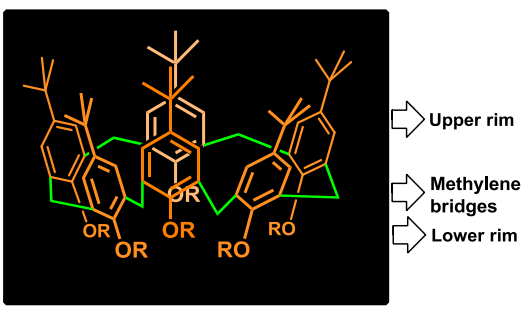
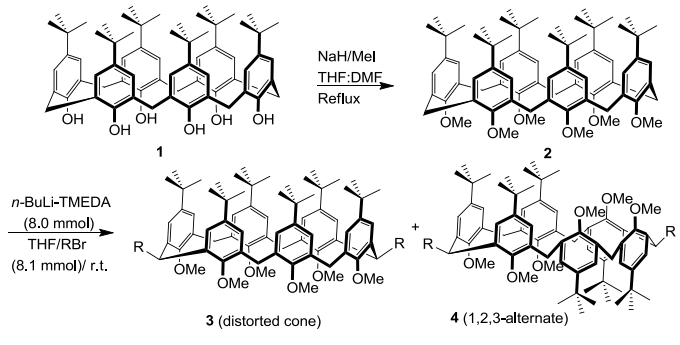


Figure 1. Structure representation of calix[6]arene alkylethers.

A synthetic methodology that achieves symmetrical substitution of the methylene bridges of calix[6]arene would be of considerable synthetic consequence. In contrast to calix[4]arenes, which adopts thermodynamically stable C_{4V} conformation, the lower symmetric calix[6]arenes are more flexible and thus present more challenges w.r.t their methylene bridge substitution as well as characterization of the resultant products owing to the possibility of alternating orientation of the aryl groups.[8] While there are a few reports available describing the conformational behavior and solution structure calix[6]arene derivatives,[9] with lower rim modified, in no instance has a direct synthetic route to the calix[6]arenes with two methylene bridges substituted and their conformational behavior been described. Having more than one similarly substituted methylene groups will open new possibilities for calix[6]arenes to act as a bifunctional building blocks for designing more complex supramolecular constructions. We envisaged, since a molecule of calix[6]arene possesses six benzylic type methylene bridges, the possibility of multiple yet regioselective deprotonations upon treatment with a suitable base could allow formation of substituted products. In this paper, we wish to report a direct and regioselective route to the disubstitution of the methylene bridges of calix[6]arene and the first example of isolation and structural characterization (variable temperature NMR, single crystal X-ray analysis) of two stable conformers of a – di(methylene) substituted calix[6]arene ether.

5,11,17,23,29,35-Hexakis(1,1-dimethylethyl)-37,38,39,40,41,42-hexahydroxycalix[6]arene **1** was prepared[10] by the base-catalysed



R = a) Et; b) *n*-pentyl; c) *n*-decyl; d) Bn; e) CH_2COOEt; f) allyl

Scheme 1. Synthesis of hexamethoxycalix[6]arene **2** and disubstituted calix[6]arenes **3** (distorted cone) and **4** (1,2,3-alternate) conformers.

Table 1. Optimization of reaction parameters for metalation of **2** and subsequent reaction with bromoethane (entries 1-6) and other electrophiles (entries 7-11).

entry	Base (equiv)	Temp (°C)	Product (R)	Isolated yield (%)
1	*n*-BuLi (1.0 to 8.0)	0	-	No reaction
2	*n*-BuLi (8.0)	-20	-	No reaction
3	*n*-BuLi (4.0 to 8.0)	Room temp.	-	No reaction
4	*n*-BuLi:TMEDA (4.0)	Room temp.	-	No reaction
5	*n*-BuLi:TMEDA (6.0)	Room temp.	**3a/4a** (C_2H_5)	40/16
6	*n*-BuLi:TMEDA (8.0)	Room temp.	**3a/4a** (C_2H_5)	47/19[a]
7	*n*-BuLi:TMEDA (8.0)	Room temp.	**3b/4b** (*n*- C_5H_{11})	44/20
8	*n*-BuLi:TMEDA (8.0)	Room temp.	**3c/4c** (*n*- $C_{10}H_{21}$)	46/18
9	*n*-BuLi:TMEDA (8.0)	Room temp.	**3d/4d** ($CH_2C_6H_5$)	41/22
10	*n*-BuLi:TMEDA (8.0)	Room temp.	**3e/4e** (CH_2COOEt)	42/18
11	*n*-BuLi:TMEDA (8.0)	Room temp.	**3f/4f** ($CH_2CH=CH_2$)	40/17

[a]*Ratio of* **3a**:**4a** (52.84: 47.19) *was deduced from* ^{1}*H NMR spectrum of the crude product mixture.*

condensation of *p-tert*-butylphenol with formaldehyde. In case of calix[4]arenes, the four conformers (i.e., cone, partial cone, 1,2-alternate and 1,3-alternate) are isolable as discrete chemical entities after appropriate *O*-alkylation of the tetrahydroxy groups, we introduced methoxy groups at the lower rim of **1** to reduce the degree of conformational flexibility in favour of a stabilized cone like conformation. Thus, treatment of **1** with methyl iodide and NaH in refluxing THF:DMF mixture furnished[11] hexamethoxycalix[6]arene **2** in good yield (Scheme 1).

We examined the direct lithiation substitution reactions of **2** for the synthesis of *meso*-substituted calix[6]arene derivatives (Scheme 1), using base catalyzed lithiation reaction followed by treatment of the anionic species of **2** with bromoethane (Table 1). When a THF solution of **2** was treated with *n*-BuLi (1.0-8.0 equiv) at 0 °C under the blanket of anhydrous dry nitrogen gas, no change in the reaction was observed and **2** was recovered as such after quenching the reaction with aqueous HCl (1M). Lowering of the reaction temperature (-20 °C), while maintaining similar equivalents of *n*-BuLi also did not initiate the reaction and the precursor **2** could be isolated after aqueous work-up. In order to enhance the reactivity, *N,N,N',N'*- tetramethylethylenediamine (TMEDA) was used in combination with *n*-BuLi. However, when **2** was treated with 4.0 equiv of *n*-BuLi:TMEDA at room temperature, no anion generation was observed. Using 6.0 equiv of *n*-BuLi:TMEDA at room temperature led to a short lived red colored anion solution. When **2** was treated with 8.0 equiv of *n*-BuLi:TMEDA in anhydrous THF solution at room temperature, under anhydrous N_2 gas, a persistent blood red colored anion was generated. When bromoethane (8.0 equiv) was slowly introduced at the same temperature, the color disappeared indicating quenching of the anionic species. Two products: the major **3a** (47 % yield) and the minor **4a** (19.0 % yield) were isolated after column chromatographic purification and were fully characterized by ^{1}H, ^{13}C NMR and high resolution mass spectrometry (*vide experimental*).

Variable temperature ^{1}H NMR analysis of the major and minor compounds was performed (Figures S25 and S26 in supporting information), which at low temperature (-30 and -40 °C) revealed considerable peak broadening and gave no meaningful information regarding the substitution pattern. The ^{1}H NMR ($CDCl_3$) spectrum of the major isomer **3a**, recorded at 40 °C showed well resolved peaks on the other hand. The signals corresponding to *tert*-butyl and methoxy groups appeared as two sets of singlets in the intensity ratio 1:2 (Figure 2), while the bridge unsubstituted methylenes as well as CH of the substituted methylenes appeared as single signals. The ^{1}H NMR spectral data further suggested unsymmetrical placement of at least two *p-tert*-butylanisol rings.

Appearance of a single set of signals corresponding to two ethyl groups and a triplet signal for the methinyl proton on the ethyl group

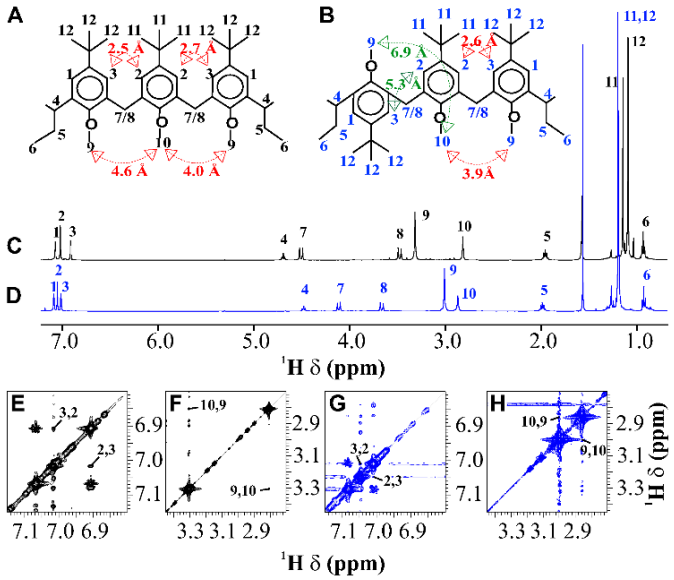


Figure 2. Schematics of molecular structure between the two ethylated bridges in (A) **3a** and (B) **4a**. Through-space contacts between chemically non-equivalent methoxy and aromatic protons are highlighted using bi-directional dashed arrows in these schematics. ^{1}H-^{1}H distance derived from the crystal structure is indicated alongside each arrow. NMR peaks corresponding to various protons (numbered 1-12) are labelled in 1D spectra of (C) **3a** and (D) **4a**. (E-H) Selective regions of 2D ^{1}H-^{1}H NOESY spectra of (E, F) **3a** and (G, H) **4a**, recorded with a mixing time of 300 ms. Through-space correlations between the (E, G) aromatic (numbered 2 and 3) and (F, H) methoxy (numbered 9 and 10) protons are highlighted using red black solid lines (For detailed 2D NMR spectra, see Fig. S35 in supporting information).

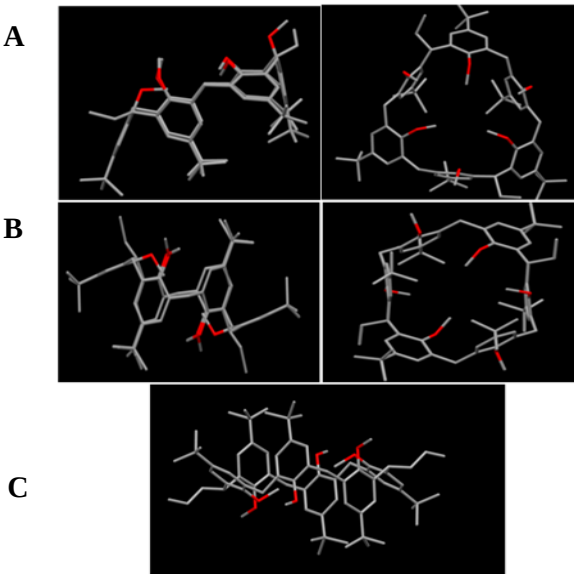


Figure 3. Stereo views of **3a** (distorted cone conformation) (A), **4a** (1,2,3-alternate conformation)(B) and **4e** (1,2,3-alternate conformation) (C) as deduced from single crystal X-ray structures (CCDC numbers: **3a**: 1015086, **3b**: 1015087 and **4f**:1015089).

substituted bridges clearly indicates the chemical equivalence of both of the methinyl bridge protons as well as ethyl groups. This split pattern further suggested that all rings rotate freely through the annulus at rates that expose the ethyl groups as well as the methinyl bridge protons to the same time-averaged environment. The ^{1}H NMR data of the disubstituted product corresponded to a distorted cone conformation.

The minor product showed identical spectral features as that of **3a** in proton NMR, with the only difference that the two sets of the signals corresponding to *p-tert*-butyl groups, methoxy groups and methinyl protons were closely placed. This feature suggested a more symmetrical structure and was assigned as the distorted cone conformation of 5,11,17,23,29,35-hexa-*t*-butyl-2,20-diethyl-37,38,39,40,41,42-hexamethoxycalix[6]arene **4a**. The ^{13}C NMR, HSQC and HMBC NMR spectra (Figures S1,S2,S13,S14, S28, S29, S32 and S33 in supporting information) of **3a** and **4a** were in full accord with the proposed structures.

^{1}H NMR spectra of **3a** and **4a** are shown in Fig. 2 C and D, respectively. All the signals could be assigned to specific protons with the help of 2D COSY and TOCSY spectra (see Fig. S35 in supporting information) and are indicated using numerals (numbered1 to 12) in the schematics shown in Fig. 2A and B. In both cases methylene protons (numbered 7 and 8) were found to be chemically non-equivalent. These two show a strong $^{2}J_{HH}$ coupling (~15 Hz) with each other resulting to a strong correlation in the COSY and TOCSY spectra.

We further compared the through-space correlations yielded by these two compounds in NOESY spectra recorded with a mixing time of 300 ms (Fig. 2 E-H, Figures S30 and S34 in supporting information). Significant differences were observed in the intensity of NOESY cross-peaks between aromatic (Fig. 2 E and G) and methoxy (Fig. 2 F and H) protons present on adjacent aromatic rings. The product **3a** (Fig. 2 E and F) yielded much stronger cross-peaks in comparison to **4a** (Fig. 2 G and H) in both cases. To make a quantitative comparison, cross-peak intensities were calculated as a percentage of the diagonal-peak intensities. This exercise yielded a cross-peak intensity of 0.59 % and 0.22 % (for methoxy protons), and 1.02 % and 0.30 % (for the aromatic protons) in case of **3a** and **4a**, respectively. In other words, through-space correlations were found to be nearly three times stronger in **3a** suggesting a close spatial proximity between its protons. The 1,2,3-alternate arrangement of the aromatic groups in **4a** renders distance between one set of adjacent protons much larger (green colored bi-directional dotted arrows in Fig. 2B) thus weakening the through-space correlations. While a smaller distance in **3a** originating from a parallel arrangement on the other hand leads to stronger cross-peaks in NOESY spectra. However, to rule out ambiguity in the identification of conformational isomerism, definitive evidence was considered

obligatory. Thus, additionally structures of these isomers were also confirmed from the single crystal X-ray analysis.

Crystals of **3a** and **4a** were grown from a mixture of methanol/DCM and methanol/chloroform, respectively. The compounds crystallized in monoclinic unit cell with P 21/n space group and triclinic unit cell with P -1 space group, respectively. The stereo views and the crystallographic numbering are shown in Figure 2 and the crystallographic data is tabulated in the (Crystallographic Tables at pages S37-S42 in supporting information, CCDC numbers in Fig. 3). Examination of the single crystal X-ray structures (Figure 3) confirmed to the NMR assignments and confirmed (i) the 2,20-disubstitution pattern as inferred from the NMR spectral data. (ii) it also allowed identification of the conformations of the two products, which could be best described as a "distorted cone" and "1,2,3-alternate" conformations for **3a** and **4a**, respectively, which differ from the conformations adopted by the methylene bridge unsubstituted as well as mono-substituted calix[6]arenes reported in literature.

Similar reactions were performed by reacting dianion of **2** with other alkyl halides such as *n*-pentyl bromide, *n*-decyl bromide, benzyl bromide, ethyl bromo acetate and allyl bromide. In all these reactions, the corresponding two products **3b-f/4b-f** were obtained in good yields (Table 1). The structural assignments were made in analogy to the assignments of **3a** and **4a**. The structure of **4f** was additionally confirmed by single crystal X-ray analysis (Fig. 3), which also corresponded to 1,2,3-alternate conformation.

Conclusions

Overall, we demonstrate an example of regioselective metalation-substitution protocol for disubstitution of the methylene bridge of calix[6]arene ethers. We have also unambiguously assigned structures as well as assigned distorted cone and 1,2,3-alternate conformations to the products. The methodology tolerates substrate variations quite efficiently. Further, investigations on similar reactions of calix[8]arenes is under progress.

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[a]*Department of Chemistry, UGC Centre of Advance Study-I, Guru Nanak Dev University, Amritsar –143 005, India. E-mail: kamaljit.chem@gndu.ac.in.*
[b]*Department of Chemistry, Kangwoon National University, Chun Cheon 200 701, South Korea. E-mail: chhlee@kangwon.ac.kr.*

Electronic Supplementary Information (ESI) available: [1D, 2D and VT NMR spectra, crystallographic data of **3a**, **4a** and **4f**, HRMS spectra of all compounds, experimental procedures and characteristic data of all compounds,]. See DOI: 10.1039/c000000x/

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