Calix[4]arenes Comprised of Aniline Units

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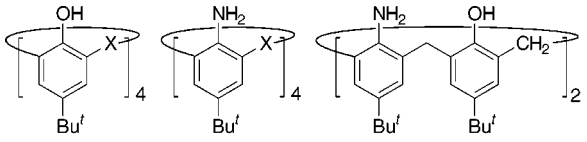
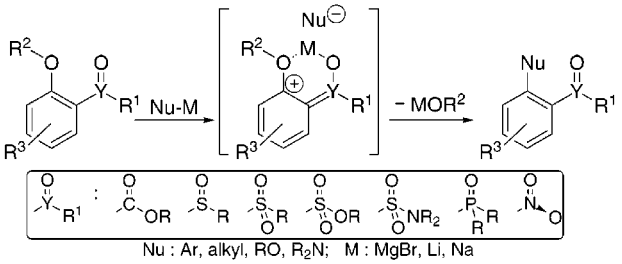
Calix[*n*]arenes (e.g., **1**) have provided versatile platforms for supramolecular host compounds via various chemical modifications.[1] For example, the hydroxy function has been advantageously utilized for introducing quite a number of functional groups to provide numerous derivatives of novel functions.[2] On the other hand, it has been well-known that introduction of any substituents to the aromatic nucleus through cleavage of an aryl-oxygen bond is quite difficult.[3] Therefore, it is not surprising that there have been only few examples of calixarenes bearing substituents other than those of −OR types at the lower rim.[4] In this context, development of a method for introducing amino substituent to the lower rim is highly desirable because such substituent is not only a potential metal-ligating moiety but also the most reliable starting functional group in synthetic aromatic chemistry for transformation to various entities via diazonium methodology. Although partially aminated calix[4]arenes such as **9** were reported by Shinkai et al.,[5] those comprised of only aniline units (i.e., **5**) are not precedented to the best of our knowledge.



1 (X = CH_2)
2 (X = S)
3 (X = SO)
4 (X = SO_2)
5 (X = CH_2)
6 (X = S)
7 (X = SO)
8 (X = SO_2)
9

Previously, we have developed the chelation-assisted nucleophilic aromatic substitution (S_NAr) reaction for replacement of an *ortho* alkoxy group of aromatic substrates bearing substituents such as ester, sulfinyl, and sulfonyl groups by a *C*-, *O*-, or *N*-centered nucleophile (Scheme 1).[6,7] This type of substitution proceeds far more readily than the "classical" S_NAr process,[3] because strong chelation of the substrate to the metal center of the nucleophile facilitates a Michael-type conjugate addition of the anionic moiety across the aromatic ring followed by displacement of the alkoxy group to eventually afford the net-substitution product.

Scheme 1. Chelation-assisted S_NAr Reaction



Then, is it possible to extend the chelation-assisted S_NAr methodology to the calix[*n*]arene family to displace the lower-rim hydroxy group only if we could provide cyclic oligophenols bridged by the chelation-type activating groups? Our recent success in the efficient synthesis of thiacalix[4]arene (**2**)[8] and its conversion to the sulfinyl (**3**) and sulfonyl counterparts (**4**)[9] enabled us to partly answer the question, and herein we report the transformation of the tetramethyl ethers of sulfinyl- and sulfonylcalix[4]arene (**14** and **11**) to the tetraamino derivatives of the thia-, sulfinyl-, and sulfonylcalix[4]arene (**6**, **7**, and **8**).

As we realized that a sulfonyl group has higher activating power than a sulfinyl group,[6] we first attempted the reaction of **11** rather than **14** with *N*-centered nucleophile (Scheme 2). The prerequisite substrate **11** was prepared by tetra-*O*-methylation of **2** to **10** followed by oxidation. Treatment of **11** with lithium benzylamide in THF at room temp. for 2 h displaced all the methoxy groups with benzylamino substituents to give **12** in high yield.[10] This indicates that the sulfonyl group even in a cyclic oligomer of alkoxybenzene is able to serve as an activating group for the S_NAr. Interestingly, the benzylamine **12** adopted 1,3-alternate conformation as evidenced by X-ray crystallography (Figure 1a), suggesting that the substitution reaction proceeded to avoid steric congestion imposed by four benzyl groups. Although attempted hydrogenolytic removal of the benzyl moiety of **12** was unsuccessful, treatment with NBS−BPO caused dehydrogenation to give imine **13**, which was then hydrolyzed to tetraaminosulfonylcalix[4]arene **8** with four free amino substituents at the lower rim. Attempts to reduce the bridging SO_2 of both **8** and **12** to S by use of $LiAlH_4$−$TiCl_4$ in THF at −78−0 °C were unsuccessful and cleaved the calix[4]arene ring.

To our pleasure, the S_NAr process proceeded quite smoothly even via the SO route for the synthesis of tetraaminosulfinylcalix[4]arene **7** and tetraaminothiacalix[4]arene **6** (Scheme 2): As has been shown before, controlled oxidation of **2** afforded sulfinylcalix[4]arene **3** with *trans*−*trans*−*trans* configuration with regard to the disposition of four SO linkages.[11] The substrate **14** was obtained by tetra-*O*-methylation of **3**. By the same method used for **11**, all of the methoxy groups of **14** were substituted by benzylamino groups to give **15** in a comparable yield. The

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(10) Among the several metal amides examined which included alkali metal and magnesium amides and alkylamides, lithium benzylamide gave the best results with respect to the yield of the desired product.
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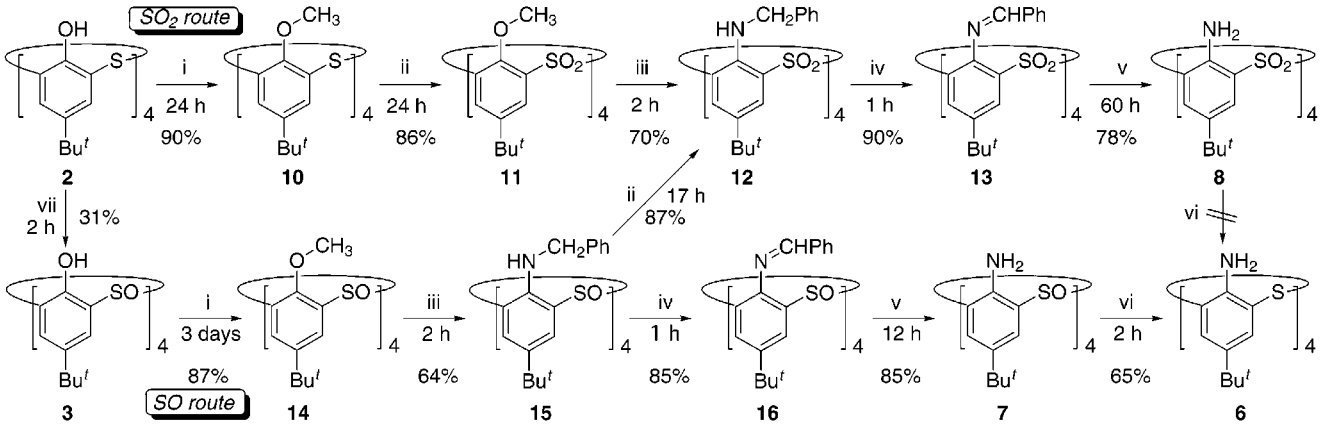
Scheme 2. Reaction Conditions, Reagents, and Yields[a]



[a] (i) CH_3I, K_2CO_3, acetone, reflux; (ii) H_2O_2, $CHCl_3-CF_3CO_2H$, reflux; (iii) $PhCH_2NHLi$, THF, rt; (iv) NBS, BPO, PhH, reflux; (v) *conc*. HCl, $CHCl_3$, reflux; (vi) $LiAlH_4-TiCl_4$, THF, rt; (vii) $NaBO_3$, $CHCl_3-CH_3CO_2H$, 50 °C.[9]

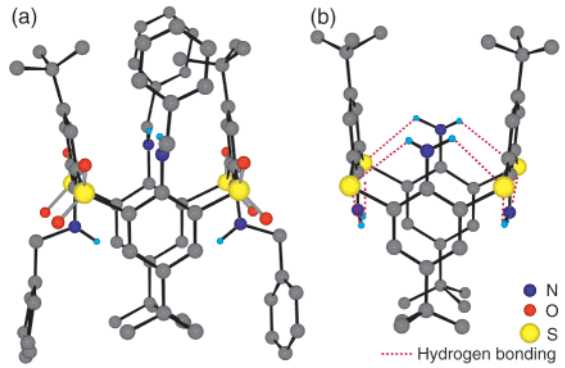


Figure 1. X-ray structure of **12** (a) and **6** (b).

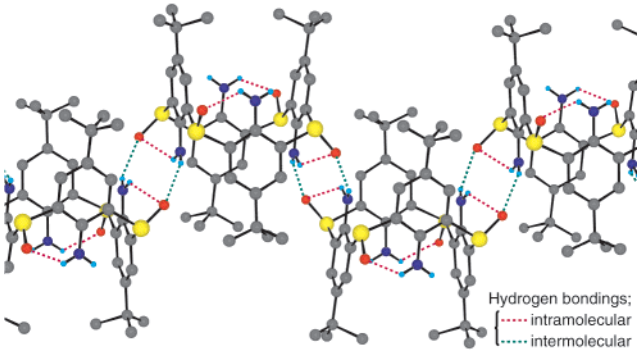


Figure 2. X-ray structure of **7** showing a portion of 2-dimensional network via intermolecular hydrogen bondings.

conformation of **15** was assigned to be 1,3-alternate by its oxidation to 1,3-alternate **12**. Here again, the dehydrogenation with NBS−BPO afforded imine **16**, which was then hydrolyzed to amine **7**. Treatment of **7** with $LiAlH_4-TiCl_4$ in THF at room temperature smoothly afforded tetraaminothiacalix[4]arene **6**.

The calix[4]arene analogues (**6**−**8**) comprised of four aniline units bridged by S, SO, and SO_2 have some interesting structural features. The X-ray crystallographic analysis revealed that **6** adopts 1,3-alternate conformation with crystallographic $\bar{4}$ symmetry (Figure 1b). The dihedral angle between the distal phenyl rings is 10.57(8)° to form an almost rectangular cavity. The intramolecular NH·····S bondings are observed between an amino group and the *ortho* sulfides.[12] This may cause the lone pair of amino group to direct toward outside the cavity.

Sulfinyl derivative **7** also adopts 1,3-alternate conformation with crystallographic $\bar{4}$ symmetry (Figure 2). The dihedral angle between distal phenyl rings is 10.9(1)°, showing a cavity quite similar to that of **6**. Contrary to **6**, there are found not only intramolecular but also intermolecular hydrogen bondings, NH···O═S, between an amino group and sulfinyl oxygen atoms.[13] This may let the lone pair of the amino group direct toward inside the cavity. The significant outcome of the intermolecular hydrogen bonding is that molecules of **7** form 2-dimensional molecular network.

Table 1 lists the selected spectroscopic data of **6**−**8**. Although crystallographic evidence for **8** is not yet available, it may be said that the larger δ_{NH2} value of **8** than that of **7** may be caused by formation of hyrdogen bonding NH···O═SO as well as by the deshielding effect of SO_2 to withdraw electrons more strongly.

Table 1. ^{1}H NMR Chemical Shift and IR Absorption Band of Interest

	δ_{NH2}/ppm	ν_{NH2}/cm^{-1} [a]	$\nu_{S=O}$/cm^{-1} [a]
6	4.88[b]	3464, 3362	–
7	5.06[c]	3452, 3371	1030
8	5.64[c]	3468, 3389	1313, 1151

[a] Measured in KBr matrix. [b] In $CDCl_3$ at 27 °C. [c] In $CDCl_3$ at 50 °C.

In conclusion, we have shown here that the chelation-assisted S_NAr methodology is applicable to the calix[4]arene analogues bearing sulfinyl and sulfonyl bridges for the synthesis of tetraaminocalix[4]arene derivatives (**6**−**8**), which should provide a new series of molecular platforms for functional materials and supramolecular assembly.

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Supporting Information Available: Details of syntheses and properties of compounds shown in Scheme 2, tables of crystallographic data, and ORTEP drawings (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) N−S: 3.060(2), 3.072(2); N−H: 0.91(3), 0.84(2); H···S: 2.58(3), 2.68(2) Å; N−H···S: 113(2), 110(2)°.

(13) For intramolecular hydrogen bonding, O−N: 3.071(4), N−H: 0.84(4), O···H: 2.46(4) Å, N−H···O: 130(3)°. For intermolecular one, O−N: 2.997(4), N−H: 0.82(3), O···H: 2.27(4) Å, N−H···O: 146(3)°.