

Can Thiacalixarene Surpass Calixarene?

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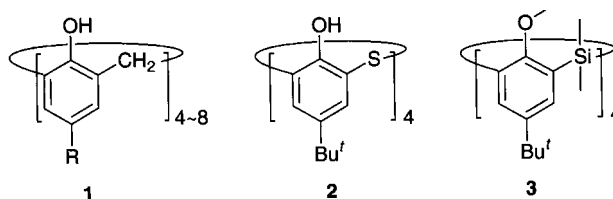
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Abstract

Heteroatom-bridged calixarenes have been confined into the unexplored frontier of the vast realm of the calixarene chemistry because of their synthetic difficulty. Since we found facile one-step synthesis of thiacalix[4]arene, in which four methylene bridges of calix[4]arene are replaced by four sulfides, we have been engaged in the study on this new molecular platform regarding the improvements for the synthetic procedures, structural analyses, chemical modifications, and functional developments. In this review are described the results of our own study to demonstrate the potentials over the limits of the conventional calixarenes, putting emphasis on the indispensable role of the bridging sulfur. Highlighted examples are (1) enlargement of the calix skeleton to provide larger cavity, (2) ready oxidizability to sulfoxide and sulfone for providing new members of S bridged calixarenes, and (3) coordination to specific metal ions controlled by the oxidation state of S. These indicate a hopeful future for the thiacalixarene platform in the forthcoming applications to functional molecular devices.

Introduction

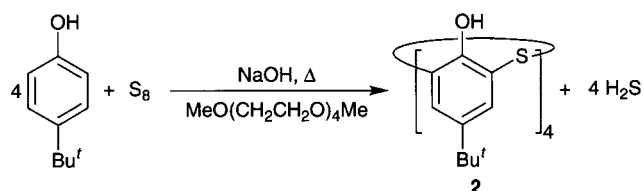
Calixarenes (**1**) are often described as “macrocycles with (almost) unlimited possibility” [1] because of their versatility and utility as host molecules, which mostly comes from the ease in the synthesis of the basic platform and ready functionalization at the lower and upper rims to construct variously modified three-dimensional structures [2]. Although replacement of the CH₂ linkage by heteroatoms such as NH, O, and S had been a challenge in the calixarene history [3], synthetic difficulty retarded the emergence of heteroatom-bridged calixarenes to explore the interesting properties expected. Rare examples of such heterocalixarenes are thiacalix[4]arene (**2**) by Sone *et al.* [4] and silacalix[4]arene (**3**) by König *et al.* [5], both of which were prepared in low yields by stepwise joining of phenol units followed by cyclization. By contrast, in 1997, we reported the facile one-step synthesis of **2** by simply heating a mixture of a *p*-alkylphenol and S₈ in the presence of a base [6]. Soon after the ready obtainment of **2** in substantial quantities, we were aware of the potential importance of **2** as a new member of the calixarene family by possessing structural as well as electronic characteristics due to sulfide functionality, which led us [7], and also other research groups [8], to engage in the studies on the modifications, stereochemical aspects, and applications to functional materials. In this paper, we review our own results of such endeavors to demonstrate the inherent properties and functions not attainable by the conventional calixarenes.



Synthesis and structure of thiacalix[n]arenes

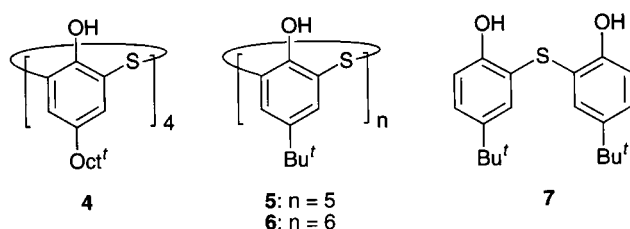
Although it has been documented that heating a mixture of a phenol and elemental sulfur gives linear oligomers of the phenol linked by sulfides [9], formation of the corresponding cyclic oligomers had not been mentioned. In this context, a paper by Hori *et al.* [10] attracted our attention, in which they disclosed a mass spectrum of a reaction mixture obtained by the treatment of calcium salt of *p*-nonylphenol with sulfur. Close inspection of the spectrum showed the presence of a peak of mass number of 1,000, coinciding with that of a cyclic tetramer of the phenol joined by sulfide, i.e., *p*-nonylthiacalix[4]arene. After extensive collaboration with Hori's group, it was eventually successful to obtain *p*-*tert*-butylthiacalix[4]arene (**2**) by heating a mixture of *p*-*tert*-butylphenol and elemental sulfur in the presence of a base catalyst, NaOH, at 230 °C in 54% yield (Scheme 1) [6]. The procedure is equally applicable to *p*-*tert*-octylphenol (*tert*-octyl = Oct^t = 1,1,3,3-tetramethylbutyl) to give *p*-*tert*-octylthiacalix[4]arene (**4**) [11]. This allowed us to obtain several tens of grams of thiacalix[4]arenes at one time for studying their behaviors or further modifications for preparing functional materials as described below. Also

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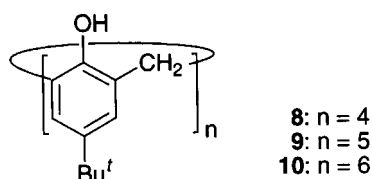


Scheme 1. Facile one-step synthesis of *p*-tert-butylthiacalix[4]arene.

isolated from the reaction of *p*-tert-butylphenol were *p*-tert-butylthiacalix[*n*]arenes ($n = 5$ (**5**), $n = 6$ (**6**)), though only in small amounts. By changing CsOH for NaOH as the base, [6]arene **6** was obtainable in a 0.8% yield [12]. Recently, the yield of **6** was improved up to 11% by starting from a sulfur-bridged acyclic dimer of *p*-tert-butylphenol **7** [13].



The X-ray structure of thiacalix[4]arene **2** was first reported by Hosseini *et al.*, showing that **2** adopted cone conformation of exact C_4 symmetry stabilized by cyclic array of hydrogen bonding comprised of four OH groups [14]. Notably, bond length between the aromatic residue and bridging group is a 15% larger than the one in methylene bridged calix[4]arene **8**, indicating that the cavity of thiacalix[4]arene is larger than the one of calix[4]arene. Solvent molecules such as MeOH, CH_2Cl_2 , and CHCl_3 were included in the cavity by a 1:1 manner. We ourselves reported X-ray structure of a crystal including one 1,2-dichloroethane molecules in a cavity of **2** and another one in the crystal lattice (Figure 1a) [11]. Interestingly, **2** showed somewhat distorted cone conformation due to the presence of the included and neighboring guests. On the other hand, the 1,2-dichloroethane sitting in the thiacalix cavity adopted *gauche* rather than *anti* conformation, meaning that the cavity could provide highly strained space to a guest molecule in the crystal state. The X-ray structure of thiacalix[6]arene **6** revealed a “winged” conformation having nearly C_{2v} symmetry (Figure 1b) [12]. There are two cavities comprising of three benzene rings, one of which accommodates a dichloromethane molecule.



In the solution state, the ^1H NMR spectra of *p*-tert-butylthiacalix[*n*]arenes **2** and **6** are quite simple, showing the averaged signal of rapid inter-conversion among stable conformers such as cone. Although the ^1H NMR chemical shift for OH group of **2** and **6** in CDCl_3 suggested the forma-

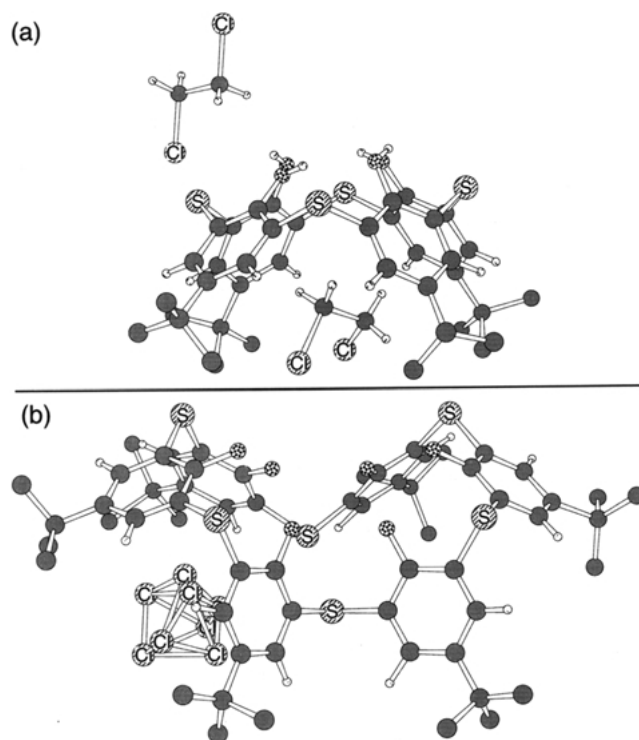


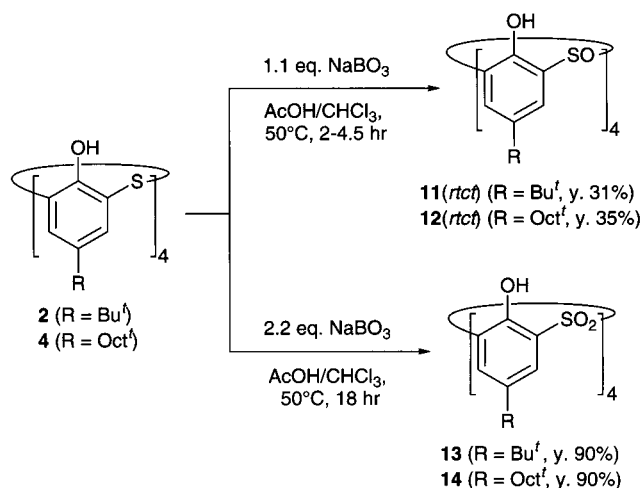
Figure 1. Crystallographic structures of (a) **2**·2($\text{C}_2\text{H}_4\text{Cl}_2$) and (b) **6**· CH_2Cl_2 .

tion of intramolecular hydrogen bonding, the strength seems to be weaker than the one in *p*-tert-butylcalix[*n*]arenes **8–10** ($n = 4–6$) [11]. This maybe ascribed to the enlarged skeleton of thiacalix[*n*]arene ring to separate OH groups further from each other. In terms of dynamic structure, Sone *et al.* evaluated the conformational mobility of calix **8** and the analogues with various combination of bridging groups of $-\text{CH}_2-$ and $-\text{S}-$ by measuring ^1H spin-lattice relaxation time in CDCl_3 , suggesting that thiacalix **2** has higher fluxionality than **8** does [4].

Chemical modification

Oxidation of the bridging sulfur

It may be trivial to apply any procedures established for modification of the conventional calixarenes [2] to thiacalixarene counterparts. In fact, conformation- and regioselective *O*-alkylation [15, 16], de-*tert*-butylation [17], and direct sulfonation [18] were successfully applied to the thiacalix[4]arene platform. It should be noted that the bridging sulfide in thiacalix[4]arene could provide another site for modification such as oxidation to sulfoxide and sulfone. In this line, we first reported the oxidation of thiacalix[4]arenes (**2**, **4**) to sulfinylcalix[4]arene (**11**, **12** with *rtct* configuration) and sulfonylcalix[4]arene (**13**, **14**) in acceptable and good yields, respectively, by use of controlled amount of oxidizing agent such as NaBO_3 and H_2O_2 under mild conditions (Scheme 2) [19, 20]. The ^1H and ^{13}C NMR spectra suggested that sulfones **13** and **14** have highly symmetrical structure adopting cone or 1,3-alternate, whereas sulfoxides



Scheme 2. Oxidation of the bridging sulfur in thiacalix[4]arenes.

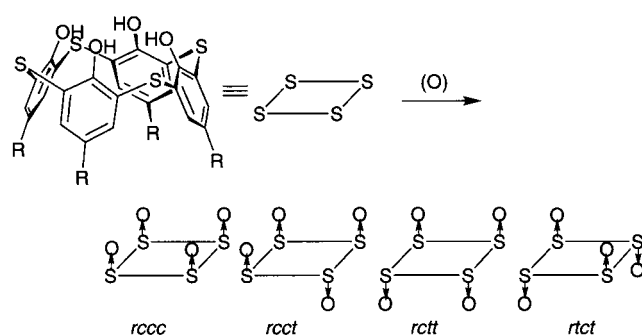


Figure 2. Four possible stereoisomers of sulfinylcalix[4]arene by configuration of four S=O groups. Abbreviations: *r*, *c*, *t* stand for reference S=O group, *cis*, and *trans* with respect to the reference, respectively; reference S=O is selected so as to have *cis* S=O groups as many as possible.

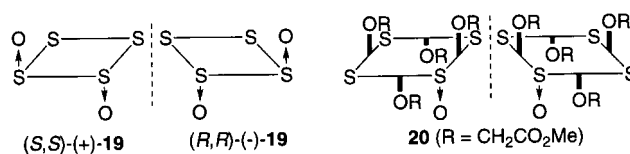
11 and **12** have a complexity arising from the configuration of S=O [19]. Theoretically, sulfinylcalix[4]arene platform has four stereoisomers depending upon the disposition of the four bridging SO groups with respect to the plane containing the four S atoms, namely *rccc*, *rcct*, *rctt*, and *rtct* (Figure 2) [21]. The products **11** and **12** were assigned to be *rtct* with the aid of X-ray analysis [22, 23]. Recently, it was found that **11**(*rctt*) was also obtainable as a methanol-soluble part of the crude product in 17% yield as well as **11**(*rtct*) in 28% by crystallization from CHCl₃ [24].

The other two stereoisomers *rccc* and *rcct* were prepared via somewhat sophisticated routes by (1) *O*-benzylation of thiacalix[4]arene **2** to fix the conformation to cone or partial cone, (2) stereoselective oxidation to tetra SO derivatives by avoiding steric bulk imposed by the benzyl moiety, and (3) debenylation to give **11** with the desired configuration (Scheme 3) [24, 25].

Creation of novel molecular chirality

Construction of chiral host compounds is one of the major interests in the calixarene chemistry. The easiest strategy is to introduce a chiral substituent to the upper or lower rim. The more sophisticated one is to bring about molecular asymmetry by introducing at least two achiral functional groups to the rim or one substituent at the *meta* position

of the phenol unit in calixarene framework [26]. In addition to these strategies, thiacalix[4]arene scaffold could have its own advantage to create (1) *S*-centered chirality and (2) molecular asymmetry by virtue of the oxidizability of bridging sulfides. As an example of case (1), disulfinyldithiacalix[4]arene (**19**) having two *S*-centered chirality was prepared by simply oxidizing tetra-*O*-methylether of thiacalix **2** with 2-fold excess of oxidizing agent (NaBO₃) followed by isolation of disulfoxide and the optical resolution [27]. X-ray crystallographic analysis of (+)-**19** allowed the assignment of the absolute configuration of (+)-**19** to be (*S*, *S*), and thus (–)-**19** to be (*R*, *R*), showing CD absorption bands of high symmetry each other. In the case (2), tetra-*O*-(methoxycarbonyl)methyl ether of thiacalix **2** adopting 1,3-alternate was oxidized to chiral mono-sulfoxide **20**, which was resolved by chiral LC [28].

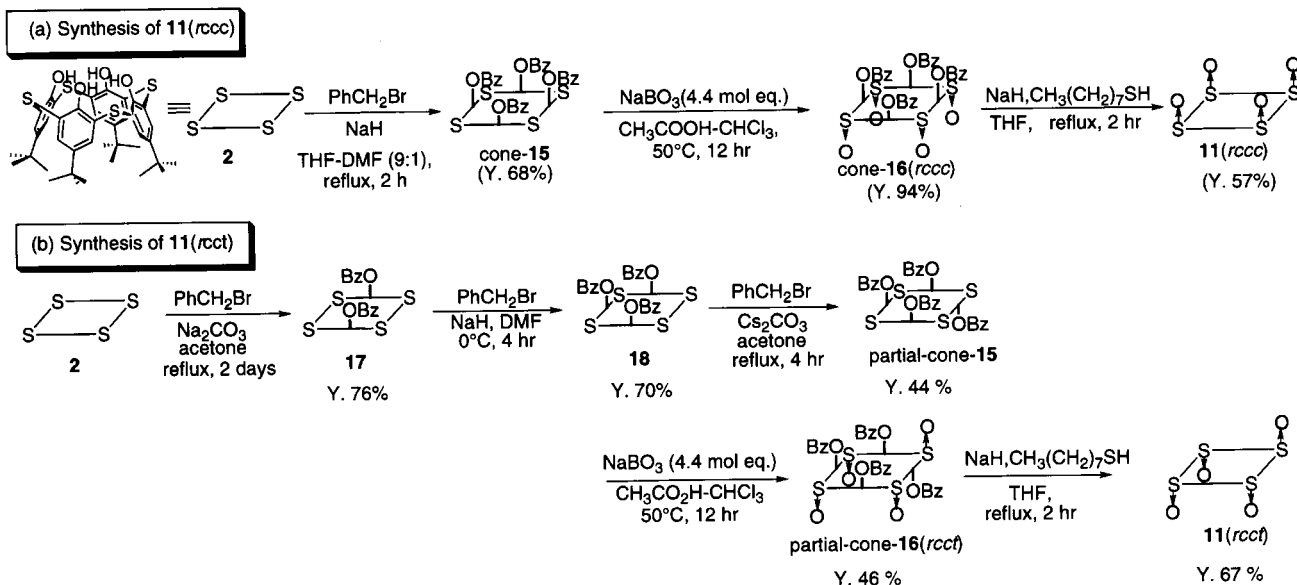


Displacement of OH substituents with amines

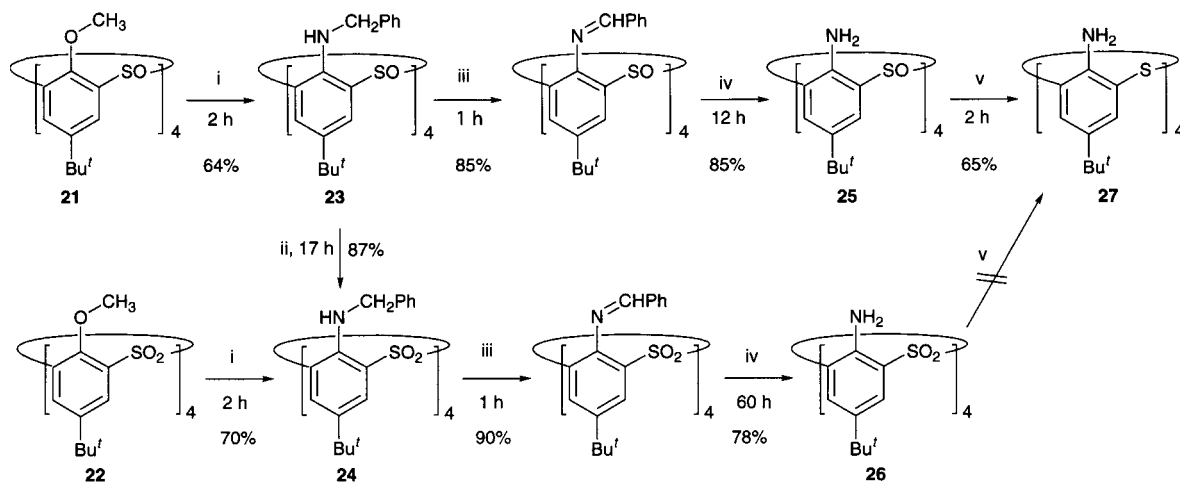
Since cleavage of an aryl-oxygen bond is quite difficult for introduction of any substituents to the aromatic nucleus [29], it is not surprising that there have been only few examples of calixarenes bearing substituents other than those of -OR types at the lower rim [30]. Previously, we have developed 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 [31]. One of the merits of this type of substitution is that it proceeds far more readily than the “classical” S_NAr process [29]. The ready availability of tetramethyl ethers of sulfinyl-(*rtct*) **21** and sulfonylcalix[4]arene **22** led us to apply this non-classical S_NAr methodology; treatment of **21**, **22** with lithium benzylamide in THF at room temp. for 2 h displaced all the methoxy groups with benzylamino substituents to give **23**, **24** in high yields (Scheme 4) [32]. De-benylation of **23** and **24** afforded aminocalix[4]arenes with sulfinyl (**25**) and sulfonyl (**26**) bridgings, the former was reduced to tetraaminothiocalix[4]arene (**27**) by LiAlH₄-TiCl₄. To the best of our knowledge, the synthesis of calix[*n*]arene derivatives comprised of only *n* aniline units is unprecedented. It may be said that calixarene chemistry has obeyed phenol chemistry. Thus, we are sure that aminocalix[4]arenes **25** ~ **27** would widen the border of the calixarene realm by equipping with aniline chemistry.

Functions

Undoubtedly, functions of calixarenes have been greatly developed via modifications of the original molecular structure [2c, d]. Although it is obvious that these conventional strategies should be readily applicable to thiacalixarenes, it



Scheme 3. Stereocontrolled oxidation of the bridging sulfur of thiacalix[4]arene **2** to sulfinylcalix[4]arene **11** with *rcc* and *rcct* configurations.



Scheme 4. Reaction conditions, reagents, and yields for the preparation of aminocalix[4]arenes. (i) PhCH_2NHLi , THF, r.t.; (ii) H_2O_2 , CHCl_3 — $\text{CF}_3\text{CO}_2\text{H}$, reflux; (iii) NBS, BPO, PhH, reflux; (iv) *conc.* HCl, CHCl_3 , reflux; (v) LiAlH_4 — TiCl_4 , THF, r.t.

seems more exciting to take advantage of the characteristic features of bridging sulfurs. Herein some examples of such challenges are reviewed to show crucial roles of the bridging sulfur and usefulness of the thiacalixarene platform.

Inclusion of guest molecules

As shown by some examples of X-ray structures of thiacalix[4]arene **2** (Figure 1a), it included solvent molecules in its cavity and/or the crystal lattice. For a variety of solvent molecules, content of the guests held in the crystal of **2** was evaluated by measuring ^1H NMR of the crystals obtained by recrystallization from the solvents [11]. In general, solvents such as CHCl_3 , benzene, cyclohexane, 1,4-dioxane, and decaline are included by 1:1 (= H:G) manners, but some exceptions are found: The content of 1,2-dichloroethane was 1:2, which coincided with the value shown by X-ray structure (Figure 1a). Interestingly, the inclusion manner of mono-substituted benzene varied depending upon the sub-

stituent; benzene, toluene and ethylbenzene were included by 1:1, 2:1, and 1:0 manners, respectively. On the other hand, thiacalix[6]arene **6** was able to form inclusion complexes with more members of the solvents, probably owing to the expansion of the cavity and/or the crystal lattice [12].

The inclusion ability of water-soluble thiacalix **28** toward small organohalogens was evaluated by ^1H NMR titration [33]. It was found that the average number of guest bound to host, \bar{n} (= [guest bound to host]/[all host]), was nearly 1 for CHCl_3 , CHBr_3 , 1,2-dichloroethane, 1,1,2-trichloroethane, and 1,1,2,2-tetrachloroethane, whereas more than one CH_2Cl_2 molecules were included. Bulkier molecules such as benzene and toluene were not included. These suggest that **28** has size-dependent selectivity. Interestingly, 1,1,2-trichloroethane was included by a 1:1 manner, while 1,1,1-counterpart was not, indicating shape selectivity is also operative. The methylene bridged **29**, on the other hand, exhibited smaller number of \bar{n} in most cases. This suggests that sulfur bridged **28** has a larger cavity to accommodate the

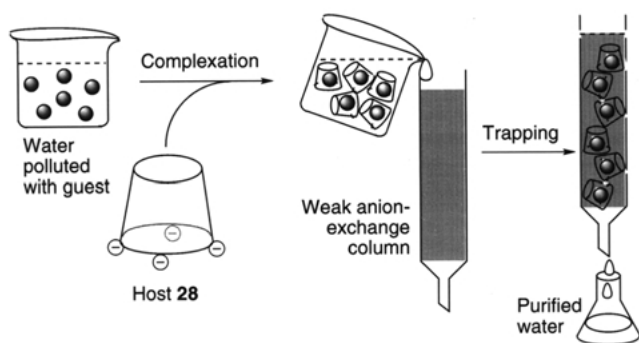
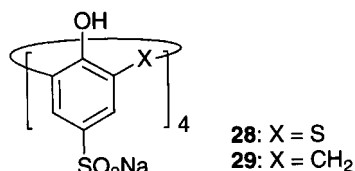


Figure 3. Schematic diagram of the procedure for removal of organohalogen. Sample solution: $C_{\text{initial}} = 2.0 \text{ mM}$, $[\mathbf{28}]_{\text{Total}} = 5.0 \text{ mM}$, 25 cm^3 . Column: 20 cm^3 of a weak anion-exchange resin having dimethylamino groups. Flow rate: $2 \text{ cm}^3/\text{min}$.

guest more comfortably than methylene bridged **29** does. Interestingly, the chemical shift change, $\Delta\delta$, upon inclusion of 1,1,2-trichloroethane showed that CHCl_2 group penetrates more deeply into the cavity of **28** than CH_2Cl does. The preference of CHCl_2 moiety suggests that $\text{CH}-\pi$ interaction contributed to some extent, although hydrophobic interaction seems to be the main driving force of the inclusion.



The high complexation ability of **28** toward organohalogen is quite attractive from the environmental viewpoint, because this class of compounds makes one of the major environmentally hazardous substances. If one can trap the host-guest complex on a solid support, the guest molecules could be removed from the aqueous phase. In this view, a method to remove organohalogen from water was presented by use of an ion-exchange resin [34]. Figure 3 depicts the concept of the method; to a sample of water polluted with an organohalogen was added host **28** to form inclusion complex, then the solution was passed through a column packed with a weak base ion-exchange resin to trap the inclusion complex. The amount of the guest in the water after the treatment, C_{final} , is measured to evaluate the removal ratio defined by Equation (1),

$$\text{removal ratio} \equiv 100\% - (C_{\text{final}}/C_{\text{initial}}) \times 100\%, \quad (1)$$

where C_{initial} is the initial concentration of the guest. It was found that the C_{final} values for CH_2Cl_2 and CHCl_3 are below ppb level after the treatment. These correspond to the removal ratio of more than 99.99%, meaning that almost complete removal is attained. CHBr_3 showed the lowest removal ratio, nonetheless the value is 99.9%, suggesting this method to be highly promising for practical application.

Recently, Ungaro *et al.* suggested by ^1H NMR study that **29** includes water-miscible neutral organic molecules such as alcohols and ketones in aqueous solution [35]. We, ourselves, found that **28** showed better inclusion ability to

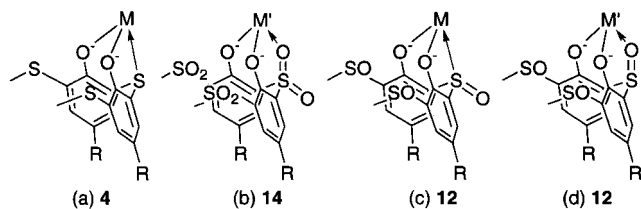
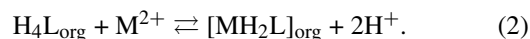


Figure 4. Proposed coordination manners of (a) *p*-tert-octylthiacalix[4]arene (**4**) and (b) the sulfonyl (**14**) and (c, d) sulfinyl (**12**) analogues. R = Oct^t. For clarity, only half part of calyx[4]arene ring is depicted. M and M' denote soft and hard metal ions, respectively.

ward a wider range of such molecules, thus providing a convenient method for recovering them from the aqueous solution simply by salt-out of the host-guest complexes [36].

Recognition of metal ions

The important features of sulfide function are related to the electronic structures of possessing lone pair electrons and vacant 3d orbital, suggesting the binding ability of thiacalixarenes to metal ions. In fact, solvent extraction study has shown that thiacalix[4]arene **2** can extract transition metal ions [37]. On the other hand, conventional calix[4]arene **8** cannot extract them at all, substantiating that the bridging sulfur plays some important roles in the recognition of metal ions. Equilibrium study showed that **2** (abbreviated as tetraprotic ligand, H_4L) formed 1:1 complexes with divalent metal ions M^{2+} ($= \text{Co}^{2+}$, Cu^{2+} , and Zn^{2+}) to release 2 protons, indicating that the extraction proceeded via a chelate extraction mechanism (Equation (2)).



The role of the bridging sulfur was eventually clarified by an X-ray structural analysis of a Zn^{2+} complex obtained by recrystallization of the extracted species [38]; the sulfur coordinated to Zn^{2+} center with cooperative ligation of the two adjacent phenoxide O^- (cf. Figure 4a). Obviously, the conventional calixarenes is not able to coordinate to metal ions in a similar fashion. Therefore, they must be equipped with some metal-ligating auxiliaries at the lower or upper rim to extract metal ions from aqueous phase [2c, 39]. Thus, the complexation ability of calixarenes has been governed primarily by the functional group introduced. In this sense, a calix[*n*]arene is simply a platform to assemble ligands. By contrast, thiacalix[4]arene is very unique in calixarene world in that the macrocyclic platform *per se* possess metal binding ability.

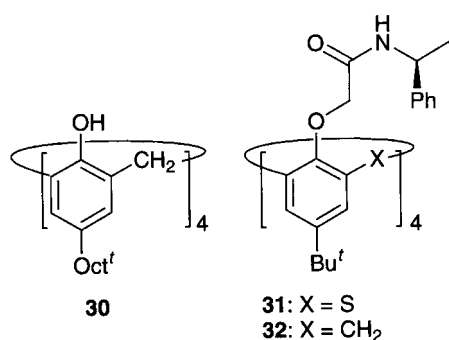
As has been discussed above, the oxidizability to sulfoxide and sulfone is another feature of sulfide function. From the viewpoint of coordination chemistry, one can easily expect that the oxidation state of the bridging sulfur will affect the complexation ability and selectivity. Then, systematic study was carried out to evaluate the extraction ability of *p*-tert-octylcalix[4]arene (**30**) and the analogues with bridging S (**4**), SO (**12** with *rtct* configuration), and SO_2 (**14**) as ligands for over 40 kinds of metal ions under various pHs [20]. As was expected, the metal ion selectivity was de-

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1																		
2	Li	Be																
3	Na	Mg											Al					
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga					
5	Rb	Sr	Y	Zr	Nb	Mo		Ru	Rh	Pd	Ag	Cd	In				Sb	
6	Cs	Ba	Ln	Hf	Ta					Pt	Au	Hg	Tl	Pb	Bi			
7																		

	Extracted by 4		Extracted by 12
	Extracted by 4 and 12		Extracted by 12 and 14
	Not extracted by 4, 12, 14, and 30		

Figure 5. Periodic tables of the extracted metal ions by *p*-tert-octylcalix[4]arene **30**, and the analogues with S (**4**), SO (**12**), and SO₂ (**14**) bridges in pace of CH₂.

pendent on the bridging moiety (Figure 5); First transition metal ions, Ag⁺, and Hg²⁺, categorized as intermediate to soft metal ions by the “hard and soft acids and bases (HSAB) rule” [40], were extracted by **4** and **12**, while hard ones such as alkaline earth, lanthanide, and group 4 metal ions were extracted by **12** and **14**. By contrast, methylene bridged calix[4]arene **30** could hardly extract any of these metal ions. Considering the tridentate nature of **2** to Zn²⁺ ion, we proposed the coordination modes depicted in Figure 4 to explain the results of metal extraction by **4**, **12**, and **14**. First, **4** binds to soft metal ions by the coordination of a lone pair electrons of sulfur atom besides two phenolic oxygens (Figure 4a) as proven for the Zn²⁺ complex with **2** [38]. Second, **14** coordinated to hard metal ions by ligation of sulfonyl oxygen (Figure 4b). Third, **12** could switch the coordinating atom between S and O of the sulfinyl group depending on the hardness and softness of the metal ions (Figure 4c and d). In this way, the extraction selectivity of these sulfur bridged calix[4]arenes (**4**, **12**, and **14**) may be explained by the HSAB rule. To our pleasure, the proposed coordination modes were substantiated by X-ray crystallography of many of these metal complexes [41]. Thus, control of metal-binding ability by the oxidation state of the bridging sulfur is another characteristic function of thiacalix[4]arene.



Chiral recognition

In the last two decades, a wide variety of chiral stationary phases (CSPs) have been developed for direct separation of enantiomers by gas chromatography (GC) [42]. Among such CSPs, those based on variously modified cyclodextrins (CDs) have been most widely utilized because of their excellent chiral recognition as well as ready availability. On the other hand, calixarenes, having macrocyclic structure like

as CDs, had never been utilized for the CSP for GC [43]. We synthesized new chiral selectors for CSPs by introducing chiral substituents to thiacalix **2** [44], the enantioselectivity of which for various chiral analytes such as alcohol, amine, and amino acid derivatives were assessed by GC. For example, CSP **31** having four (*S*)-1-phenylethylamide groups exhibited chiral separation for all the samples tested. On the contrary, the reference CSP **32** based on calix[4]arene platform could not discriminate chirality, at least partly due to the high melting point (323 °C) inhibiting sufficient interaction between the selector and a selectand. Also, flexibility of thiacalix platform [4] may play an important role to make strong hydrogen bonding with the analyte, suggesting that the bridging group is also a key factor in chiral recognition.

Conclusions

As has been shown above, thiacalixarenes are not a simple substitute for the conventional methylene-bridged calixarenes, but have their own irreplaceable advantages, some of which cannot be attained by the latter, by virtue of the sulfide linkage. For instance, the ready oxidizability of thiacalix[4]arene to the sulfinyl and sulfonyl counterparts can provide a wide variety of calix members of quite differing host properties with divergent stereochemical aspects. Direct replacement of OR on the lower rim with an amide by the S_NAr protocol will extend far more the border of the calixarene chemistry. The specific metal-binding property should be one of the most noticeable features of this thiacalix class ligands. From the view point of host property, the enlarged cavity provided high accommodation ability towards a variety of neutral organic guest molecules including organohalides, alcohols, carbonyl compounds and so on in aqueous solutions. Also, the flexible framework seemed to play an important role in chiral recognition by hydrogen bonding interaction between the CSP and analytes. Although the chemistry of thiacalixarene has just been started, its ready availability in substantial quantities and the presence of sulfur moiety instead of methylene would surely give this new member of the calix family an unlimited applications in quite near future.

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