

## Contribution

# Thiacalixarenes: the development of new host molecules utilizing the characteristics of sulfur

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## 1. Introduction

The discovery of crown ethers by C. J. Pedersen has stimulated a lot of chemists to the design and synthesis of a variety of host molecules because of the promising new functions of these novel compounds or the fantastic features attainable by forming supramolecular complexes from the host and guest molecules. In other word, the advent of a new host compound is crucial for the development of highly advanced functional materials such as high-performance catalysts, extremely sensitive sensors, ultra-fine separation materials and so on. It is necessary for a compound to make a useful host that the basic molecular scaffold *per se* should have potential molecular recognition ability with ready feasibility to varying chemical modifications for drawing out the best performances of the molecule. Thus, a hopeful candidate host compound should be not only readily synthesized in large quantities but also easily modified for maximizing molecular recognition power toward relevant guest molecules.

One of the host molecules that meets these requirements is the calix[n]arene, a macrocyclic compound composed of phenolic units linked with methylene groups at the *o,o'*-positions. Because of the attractive features as host compound as mentioned above, calixarenes have been actively studied and utilized as the third host compounds, in addition to the well known crown ethers and cyclodextrins. During the 3-decades history of calixarene chemistry, however, general strategy adopted to improve the functions of the calix class compounds virtually relied on the modification through the phenol OH groups or at the *p*-positions. Therefore, novel approaches or alternative ideas had been highly desired for the molecular design and/or modification of calixarenes.

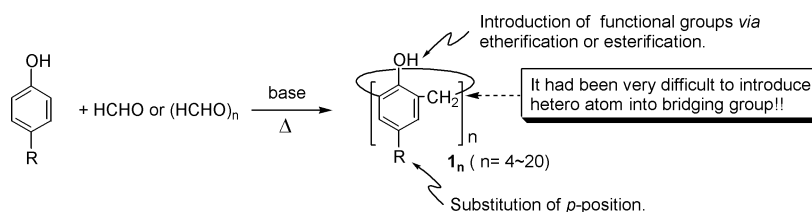
During the course of our study on the development of new host compounds, we had a lucky chance to find a facile method for the synthesis of thiacalix[4]arenes, in

which all four methylene bridges of the conventional calix[4]arenes are replaced by sulfide bonds. Needless to say, the linking sulfur possesses electrical and structural characteristics that are quite different from those of methylene group. Then, it is readily conceivable that the sulfur moiety would add new functions to the conventional calix class compounds as host molecule. Thus, soon after the appearance of our paper on the practical synthesis of *p-tert*-butylthiacalix[4]arene, many research groups have got into the study of this new host compound, and with the progress of the research it has become clear that thiacalix[4]arenes are not a simply substitute of the conventional calix[4]arenes but that they should be recognized as quite unique host molecules of vast possibilities to be developed. We would like to say that thiacalixarenes will open the age of "second-generation" calixarene chemistry.<sup>1)</sup> In this review, we will mainly report our recent results on the chemistry of thiacalix[n]arenes as compared to the methylene-bridged counterparts, laying stress on the molecular recognition ability and potentials as host molecule.

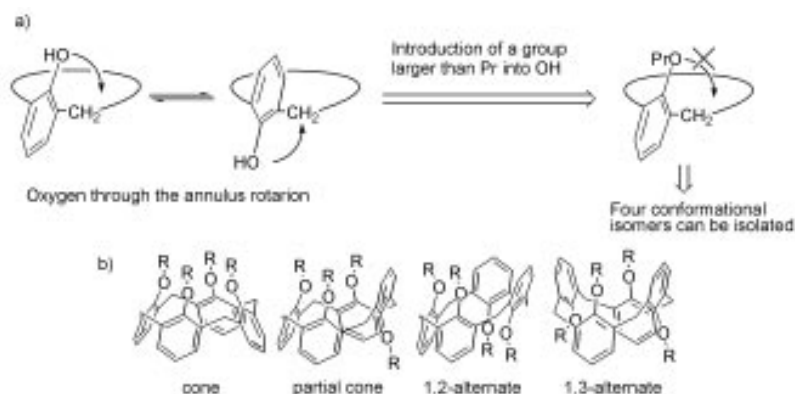
## 2. Calixarenes and thiacalixarenes

### 2.1. Calix[n]arenes

Calix[n]arenes can be synthesized by the base-catalyzed condensation of *p*-substituted phenols with formaldehyde. By selecting appropriate reaction conditions, analogues of a given number of phenolic units can be selectively obtained (Scheme 1);<sup>2)</sup> even the member of having as much as 20-phenol units has been obtained (calix[20]arene).<sup>3)</sup> Therefore it is possible to control the cavity size according to the desired purposes.



**Scheme 1.** Synthesis of calix[n]arenes and their modification strategies.



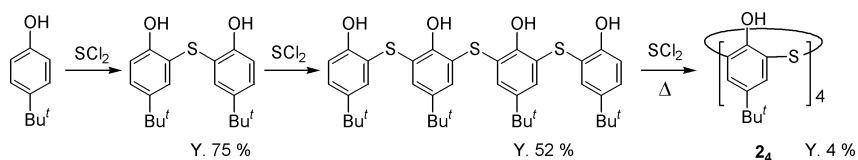
**Figure 1.** Rotation of phenyl ring (a) and four conformational isomers of calix[4]arene derivatives (b).

Furthermore, since a calix[n]arene is constructed from the alternating units of phenol and methylene group, chemical modification of the parent entity can be readily achieved by relying on the traditional phenol chemistry. Thus, various functional groups can be introduced by etherification or esterification at the phenolic hydroxy groups and by electrophilic substitution at the *p*-position of the phenol nucleus. Furthermore, calixes possess characteristic conformational features unlike other host molecules such as crown ethers and cyclodextrins. In particular, the phenol units of calix[4]arene **1**<sub>4</sub> can rotate *via* the hydroxy group going through the macrocyclic ring comprised of the phenol and methylene units in solution (Figure 1a). However, the rotation of the individual phenol unit of **1**<sub>4</sub> can be blocked by introducing a substituent bulkier than *n*-propyl group and then four conformers can be isolated as stable isomers under usual conditions (Figure 1b). This indicates that the molecular framework of calixes can be fabricated to be flexible or rigid, depending on the particular requirements for the host. This adds complexity to the conformational analysis of calix[4]arene derivatives but widens the

functions of the host molecules due to the varying structures. Preceding reviews can be referred to for details on these points.<sup>4)</sup>

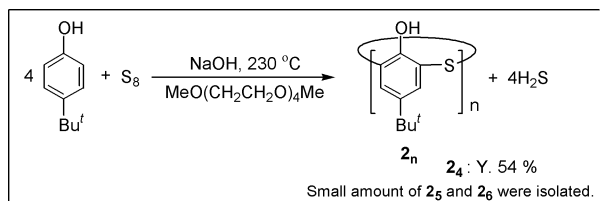
## 2.2. Synthesis of thiacalix[n]arenes

Much effort, which had been devoted to the development of new functions of calix[n]arenes, mostly relied on the modifications at the hydroxy groups or at the *p*-positions of the phenol units. On the contrary, modification of the molecular framework itself by replacing heteroatoms for the linking methylene units had scarcely been challenged because of the synthetic difficulties. Among the quite limited attempts, Sone *et al.* achieved the first synthesis of *p*-*tert*-butylthiacalix[4]arene **2**<sub>4</sub>, in which all the four methylenes of the parent calix were replaced with sulfur atoms. However, tedious stepwise treatment of *p*-*tert*-butylphenol with SCl<sub>2</sub> afforded only poor yield of the desired **2**<sub>4</sub> (Scheme 2),<sup>5)</sup> not allowing substantial research into functional development of the intriguing new arrival.



**Scheme 2.** Stepwise synthesis of *p*-*tert*-butylthiacalix[4]arene (**2**<sub>4</sub>) from *p*-*tert*-butylphenol.

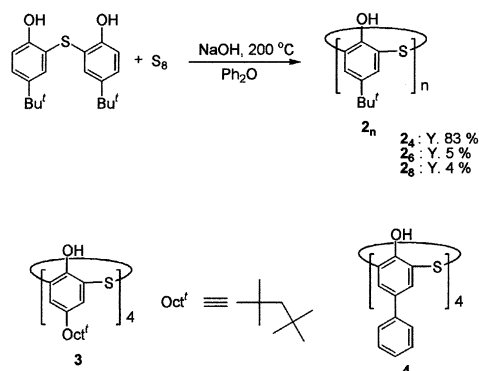
In the meanwhile, chemical engineers at the Cosmo Oil Co., Ltd. had been collaborating with the authors' group under a research program directed toward the development of a powerful alkaline-cleaning additive for lubricants used in internal-combustion engines for neutralizing acidic matter formed from combustion of petroleum fuel. The main target of the program was concentrated on the method how to increase the calcium content as highly oil-soluble phenolate salts, which led them to convert a phenol to polydentate ligands by combining plural phenol units with sulfur. Among the complex mixture of the product formed from heating a mixture of a phenol, elemental sulfur, and CaO in a solvent, a small peak found in a mass spectrum attracted one (S. M.) of the authors' attention because it had the same mass number as the compound corresponding to a cyclic tetramer of the phenol linked by sulfur reminiscent of the calix[4]arene. After enormous efforts of the Cosmo people to get the supposed sulfur analogue of the calix[4]arene in a synthetically useful yield, they eventually found that heating a mixture of *p*-*tert*-butylphenol and elemental sulfur in tetraglyme using sodium hydroxide as the base catalyst could lead to the formation of **2<sub>4</sub>** in the yield of 54% (Scheme 3).<sup>6)</sup> The yield compares very well with that of 49% of **1<sub>4</sub>** attained by the established synthesis. In the reaction mixture, also detected were the presence of trace amounts of [5]arene (**2<sub>5</sub>**) and [6]arene (**2<sub>6</sub>**). (It should be noted that more than 60% yield can now be attained in the commercial production of **2<sub>4</sub>** in a several tens of kilograms scale reaction at the Cosmo Oil Co., Ltd.)



**Scheme 3.** Facile one-step synthesis of *p*-*tert*-butylthiacalix[4]arene.

On the other hand, during the course of our study on the elucidation of the mechanism of the formation of **2<sub>4</sub>** according to Scheme 3, one of the crucial steps of the reaction seemed to be the formation of the sulfur-bridged phenol dimer. Therefore, it occurred to us to use the dimer as the starting material, which afforded the yield of **2<sub>4</sub>** as high as 83% (Scheme 4).<sup>7)</sup> Also by starting from the dimer, proper choice of the reaction conditions afforded **2<sub>6</sub>** and **2<sub>8</sub>** in synthetically appreciable yields of 5 and 4%, respectively. It is an interesting subject to know how the substituents at the *p*-position affect the characteristics of calixarenes, such as cavity size, conformational preference and so on. In this respect, one-pot synthesis of *p*-*tert*-octyl (**3**) and *p*-phenyl (**4**) derivatives have been provided by using the corresponding phenols as the starting material (Scheme 3).<sup>8,9)</sup>

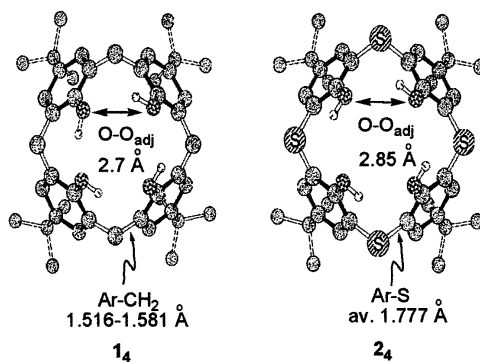
As mentioned above, the traditional calixarene chemistry had scarcely exploited the method for replacing the methylene-bridge by a heteroatom, but now the base-catalyzed condensation of phenols with elemental sulfur has opened a practical route to sulfur-bridged calixarenes. In particular, the most basic *p*-*tert*-butylthiacalix[4]arene (**2<sub>4</sub>**) can now be commercially available from Tokyo Kasei Kogyo Co., Ltd, which should promote substantial progress in the development of heteroatom-calixarene chemistry.



**Scheme 4.** Synthesis of **2<sub>n</sub>** from sulfur-bridged phenol dimer.

### 2.3. Structure and characteristics of *p*-*tert*-butylthiacalix[*n*]arenes

The X-ray structural analysis of **2<sub>4</sub>** was first reported by Hosseini *et al.*<sup>10)</sup> It was shown that the four hydroxy groups of **2<sub>4</sub>** form an intramolecular cyclic hydrogen bond in the solid state, forming a *C<sub>4</sub>* symmetric cone conformation similar to that of the methylene-bridged counterpart **1<sub>4</sub>**. As shown in Figure 2, the bond-length of Ar-S of **2<sub>4</sub>** is longer than that of Ar-CH<sub>2</sub> of **1<sub>4</sub>** by a 15%, and then the distance of O-O<sub>adj</sub> of the former is 2.85 Å, which is longer than that of the latter of 2.7 Å.



**Figure 2.** Model structure of *p*-*tert*-butylcalix[4]arene **1<sub>4</sub>** and *p*-*tert*-butylthiacalix[4]arene **2<sub>4</sub>**.

Sone *et al.* carried out detailed measurements of  $^1\text{H}$  NMR spin-lattice relaxation time  $T_1$  to estimate the rate of the inversion between the cone-cone conformations.<sup>4)</sup> The results showed that the activation energy of the inversion of the **2**<sub>4</sub> scaffold is 56.5 kJ/mol, which is smaller than that of **1**<sub>4</sub> (64.9 kJ/mol), indicating the increase in mobility of the molecular framework of **2**<sub>4</sub> due to the enlarged ring. Cabral *et al.* reported the results of theoretical calculations on **2**<sub>4</sub>, which was in good accordance with the results of X-ray structural analysis.<sup>11)</sup> On the other hand, the authors succeeded in the X-ray crystal analysis of [6]arene **2**<sub>6</sub>.<sup>12)</sup> This compound has a  $C_{2v}$  symmetric structure, two of the bridging sulfurs directing inwardly as is observed in the conventional methylene-bridged counterpart **1**<sub>6</sub>. Although single crystals of [8]arene **2**<sub>8</sub> have not yet been obtained, octamethoxy derivative of it crystallized well to allow X-ray analysis.<sup>7)</sup>

As can be seen from the above descriptions, the cavity size and flexibility of a series of thiacalix[n]arenes can significantly vary with the unit number  $n$ , keeping the basic molecular framework which is composed of a cyclic array of alternating phenol and sulfur components.

#### 2.4. Chemical modifications of thiacalix[n]arenes and their characteristics

Both thiacalix[n]arenes and calix[n]arenes are feasible to chemical modifications intrinsic to phenols, that is, modifications at the phenolic hydroxy group and/or the  $p$ -position (Figure 3). Therefore, a variety of thiacalix derivatives corresponding to the calix parents can be prepared according to the well-established calixarene chemistry. Moreover, the sulfide bonds also bring about characteristic features to thiacalixes due to the steric and electronic effect of sulfur. In particular, possibility of the oxidation of the sulfide bond to sulfoxide and sulfone should be pointed out. Thus, reaction conditions used for the synthesis of a particular thiacalix derivative may considerably differ from those used for the methylene-bridged calix counterpart, and furthermore, these two pairs may show quite different characteristics with each other. Herein, the authors will concentrate on the chemical modifications of the thiacalix[4]arenes.

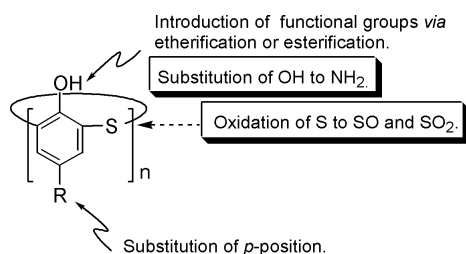
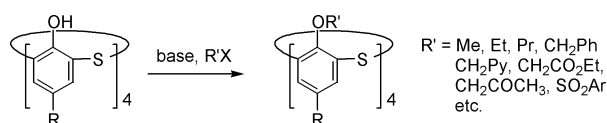


Figure 3. Strategies for modification of thiacalix[n]arene.

#### 2.4.1. Modification of phenolic hydroxy group

Various functional groups can be introduced at the hydroxy groups by simple base-catalyzed etherification (the Williamson synthesis) or esterification (Scheme 5).<sup>13)</sup> Reaction products ranging from mono- to tetra-substituted derivatives can be selectively synthesized by using appropriate reaction conditions for a given substituent. Recently, it has been shown that the Mitsunobu reaction sometimes works well to introduce several substituents.<sup>14)</sup> Any of the four conformational isomers shown in Figure 1 may also be selectively prepared by introducing four same or different substituents which are bulky enough to stop the rotation of the phenol units. These conformers should make a good resource for the design and synthesis of particular host molecules equipped with functional groups arranged in a desired three-dimensional alignment.



Scheme 5. Etherification and esterification of thiacalix[4]arene.

As stated before,  $n$ -propoxy substituent is bulky enough to retard the rotation of a phenol unit of the classical calix[4]arenes (see Figure 1). Interestingly, however, Lhoták *et al.* found an unambiguous evidence that **2**<sub>4</sub> has a larger ring size than **1**<sub>4</sub> by showing that the  $O$ - $n$ -propylated phenol nucleus of **2**<sub>4</sub> still retains the freedom to rotate though very slowly (Figure 4).<sup>15)</sup>

It is also interesting to introduce heteroatom functional groups to the phenol hydroxy groups and pioneering works in this line by converting to phosphates or silyl ethers have appeared.<sup>16,17)</sup> Hosseini *et al.* have succeeded in replacing the four phenolic OH groups by SH functions to give calix[4]arene derivatives having 8 sulfur atoms.<sup>18)</sup>

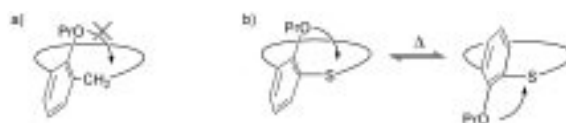
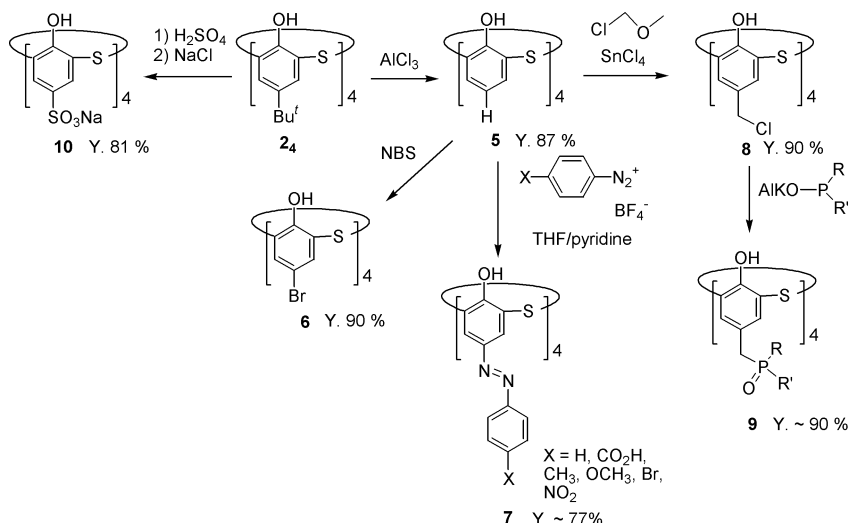


Figure 4. Rotation of phenyl ring of calix[4]arene propyl ether (a) and thiacalix[4]arene propyl ether (b).

#### 2.4.2. Modification at the $p$ -position

Electrophilic aromatic substitution ( $\text{S}_{\text{E}}\text{Ar}$ ) reaction provides the most general method for modification of calixarenes at the  $p$ -position of the phenol residue, which basically stands for thiacalixarenes. For example, de-*tert*-butylation of **2**<sub>4</sub> can be achieved to give thiacalix[4]arene **5** by the similar treatment with aluminum chloride used for the reaction of **1**<sub>4</sub> (Scheme 6).<sup>10,19)</sup> Depending on the



**Scheme 6.** Modification of *p*-position of thiacalix[4]arene.

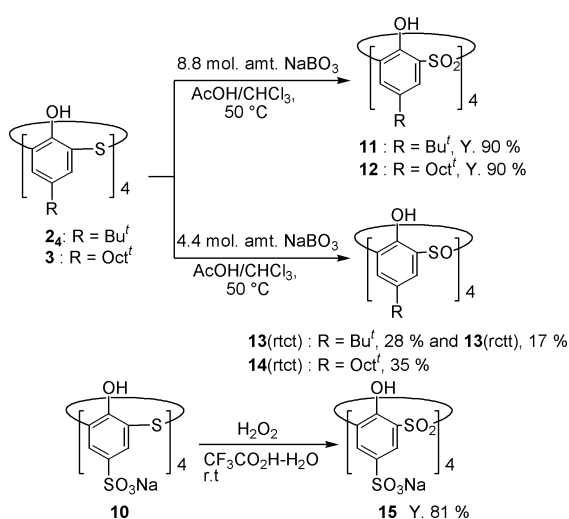
reaction conditions, partially *de-tert*-butylated thiacalixes ranging from mono- to tri-substituted derivatives were obtainable. Direct treatment of **2<sub>4</sub>** with concentrated sulfuric acid (80 °C) followed by salting out with sodium chloride gave the 4-sulfonic acid sodium salt (**10**) in good yield.<sup>21</sup> This salt is highly soluble in water and proved to be a potential host compound in aqueous solutions. Compound **5** makes a good starting material to a wide range of thiacalix[4]arenes *via* the  $S_EAr$  methodology, among which are diazo-coupling reaction, bromination, and chloromethylation as shown in Scheme 6.

#### 2.4.3. Chemical modifications unique to thiacalixarenes

By virtue of the sulfide function, thiacalixarenes are feasible to unique transformations that are not applicable to methylene-bridged calixarenes, the most important of which is oxidation to sulfinyl and sulfonyl function. Treatment of **2<sub>4</sub>** with a small excess amount of an oxidant such as hydrogen peroxide or sodium perborate in an organic acid solvent converted all four sulfide bonds to sulfone, giving **11** almost quantitatively (Scheme 7).<sup>22</sup> Similar treatment of **3** and **10** gave the corresponding sulfones (**12**, **15**) in high yields. An X-ray structural analysis showed that sulfonyl derivative **11** has 1,3-alternate conformation due to hydrogen bonding between phenolic hydroxy groups and sulfonyl oxygens, making contrast to the cone-conformation of **1<sub>4</sub>** and **2<sub>4</sub>**.<sup>22b</sup>

On the other hand, a sulfinylcalix[4]arene, in which all the four bridging groups are sulfinyl function, can theoretically take four stereoisomeric forms (rccc, rcct, rctt, and rctc) due to the disposition of the sulfinyl moiety, and their synthesis and elucidation of the characteristics stimulated the authors' interest (Figure 5). Actually, all the four isomers were obtained *via* direct oxidation of **2<sub>4</sub>** or *via* stepwise oxidation of properly protected intermediates.<sup>23</sup> Lhoták *et al.* reported stereo-controlled oxidation of **16**, in which  $\text{NaNO}_3\text{-CH}_3\text{COOH}$  was effective for the oxidation of the sulfide to sulfoxide function (Scheme 8).<sup>24</sup>

Thus, thiacalixarenes have significant advantages over classical calixarenes in that the formers are viable to additional modification by oxidation of the bridging sulfide bonds to the sulfoxides and/or sulfones. This oxidizability, however, sometimes forces to explore alternative transformation methods other than those used in the methylene-bridged calixarenes. For instance, *p*-bromothiacalix[4]arene **6** should be a potential starting material for various derivatizations. However, attempted bromination of **5** by conventional methods including the ones used for the synthesis of *p*-bromocalix[4]arene resulted in the formation of complex mixtures due to the concomitant oxidation of the sulfide linkage (Scheme 9). It is interesting to note that dibromo- (**19**) and tetrabromothiacalix derivative (**20**) were successfully obtained in high yields by Lhoták *et al.* by the bromination of 1,3-diether **18**.

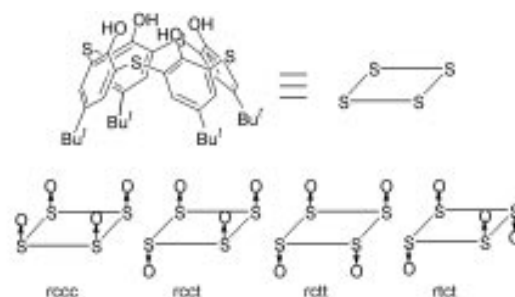


**Scheme 7.** Oxidation of thiacalix[4]arenes to sulfonyl- and sulfinylcalix[4]arenes.

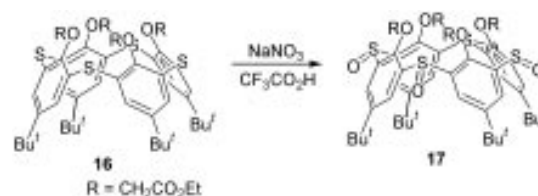
Later, Kalchenko *et al.* reported the synthesis of tetrabromo derivative **6** in high yield by a direct NBS-bromination of free hydroxy compound **5** (Scheme 6).<sup>26</sup> Attempted nitrations of **5** also accompanied oxidation of the sulfide function to give complex mixtures. Protection of the phenolic hydroxy groups by etherification and previous conversion of the sulfide to sulfone enabled *p*-nitration.<sup>27</sup> Although it has been traditional for the synthesis of aromatic amines to rely on the reduction of the corresponding nitro compounds, *p*-aminothiacalix[4]arene was alternatively obtained by hydrolyzing the diazo-coupling products **7**.<sup>20a)</sup>

It is well known in the basic organic chemistry that phenolic OH groups highly resist to the displacement by other substituents, which has limited the available calixarenes to only those of phenol derivatives. Therefore, development of the methodology for substitution of the lower-rim OH group has been highly desired in the field of calixarene chemistry. In this context, thiacalixarenes are very promising entities as follows:

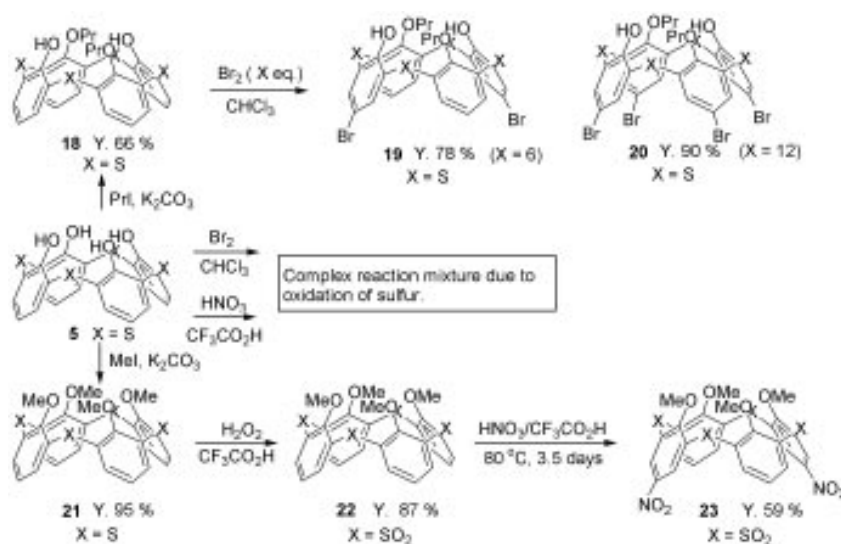
The authors had developed the chelation-assisted nucleophilic aromatic substitution ( $S_NAr$ ) protocol, in which electron-withdrawing substituents by mesomery such as carbonyl, sulfinyl, phosphinyl and the like highly activate an *o*-alkoxy group toward nucleophiles containing cationic center that can form a chelate complex with the substrate. As an extension of the principle, treatment of tetramethyl ether of sulfinylcalix[4]arene **24** with lithium benzylamide displaced all the methoxy groups with benzylamino moiety to give 1,3-alternate **25** with high stereoselectivity (Scheme 10).<sup>28</sup> Subsequent debenzylation followed by reduction of the sulfinyl function afforded aminothiocalix[4]arene (**28**) which provided the first example of calix derivative comprised of only *aniline* units. Considering the fact that methylene-bridged calix[4]arenes allowed amination of up to two hydroxy groups at most under harsh reaction conditions, it may be said that thiacalixarenes will open a new field of calixarene chemistry based on not only phenol but aniline chemistry.



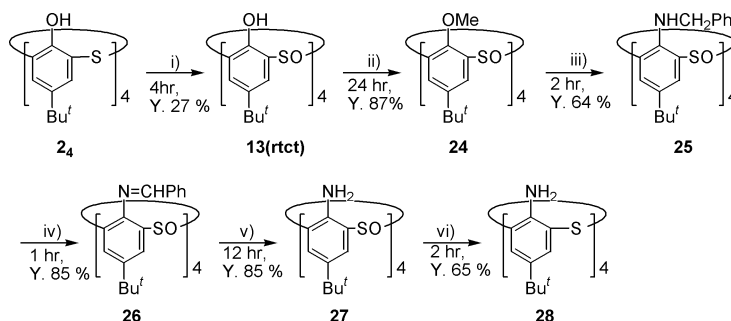
**Figure 5.** Schematic representation of four stereoisomers of sulfinylcalix[4]arene.



**Scheme 8.** Stereocontrolled oxidation of tetraether derivatives by treatment with  $\text{NaNO}_3$ .



**Scheme 9.** Alternative method for bromination and nitration of thiacalix[4]arenes.



**Scheme 10.** Syntheses of *p*-*tert*-butylaminothiocalix[4]arene **28**.

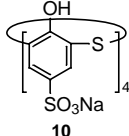
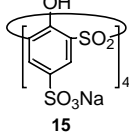
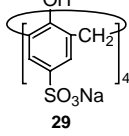
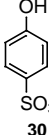
i)  $\text{NaBO}_3$ ,  $\text{CH}_3\text{CO}_2\text{H}\cdot\text{CHCl}_3$ ; ii)  $\text{K}_2\text{CO}_3$ , MeI, acetone, reflux; iii)  $\text{PhCH}_2\text{NHLi}$ , THF, r.t.; iv) NBS, BPO, PhH, reflux; v) conc. HCl,  $\text{CHCl}_3$ , reflux; vi)  $\text{LiAlH}_4\text{-TiCl}_4$ , THF, r.t.

#### 2.4.4. Acidity of sulfonic acid derivatives

It is essential for the development of novel functions of calixarenes to know the acidity of the relevant phenol residues. Calixarenes having *p*-sulfo functions are highly water-soluble. Then, the authors measured the acidity of the phenolic hydroxy groups of **10** and **15** in water for comparing them with those of methylene-bridged **29** and

monomeric **30** (Table 1).<sup>29)</sup> It was found that phenolic OH of **10** is more acidic than that of **29**, especially a large difference being observed in  $\text{p}K_{\text{a}2}$ . These differences may be ascribed to the electronic effect of sulfur moiety as well as the changes in hydrogen bonding due to the enlargement of the ring. It was also seen that conversion of the sulfide to sulfone further strengthened the acidity.

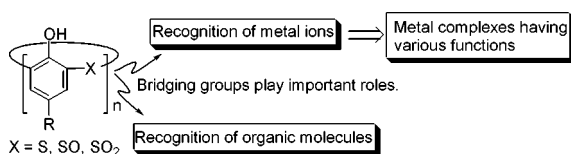
**Table 1.** Comparison of  $\text{p}K_{\text{a}}$  value of *p*-sulfonated calixarenes.

compound	$\text{p}K_{\text{a}1}$	$\text{p}K_{\text{a}2}$	$\text{p}K_{\text{a}3}$	$\text{p}K_{\text{a}4}$
 <b>10</b>	$2.18 \pm 0.05$	$8.45 \pm 0.10$	$11.19 \pm 0.15$	$11.62 \pm 0.12$
 <b>15</b>	.a)	$1.28 \pm 0.09$	$4.60 \pm 0.11$	$4.42 \pm 0.13$
 <b>29</b>	$3.08 \pm 0.05$	$12.02 \pm 0.02$	.a)	.a)
 <b>30</b>	8.9			

a) Not estimated.

### 3. Functions of thiacalix[n]arenes

Thiacalix[n]arenes have intrinsic features due to the sulfide function, which allowed various transformations unique to them in addition to those common to conventional calixarenes. These merits have been effectively utilized for the development of new functions of calixarene class compounds, among which are recognition of organic molecules and metal ions, synthesis and utilization of metal complexes (Figure 6). Herein, these new functions of thiacalix[n]arenes will be discussed in regard to the role of the sulfur function.



**Figure 6.** Functions of thiacalix[n]arene.

#### 3.1. Recognition of organic molecules

##### 3.1.1. Inclusion by crystallization

The inclusion of organic molecules into the cavity formed by the aromatic rings is one of the major characteristics of calix[n]arenes. The inclusion manner has actually been substantiated by X-ray structural analysis of the many host-guest complexes.<sup>10,12)</sup> Sone *et al.* and the authors studied the inclusion behavior of calixarenes by measuring the amount of the solvent molecule retained in the crystals formed upon crystallization from the solvent (Table 2).<sup>5c,8,12)</sup> In the cases where crystals were obtained, methylene-bridged calixarene **1**<sub>4</sub> gave 1 : 1 host-guest complexes with solvents but acetone to give a 1 : 2 complex, while sulfur-bridged **2**<sub>4</sub> afforded crystals of somewhat different composition ranging from 2 : 1 to 1 : 2 host to guest ratio. Compound **2**<sub>6</sub> which has six phenol units formed stable inclusion complexes with many of the solvents examined. These crystallization experiments could not definitely tell whether the guest molecules were really included in the cavity or retained among the crystal lattice. These and other results, however, have indicated that the enlarged cavity and increased flexibility of the sulfur-bridged calixarenes bring about molecular recognition ability rather different from those of the methylene-bridged counterparts. For instance, it has been shown that some guests are included into these two types of the calixarenes in different manners with each other.

**Table 2.** The host versus guest (H:G) ratio in the inclusion complexes formed with calixarenes.

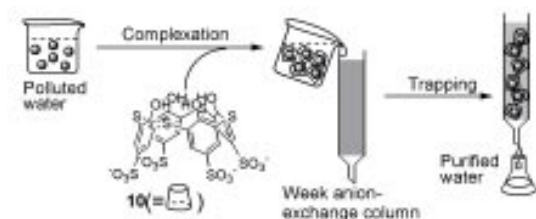
Solvent			
	<b>1</b> <sub>4</sub> H : G	<b>2</b> <sub>4</sub> H : G	<b>2</b> <sub>6</sub> H : G
Acetone	1:2	3:2	1:1
Chloroform	- <sup>a</sup>	1:1	2:3
Benzene	1:1	1:1	1:1
1,2-Dichloroethane	1:1	1:2	1:1
Toluene	1:1	2:1	1:1
Ethylbenzene	- <sup>a</sup>	- <sup>b</sup>	1:1
Cyclohexene	- <sup>a</sup>	1:1	1:1
Aniline	- <sup>a</sup>	- <sup>c</sup>	1:3
1,4-Dioxane	1:1	1:1	1:1
<i>n</i> -Octane	- <sup>a</sup>	- <sup>c</sup>	2:1
<i>m</i> -Xylene	- <sup>a</sup>	- <sup>c</sup>	1:1
<i>o</i> -Xylene	1:1	- <sup>c</sup>	1:1
<i>p</i> -Xylene	- <sup>a</sup>	- <sup>c</sup>	1:2
Decaline	- <sup>a</sup>	1:1	1:1
Dichloromethane	1:1	- <sup>a</sup>	- <sup>a</sup>
1,2-Dibromoethane	1:1	- <sup>a</sup>	- <sup>a</sup>

a: Not examined. b: Inclusion complex dose not form. c: Host to guest ratio is not clear.

### 3.1.2. Removal of organic halides

It is known that hydrophobic interaction is the major driving force for the inclusion of organic guests into the calix cavity, which was advantageously utilized for removing organic halides of environmental concern from water (Table 3).<sup>30)</sup> Thus, water-soluble thiacalix[4]arene **10** was added to an aqueous solution containing the organic halides to form host-guest complexes. The solution was subsequently passed through a column packed with a weakly basic ion-exchange resin. Then, the host-guest complex was trapped onto the resin by electrostatic interactions between the sulfo function of the complex and the cationic moiety of the resin. As can be seen from the data in Table 3, organic halides were almost completely removed; the resin could be regenerated by eluting the complexes with alkaline solution. It should be noted that the inclusion ability of **10** toward organic halides is far more superior to that of the corresponding methylene-bridged analogue **29**.

**Table 3.** Removal of halogenated organic compounds from water.



Guests	$C_{\text{initial}} / \text{ppm}$	$C_{\text{final}} / \text{ppm}$	Removal ratio
$\text{CH}_2\text{Cl}_2$	170	$6.58 \times 10^{-3}$	99.99613%
$\text{CHCl}_3$	239	$1.23 \times 10^{-2}$	99.99485%
$\text{CHBrCl}_2$	328	$3.44 \times 10^{-2}$	99.9895%
$\text{CHBr}_2\text{Cl}$	417	$2.33 \times 10^{-1}$	99.9441%
$\text{CHBr}_3$	508	$4.60 \times 10^{-1}$	99.9094%
$\text{CH}_2\text{Cl-CH}_2\text{Cl}$	198	$4.08 \times 10^{-2}$	99.9794%
$\text{CH}_2\text{Cl-CHCl}_2$	267	$1.35 \times 10^{-1}$	99.9495%

Conditions are as follows. Sample solution:  $C_{\text{initial}} = 2.0 \text{ mmol dm}^{-3}$ ,  $[\mathbf{10}]_{\text{Total}} = 5.0 \text{ mmol dm}^{-3}$ . Column:  $20 \text{ cm}^3$  of weak anion-exchange resin having dimethylamino groups. Flow rate:  $2 \text{ cm}^3/\text{min}$ .

### 3.1.3. Recognition of organic molecules by thiacalix[4]arene derivatives

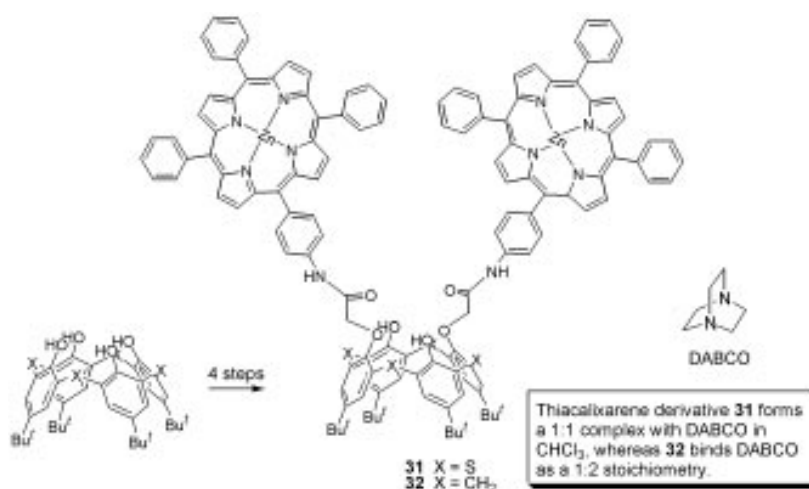
Lhoták *et al.* synthesized calix[4]arene derivatives **31** and **32** which had two zinc-porphyrin residues attached to the distal two phenolic oxygens. They compared their recognition ability toward an organic guest 1,4-diazabicyclo[2.2.2]octane (DABCO) (Scheme 11).<sup>31)</sup> The study revealed that **31** trapped one DABCO molecule by pinching with the two porphyrin rings to give a 1 : 1 complex, while each of the porphyrins of **32** independently caught the guest molecules to form a 1 : 2 complex. This difference was ascribed to the difference in the ring size of the two hosts and the degree of preorganization by hydrogen bonding.

Optically-active thiacalix[4]arenes were prepared by introducing chiral amine derivatives, which were effective as chiral stationary phase for gas chromatographic separation of enantiomers.<sup>32)</sup>

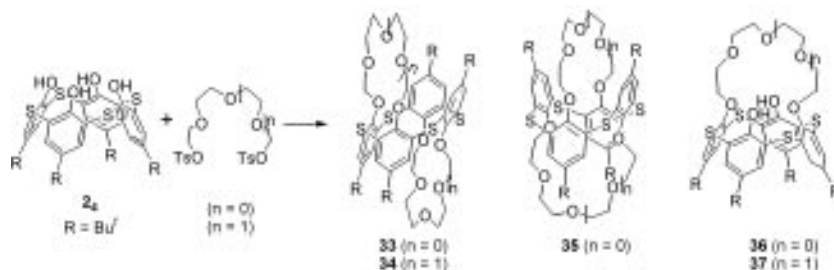
### 3.2. Recognition ability of metal ions

#### 3.2.1. Extraction of metal ions

Since the conventional calix[4]arenes have poor coordination ability to metal ions, it has been a common practice to design and synthesize calix-type ligands by introducing functional groups having metal-ligating ability. Similar methodology is also applicable to thiacalix[4]arenes to improve the metal-recognition ability. For example, thiacalix[4]arene-based ligands with high metal-extraction ability have been prepared by introducing functional groups such as ester, ketone, carboxylic acid, amide and the like.<sup>13a,13b,33)</sup> Among the calixarene derivatives, calixcrowns are those in which any two of the phenolic hydroxy groups are bridged with a polyether chain, which have been proved to be ligands with high metal-recognition ability.<sup>34)</sup> Various thiacalixcrowns, the corresponding sulfur analogues of calixcrowns, have been prepared and their metal-extraction ability has been examined. For example,



**Scheme 11.** Synthesis of calix[4]arenes having metalloporphyrins and their binding property toward DABCO.



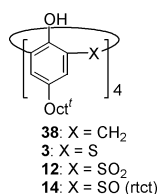
**Scheme 12.** Synthesis of *p*-*tert*-butylthiacalix[4]crowns.

**Table 4.** Periodic table of extracted metal ions by **3**, **12**, and **14**.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
1																			
2		Be																	
3		Mg												Al					
4		Cu	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	In	Hf	Ta								Pt	Au	Hg	Tl	Pb	Bi
7																			

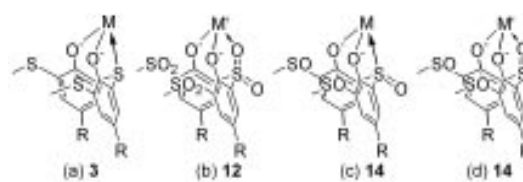
  

	Extracted by <b>3</b>		Extracted by <b>12</b> and <b>14</b>
	Extracted by <b>3</b> and <b>14</b>		Not extracted by <b>3</b> , <b>12</b> , <b>14</b> and <b>38</b>



Reinhoudt *et al.* reported the reaction of **24** with polyethylene glycol diols catalyzed by alkali metal carbonates to give thiacalix[4]crowns (**33-37**), any of which could be obtained selectively by the choice of the base catalyst (Scheme 12).<sup>34c</sup> It is interesting to note that **33** and **34** show higher extraction ability toward Ag<sup>+</sup> ion rather than alkali metal ions, making sharp contrast to the fact that classical calix[4]crowns like K<sup>+</sup> and Cs<sup>+</sup>. The difference was ascribed to the presence or absence of the coordination by bridging sulfurs in addition to crown-ether oxygens of the thia- or calixcrowns.

The authors have found that the sulfur-containing calix[4]arenes can extract various metal ions without requiring the introduction of coordinating auxiliaries, which is one of the most advantageous characteristics of the thiacalixes as compared to the corresponding classical methylene-bridged counterparts. Thus, the metal-extraction abilities of *p*-*tert*-octylcalix[4]arenes (**3**, **12**, **14**, **38**) toward as many as 40 metal ions were investigated in the term of the percent extraction *E*% under varying pH conditions (Table 4).<sup>35</sup> It was found that methylene-bridged **38**



**Figure 7.** Schematic views of the coordination manners of (a) *p*-*tert*-octylthiacalix[4]arene (**3**) and the sulfonyl (**12**) and (c, d) sulfinyl (**14**) analogues. M and M' denote soft and hard metal ions, respectively. R = Oct'.

hardly extracted any metal ions, while **3**, **12**, and **14** did soft, hard, and both soft and hard metal ions, respectively. These extraction behaviors can be reasonably explained based on the HSAB principle (Figure 7), in which compound **3** can ligate to soft metal ions with the bridging sulfur in addition to the phenoxide oxygen, and **12** to hard metal ions with sulfonic oxygen, while **14** alters its coordination site between the oxygen atom and the sulfur atom of SO function depending on the soft- and hardness of the relevant metal ion. Such coordination of the bridging moiety is unique to the thiacalixarenes and not attainable by the conventional methylene-bridged calixarenes. It should also be stressed that oxidation state of the sulfur moiety can control the selectivity of metal ions.

The excellent coordination ability of the thiacalixes to metal ions can be utilized for the removal of harmful heavy metal ions such as cadmium and mercury by applying the procedure similar to that described in 3.1.2.<sup>36</sup> On the other hand, it is interesting to note that aminothiacalix[4]arene **28** selectively extracts noble metal palladium and gold ions from a mixture containing several heavy metal ions.<sup>37</sup>

### 3.2.2. Preparation of metal complexes

Under the mild conditions of solvent extraction, extraction behavior of the calix[4]arene derivatives follow the HSAB principle as stated above. In organic solvents, however, it has been shown that these ligands can easily form stable complexes with various metal ions not necessarily limited by the HSAB prediction. Furthermore, they frequently assemble to form multi-nuclear complexes using many ligating sites. A variety of metal complexes have already been prepared, their structures being elucidated by X-ray crystal analysis to show many interesting features.<sup>38)</sup> For example, thiacalix[4]arene **2**<sub>4</sub> formed a 2 : 4 complex with Cu<sup>2+</sup>, while Zn<sup>2+</sup> afforded a 3 : 4 complex (Scheme 13, Figure 8).<sup>38b,c)</sup> In these structurally elucidated complexes, coordination of the phenolic oxygens as well as the bridging moieties to the metal centers has been proved. As an example of the complexes of particular interest, sulfonylcalix[4]arene **11** formed a ternary complex with Zn<sup>2+</sup> and 1,4,7-triazacyclononane, temperature-variable NMR of which indicated that the Zn<sup>2+</sup> are freely going around among the 8 oxygen atoms including 4 sulfonyl oxygens and 4 phenolic oxygens of the thiacalix **11** arranged on a plane as shown Scheme 14.<sup>38e)</sup> On the

other hand, aminothiocalix[4]arene **28** formed stable complexes with soft metal ions by coordination of the bridging sulfur and amine nitrogen. For example, a **28**-Pd<sup>2+</sup> complex of 2 : 2 composition was prepared and its structure was elucidated.<sup>39)</sup>

### 3.2.3. Sensing of metal ions

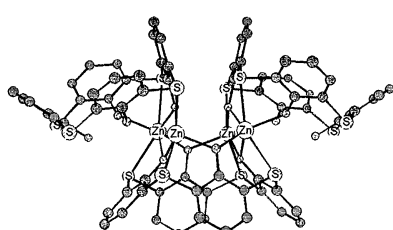
The remarkable complexation ability of thiacalixarenes and their derivatives toward metal ions has been utilized for the sensing of them.

Hamada *et al.* converted the phenolic hydroxy function of **2**<sub>4</sub> and its *de-tert*-butylated compounds **39** with dansyl moiety to the corresponding derivatives (**40**, **41**), which were used as host molecules for the fluorescent-sensing of metal ions in aqueous solutions (Scheme 15).<sup>19a,40)</sup> It was found that the number of the *tert*-butyl moiety significantly affected the fluorescent intensity, which increased with decrease of the number of *tert*-butyl groups.

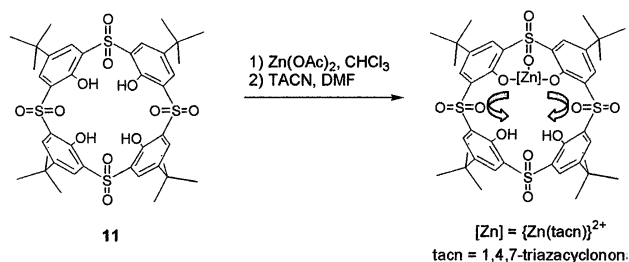
J-Renault *et al.* applied **2**<sub>4</sub> to a component of thin-films for EIS, ISFET, and gold electrodes, which allowed detection of Cu<sup>2+</sup> ion at the level of as low as 10<sup>-7</sup> M.<sup>41)</sup>



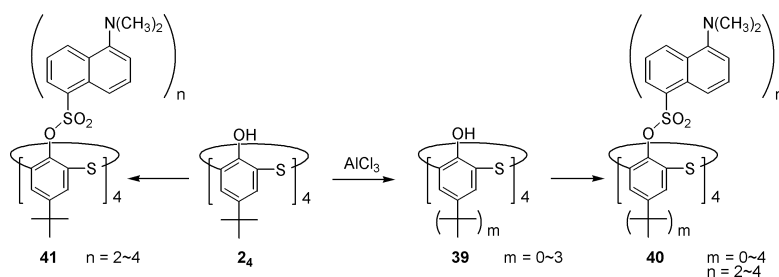
**Scheme 13.** Synthesis of **2**<sub>4</sub>-Cu<sup>2+</sup> complex.



**Figure 8.** X-ray structure of **2**<sub>4</sub>-Zn<sup>2+</sup> complex ([Zn<sub>4</sub>L(H<sub>2</sub>L)<sub>2</sub>]). H atoms, Bu<sup>t</sup> groups, and included solvents are omitted for clarity.



**Scheme 14.** Synthesis of *p-tert*-butylsulfonylcalix[4]arene **11**-Zn<sup>2+</sup>-tacn complex.



**Scheme 15.** Synthesis of dansyl-modified thiacalix[4]arene analogues.

### 3.3. Functions of the metal complexes

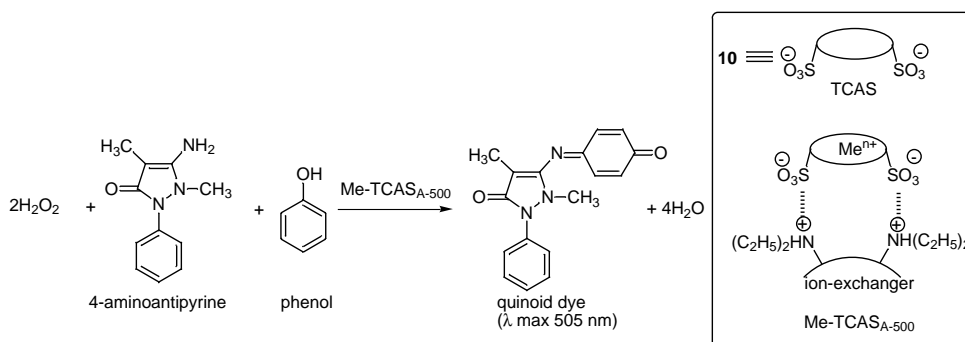
As stated above, thiacalixarenes form stable and unique complexes with various metal ions. Therefore, it is quite natural to challenge the exploitation of novel functional materials by combining the intrinsic nature of a given metal and the specific character of a thiacalix ligand.

#### 3.3.1. Oxidation catalyst (quantitative determination of hydrogen peroxide)

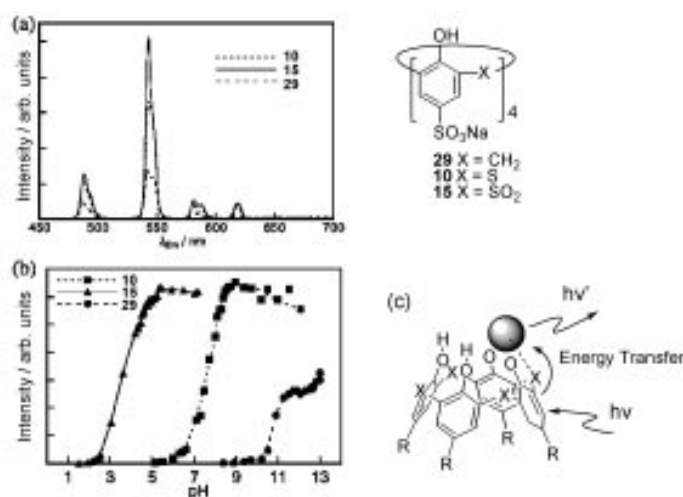
Quantitative determination of hydrogen peroxide is a subject of particular importance in the field of clinical chemistry and food chemistry. Odo *et al.* showed that a metal complex of **10** fixed on an ion-exchange resin could be used for quantitative determination of hydrogen peroxide, by measuring the oxidation of phenol by hydrogen peroxide using Me-TCA<sub>SA-500</sub> as the catalyst in the presence of 4-PPA (Scheme 16).<sup>42</sup> Progress of the reaction could be monitored by tracing the absorbance of the quinoid-type dye formed. Among the complexes examined, **10-Fe<sup>3+</sup>** showed the highest activity. The absorbance increased linearly with the concentration of hydrogen peroxide, thus allowing quantitative analysis.

#### 3.3.2. Energy-transfer luminescence

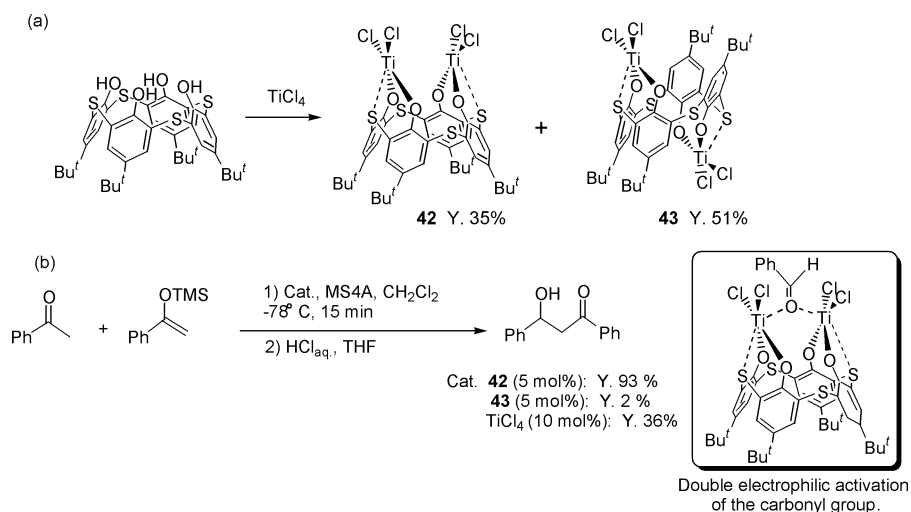
The energy-transfer luminescence of lanthanide complexes has been widely applied to dye-lasers and luminescent probes, owing to their characteristic properties such as long lifetime, narrow emission band, and large Stokes' shift.<sup>43</sup> Therefore, efforts to develop effective ligands have been continuing to further improve the luminescent ability. Considering that the calixarenes are one of the potential ligands of lanthanoid metals, the authors compared **10** and **15** with methylene-bridged **29** in the term of complexation ability with Tb<sup>3+</sup> and then energy-transfer luminescent capability of the resulting complexes (Figure 9).<sup>44</sup> It was found that **10** as well as **15** are superior to **29** in both the complexation ability toward Tb<sup>3+</sup> and luminescent strength of the complex, with **15** giving somewhat better results than **10**. Thus, it was shown that **15** makes a practical reagent for high-sensitivity detection of Tb<sup>3+</sup> in aqueous solutions (detection limit of 37 ppt).<sup>45</sup>



**Scheme 16.** Peroxidase-like catalysis by ion-exchanges modified metal complexes of **10**.



**Figure 9.** Emission spectra of Tb<sup>3+</sup> complexes with calix[4]arenes **10**, **15** and **29** (a), the effect of the pH on the luminescence intensity (b), and schematic mechanism for energy transfer luminescence of Tb<sup>3+</sup> complex (c). [**10**, **15** or **29**]<sub>Total</sub> = 4.0 × 10<sup>-6</sup> mol dm<sup>-3</sup>, [Tb<sup>3+</sup>]<sub>Total</sub> = 2.0 × 10<sup>-7</sup> mol dm<sup>-3</sup>, [buffer] = 1.0 × 10<sup>-3</sup> mol dm<sup>-3</sup>. (a) λ<sub>EX</sub> = 314 (Tb<sup>3+</sup>-**10**), 330 (Tb<sup>3+</sup>-**15**), and 290 nm (Tb<sup>3+</sup>-**29**). The pHs are 9.7 (Tb<sup>3+</sup>-**10**), 6.5 (Tb<sup>3+</sup>-**15**), and 12.0 (Tb<sup>3+</sup>-**29**). (b) λ<sub>EX</sub> = 261 (Tb<sup>3+</sup>-**10**), 330 (Tb<sup>3+</sup>-**15**), and 263 nm (Tb<sup>3+</sup>-**29**). λ<sub>EX</sub> = 543 nm.



**Scheme 17.** Synthesis of titanium complexes of **24** (a), and Mukaiyama-aldol reaction using **42**, **43**, or  $\text{TiCl}_4$  (b).

### 3.3.3. Lewis acid catalysts

Polynuclear metal complexes have attracted much attention in the field of metal catalysis, because close location of the metals to each other in such complexes should activate substrate molecules cooperatively or simultaneously for a given reaction, which cannot be realized by mononuclear metal complexes. Therefore, intensive researches have been devoted to the design of polydentate ligands and synthesis of polynuclear metal complexes for the development of new high-performance catalysts. As shown by above complexes, thiacalixarenes have characteristic ability to form stable polynuclear metal-complexes by virtue of a bunch of the ligation sites. The authors then have started the study on the synthesis of metal-complexes which are useful for the synthetic organic chemistry.<sup>46)</sup> Treatment of **24** with  $\text{TiCl}_4$  afforded two binuclear complexes, which were readily separable by crystallization (Scheme 17a). Based on the results of X-ray crystal analysis and NMR spectra, these two were assigned to the stereoisomers of cone (**42**) and 1,2-alternate conformation (**43**), respectively. Then, catalytic activities of these complexes were evaluated at first in terms of Lewis acid catalyst on the Mukaiyama-aldol reaction (Scheme 17b). The results showed that neither  $\text{TiCl}_4$  nor **43** had sufficient activity, while complex **42** had a very high activity. The catalytic activity of the last was attributed to the double activation of aldehydes by the coordination of two titanium ions, rather than the single activation by  $\text{TiCl}_4$  or **43**. In the aldehyde complex, it can be seen that the two Ti centers take a stable six-coordinated structure by the joining of sulfurs in ligation. This example clearly shows that **24** is a very hopeful candidate for obtaining high-performance catalysts, and studies in this line are now in progress at the authors' group.

## 4. Conclusion

Since the discovery of the practical method for the synthesis of sulfur-bridged calixarenes, studies on their

modifications and the development of their functions are now vividly progressing in many laboratories. These new members of the calix family are feasible to the oxidation of the bridging sulfur moiety and to the chelation-assisted  $\text{S}_{\text{N}}\text{Ar}$  substitution of the phenolic hydroxy groups, in addition to the common transformations applicable to conventional methylene-bridged calixarenes. Furthermore, the sulfur functional groups provide the thiacalixes characteristic abilities for recognition of organic molecules as well as metal ions, which should be useful for the development of a wide range of functional materials. In other word, thiacalixarenes are novel host molecules having almost boundless potentials to be developed.

Since the evolution of life on the Earth, nature has utilized biopolymers including proteins as the main element for assembling molecular recognition devices to develop various sophisticated functions of living organisms. Mimicking of the natural system has been relied on for the development of highly advanced artificial materials, especially synzymes (artificial enzymes). Supramolecular chemists are challenging to obtain these materials by using the components which have molecular weight of at most several thousands. Progress accomplished so far is promising a hopeful future where artificial materials or systems rival quite well the nature's gifts, and the authors should be very happy to see that thiacalixarenes play a substantial role in this field of science.

## Acknowledgment

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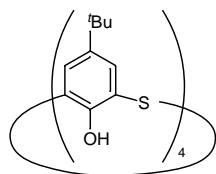
**Introduction of the authors:**

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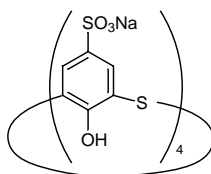
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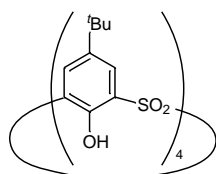
**TCI's Thiacalixarenes**



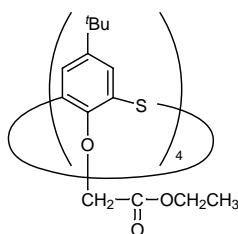
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5g, 1g [B2296]



4-Sulfothiocalix[4]arene Sodium Salt  
5g, 1g [S0477]



4-*tert*-Butylsulfonylcalix[4]arene  
5g, 1g [B2312]



4-*tert*-Butyl-1-(ethoxycarbonylmethoxy)-  
thiacalix[4]arene  
5g, 1g [B2310]