

# Thiacalixarenes

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## Contents

|                                                                            |      |                                                                               |      |
|----------------------------------------------------------------------------|------|-------------------------------------------------------------------------------|------|
| 1. Introduction                                                            | 5291 | 4.2. Recognition of Metal Ions                                                | 5306 |
| 2. Synthesis and Structural Characteristics of Thiacalix[ <i>n</i> ]arenes | 5292 | 4.2.1. Complexation with Thiacalix[4]arenes Modified at Lower Rim             | 5306 |
| 2.1. Basic Chemistry of Calix[ <i>n</i> ]arenes                            | 5292 | 4.2.2. Complexation with Intra- and Intermolecular Bridged Thiacalix[4]arenes | 5307 |
| 2.2. Synthesis of Thiacalix[ <i>n</i> ]arenes                              | 5293 | 4.2.3. Extraction by Thiacalix[4]arenes without Coordinating Auxiliaries      | 5309 |
| 2.2.1. Stepwise Synthesis                                                  | 5293 | 4.2.4. Sensing of Metal Ions                                                  | 5310 |
| 2.2.2. One-Step Synthesis                                                  | 5293 | 4.2.5. Removal and Separation of Metal Ions                                   | 5310 |
| 2.3. Structural Characteristics of Thiacalix[ <i>n</i> ]arenes             | 5294 | 4.2.6. Preparation of Metal Complexes Using Thiacalixarenes as Ligand         | 5311 |
| 3. Chemistry of Thiacalix[4]arenes                                         | 5295 | 4.3. Function of the Metal Complexes                                          | 5312 |
| 3.1. Modification of Lower Rim (Phenolic Hydroxy Group)                    | 5295 | 4.3.1. Guest Absorption by Metal Complexes                                    | 5312 |
| 3.1.1. Etherification by the Reaction with Alkyl Halides                   | 5295 | 4.3.2. Energy-Transfer Luminescence                                           | 5312 |
| 3.1.2. Conformational Behavior of Alkylated Derivatives                    | 5297 | 4.3.3. Peroxidase-like Catalyst                                               | 5312 |
| 3.1.3. Formation of 1,3-Diethers via the Mitsunobu Reaction                | 5297 | 4.3.4. Catalyst for Organic Synthesis                                         | 5313 |
| 3.1.4. Formation of Phosphoryl Ethers and Silyl Ether                      | 5297 | 5. Conclusion                                                                 | 5313 |
| 3.1.5. Synthesis of Mercaptothiacalix[4]arenes                             | 5298 | 6. Acknowledgment                                                             | 5313 |
| 3.1.6. Acylation of Phenolic OH Group                                      | 5298 | 7. Notes and References                                                       | 5314 |
| 3.2. Modification at the Upper Rim ( <i>p</i> -Position)                   | 5299 |                                                                               |      |
| 3.2.1. Friedel–Crafts Dealkylation                                         | 5299 |                                                                               |      |
| 3.2.2. Bromination and Nitration                                           | 5299 |                                                                               |      |
| 3.2.3. Friedel–Crafts Alkylation and Diazo Coupling                        | 5300 |                                                                               |      |
| 3.2.4. Sulfonation                                                         | 5301 |                                                                               |      |
| 3.3. Modification Unique to Thiacalixarenes                                | 5301 |                                                                               |      |
| 3.3.1. Reaction on Bridging Sulfur                                         | 5301 |                                                                               |      |
| 3.3.2. Displacement of OH with NH <sub>2</sub> Group                       | 5303 |                                                                               |      |
| 3.4. Acidity of Sulfonic Acid Derivatives                                  | 5303 |                                                                               |      |
| 4. Function of Thiacalixarenes                                             | 5304 |                                                                               |      |
| 4.1. Recognition of Organic Molecules                                      | 5304 |                                                                               |      |
| 4.1.1. Inclusion of Organic Molecules by Crystallization                   | 5304 |                                                                               |      |
| 4.1.2. Complexation with Water-Soluble Thiacalix[4]arene                   | 5304 |                                                                               |      |
| 4.1.3. Removal of Organic Halides from Water                               | 5305 |                                                                               |      |
| 4.1.4. Recognition of Organic Molecules by Thiacalix[4]arene Derivatives   | 5305 |                                                                               |      |
| 4.1.5. Chiral Recognition by Optically Active Thiacalix[4]arenes           | 5305 |                                                                               |      |

## 1. Introduction

The design and synthesis of a variety of host molecules is a challenging topic in the field of molecular recognition chemistry 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.<sup>1</sup> In other words, the advent of a new host compound is crucial for development of highly advanced functional materials such as high-performance catalysts, extremely sensitive sensors, ultrafine separation materials, etc. For a compound to make a useful host it is necessary that the basic molecular scaffold per se should have potential molecular recognition ability with ready feasibility to the varying chemical modifications for drawing out the best performances of the molecule for a specified application. 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*]arenes **1<sub>n</sub>**, a macrocyclic compound composed of phenolic units linked with methylene groups at the *o,o'*-positions.<sup>2</sup> Because of the attractive features as a host compound as mentioned above, calixarenes have been actively studied and utilized as the third generation of host compounds in addition to the well-known crown ethers<sup>3</sup> and cyclodextrins.<sup>4</sup> During the 3-decade history of calixarene chemistry, however, the general strategy adopted to improve the functions of the calix class compounds virtually relied on modifications through the phenol OH group or at the

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Naoya Morohashi was born in Niigata, Japan, in 1973. He studied synthetic organic chemistry at Tohoku University, where he received his Ph.D. degree in 2001 under the supervision of Professor S. Miyano. He was a postdoctoral fellow in Professor S. Miyano's group (2001–2002) and Professor M. Sodeoka's group (2002). He joined Professor Y. Ohba's group at Yamagata University as a research associate (2002–2005). He is currently a research associate in Professor T. Hattori's group at Tohoku University. His present research focuses on the development of novel host molecules and design of polynuclear metal complexes for catalysis.



Fumitaka Narumi was born in Aomori, Japan, in 1971. He received his M. degree in Biochemical Engineering from Tohoku University in 1996. In 1998, he became a research associate in the Department of Basic Sciences, Faculty of Science and Engineering, Ishinomaki Senshu University. He obtained his Dr. degree in Bioorganic Chemistry from Tohoku University in 2003 under the supervision of Professor Sotaro Miyano. His present research focuses on the design, synthesis, and characterization of novel chiral hosts for chiral recognition and catalytic asymmetric reactions.

*p*-position. Therefore, novel approaches or alternative ideas were highly desired for 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 *p*-*tert*-butylthiacalix[4]arene **2<sub>4</sub>** in which all four methylene bridges of the conventional *p*-*tert*-butylcalix[4]arene **3<sub>4</sub>** are replaced by sulfide bonds.<sup>5</sup> Needless to say, the linking sulfur possesses electronic and structural characteristics that are quite different from those of the 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<sup>5</sup> on the practical synthesis of **2<sub>4</sub>**, many research groups got into the study of this new host compound, and with the progress of the research it has become clear that thiacalixarenes are not simply a substitute for the conventional calixarenes but novel entities as quite unique host molecules of vast possibilities to be developed.



Nobuhiko Iki was born in 1966 in Sapporo, Japan, and graduated from Tohoku University in 1988. During his postgraduate course, he studied coordination chemistry at the Department of Chemistry, Imperial College, with Professor D. F. Evans (1989–1990). He received his Ph.D. degree in Analytical Chemistry from Tohoku University under the direction of Professor T. Yotsuyanagi in 1994. After postdoctoral work at Ames Laboratory, Iowa State University, with Professor E. S. Yeung, he joined Professor S. Miyano's group, Tohoku University, as a research associate to start thiacalixarene study in 1996. In 2003 he was promoted to Associate Professor at the Graduate School of Environmental Studies, Tohoku University. His research focuses on designing separation/sensing systems and analytical application of thiacalixarenes.



Tetsutaro Hattori has been studying synthetic organic chemistry at Tohoku University, Japan, where he received his Ph.D. degree in 1992 under the supervision of Professor S. Miyano. He acquired a position as a research associate at the university and was promoted to Associate Professor in 2001 and Full Professor in 2005. As a guest scientist he joined the research group of Professor M. G. Finn at the Scripps Research Institute in 2000 to study catalytic antibody chemistry. His present research focuses on the design and synthesis of high-performance molecular devices and development of novel methodologies for highly efficient organic synthesis.

Thiacalixarenes will open the new age of second-generation calixarene chemistry.<sup>6</sup> Now, almost a decade since the birth of thiacalix[4]arene **2<sub>4</sub>** in our laboratory, we provide an overview of the growth of the chemistry of thiacalixarenes by comparison with that of the methylene-bridged counterparts in which stress will be put on their reactivity, molecular recognition ability, and potential for host molecules.

## 2. Synthesis and Structural Characteristics of Thiacalix[*n*]arenes

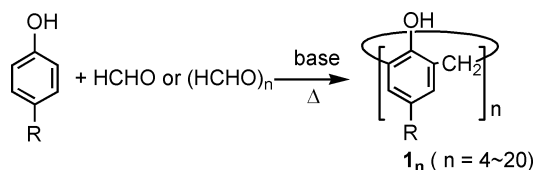
### 2.1. Basic Chemistry of Calix[*n*]arenes

Calixarenes **1<sub>*n*</sub>** can be synthesized by the base-catalyzed condensation of *p*-substituted phenols with formaldehyde (Scheme 1).<sup>7</sup> By selecting appropriate reaction conditions, analogues of a given number of phenolic units can be rather selectively obtained; even those having as many as 20-phenol

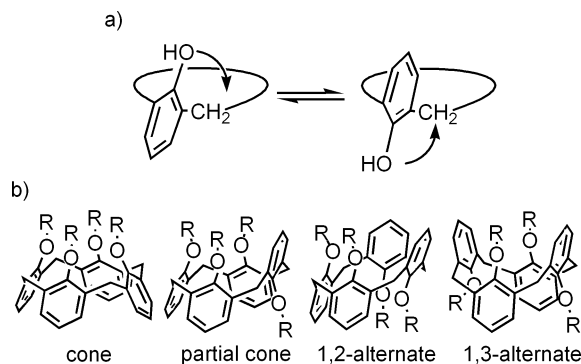


Sotaro Miyano studied chemistry in the University of Tokyo and received his Ph.D. degree in 1969 for studies on organozinc chemistry with Professor Harukichi Hashimoto. After working one year as a research associate at Tokyo University, he moved to Tohoku University, where he was promoted to Associate Professor of Organic Chemistry in 1981 and then Full Professor in 1987. His research includes development of novel synthetic methods by means of organometal reagents and molecular recognition, especially chiral recognition in host–guest complexes. In 2003, he became Professor Emeritus of Tohoku University and moved to Fukushima Technology Centre, an industrial research institute of Fukushima Prefecture, where he is now working as the Director.

### Scheme 1. One-Step Synthesis of Calix[*n*]arenes

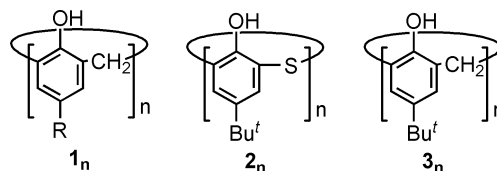


units have been obtained (calix[20]arene).<sup>8</sup> Therefore, it is possible to control the cavity size according to the desired purposes. Furthermore, since a calix[*n*]arene is constructed from alternating phenol and methylene groups, chemical modification of the parent entity can be readily achieved by relying on the traditional phenol chemistry. Thus, various functional groups can be introduced by etherification or esterification at the phenolic hydroxy groups and electrophilic substitution at the *p*-positions of the phenol nuclei. 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, rotation of the individual phenol unit of **1**<sub>4</sub> can be blocked by introducing a substituent bulkier than a propyl group to the hydroxy group, and then four conformers can be isolated as stable isomers under the



**Figure 1.** Rotation of phenol ring of **1**<sub>4</sub> (a) and four conformational isomers of calix[4]arene derivatives (b).

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>2</sup>



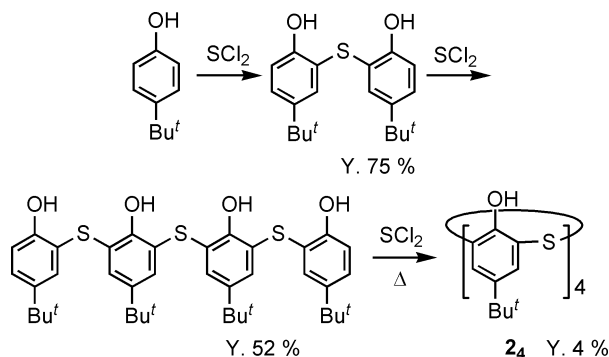
## 2.2. Synthesis of Thiacalix[*n*]arenes

Much effort devoted to development of new functions of calix[*n*]arenes mostly relied on modifications at the hydroxy groups or at the *p*-positions of the phenol units. On the contrary, modification of the molecular framework itself by placing heteroatoms for the linking methylene units had scarcely been challenged because of the synthetic difficulties.<sup>9</sup>

### 2.2.1. Stepwise Synthesis

The first synthesis of *p*-*tert*-butylthiacalix[4]arene **2**<sub>4</sub> was reported by Ohba et al. Their synthesis, however, required tedious stepwise treatment of *p*-*tert*-butylphenol with SCl<sub>2</sub>, affording the desired **2**<sub>4</sub> only in poor yield (Scheme 2).<sup>10</sup> Therefore, actual research into development of the functions of this intriguing new material had to await the arrival of a practical route to it.

### Scheme 2. Stepwise Synthesis of *p*-*tert*-Butylthiacalix[4]arene **2**<sub>4</sub> from *p*-*tert*-Butylphenol

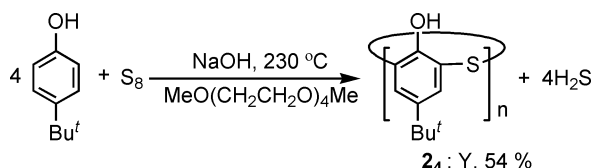


### 2.2.2. One-Step Synthesis

Chemical engineers at Cosmo Oil Co., Ltd. were collaborating with the authors' group under a research program directed toward development of a powerful alkaline-cleaning additive for lubricants used in internal-combustion engines for neutralizing acidic matter formed from combustion of petroleum fuels. The main target of the program was concentrated on a method for how to increase the calcium content as highly oil-soluble phenolate salts, which led us to convert a phenol to polydentate ligands by combining plural phenol units with sulfur. Among a 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 the mass spectrum attracted one (S.M.) of the authors attention because it had the same mass as the compound

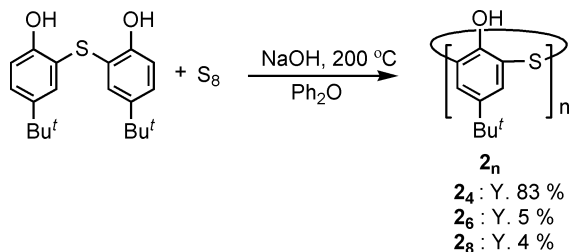
corresponding to a cyclic tetramer of the phenol linked by sulfur reminiscent of the calix[4]arene. After enormous efforts of the Cosmo people to get the supposed sulfur analogues of the calix[4]arene in a synthetically useful yield, they eventually found that heating a mixture of *p*-*tert*-butylphenol and elemental sulfur in tetraglyme using sodium hydroxide as the base catalyst could lead to formation of **2<sub>4</sub>** in a yield of 54% (Scheme 3).<sup>5</sup> The yield compares very well with that of 49% of **3<sub>4</sub>** attained by the established synthesis.<sup>7a</sup> In the reaction mixture, trace amounts of [5]arene (**2<sub>5</sub>**) and [6]arene (**2<sub>6</sub>**) were also detected.

### Scheme 3. Facile One-Step Synthesis of **2<sub>4</sub>**



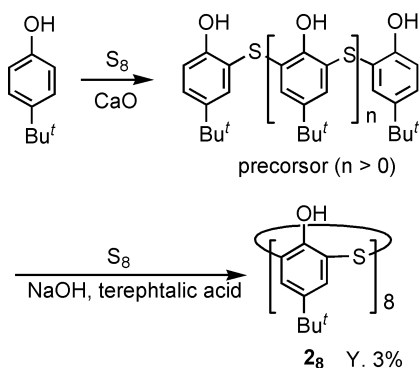
Later, during the course of our continuing study on the elucidation of the mechanism of the formation of **2<sub>4</sub>** according to Scheme 3, it was suggested that one of the crucial steps of the reaction should be formation of the sulfur-bridged phenol dimer. Therefore, it occurred to us to use the dimer as the starting material, which afforded **2<sub>4</sub>** in a yield as high as 83% (Scheme 4).<sup>11</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.

### Scheme 4. Synthesis of **2<sub>n</sub>** from Sulfur-Bridged Phenol Dimer



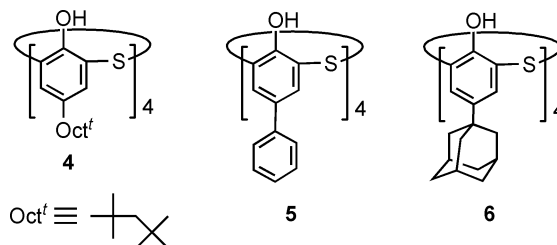
Recently, Hamada et al. reported the synthesis of *p*-*tert*-butylthiacalix[8]arene (**2<sub>8</sub>**) by the terephthalate-induced cyclization of a mixture of acyclic oligomers, which was obtained by reaction between *p*-*tert*-butylphenol and sulfur with CaO in ethylene glycol/diphenyl ether system (Scheme 5).<sup>12</sup>

### Scheme 5. Synthesis of **2<sub>8</sub>** by the Terephthalate-Induced Cyclization of a Mixture of Acyclic Oligomers



It would be interesting to know how the substituents at the *p*-position affect the characteristics of calixarenes, such

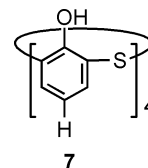
as cavity size, conformational preference, etc. In this respect, one-step synthesis of *p*-*tert*-octyl (**4**),<sup>13</sup> *p*-phenyl (**5**),<sup>14</sup> and *p*-adamantyl (**6**)<sup>15</sup> derivatives have been provided using the corresponding phenols as the starting material.



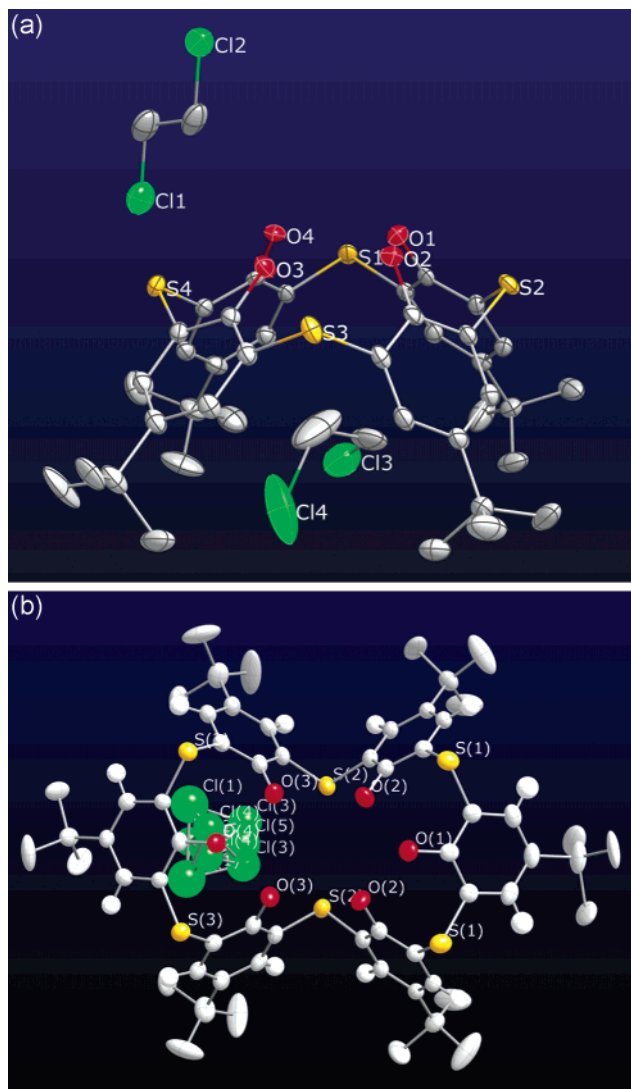
As mentioned above, the traditional calixarene chemistry had scarcely exploited the method for replacing the methylene bridge by a heteroatom, but now the base-catalyzed condensation of phenols with elemental sulfur has opened a practical route to sulfur-bridged calixarenes. The sulfur method, however, is far from satisfactory to obtain **2<sub>6</sub>** and **2<sub>8</sub>** as compared to the method for preparing **3<sub>6</sub>** and **3<sub>8</sub>**.<sup>7b,c</sup> Therefore, it should be said that development of a new strategy for preparing macrocycles having the larger number of phenol units is one of the challenges in thiacalixarene chemistry.

## 2.3. Structural Characteristics of Thiacalix[*n*]-arenes

X-ray structural analysis of **2<sub>4</sub>** was first reported by Hosseini et al.<sup>16</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 **3<sub>4</sub>**. Notably, the bond length between the aromatic residue and bridging group is 15% larger than the one in **3<sub>4</sub>**, indicating that the cavity of thiacalix[4]arene is larger than that of calix[4]arene. We reported the X-ray structure of a crystal including one 1,2-dichloroethane molecule in a cavity of **2<sub>4</sub>** and another in the crystal lattice (Figure 2a).<sup>13</sup> The structure and conformational equilibria of **2<sub>4</sub>** and de-*tert*-butylated **7** (see section 3.2.1) were theoretically studied and compared to the methylene-bridged counterparts.<sup>17</sup> These results were in good accordance with those of the X-ray structural analysis. The X-ray structure of thiacalix[6]arene **2<sub>6</sub>** revealed a “winged” cone conformation having nearly *C*<sub>2v</sub> symmetry (Figure 2b).<sup>18</sup> Furthermore, Hamada et al. reported the X-ray structure of thiacalix[8]arene **2<sub>8</sub>**.<sup>12</sup> In the crystal, **2<sub>8</sub>** exists as a plated loop conformation which is very similar to that of **3<sub>8</sub>** as reported by Gutsche et al.<sup>19</sup> The size of **2<sub>8</sub>** is slightly bigger than that of **3<sub>8</sub>** and ca. 0.5 Å longer in diameter and ca. 0.5 Å thicker in thickness.



In the solution state, the <sup>1</sup>H NMR spectra of *p*-*tert*-butylthiacalix[*n*]arenes **2<sub>n</sub>** (*n* = 4, 6, and 8) are quite simple, showing the averaged signal of rapid intraconversion among stable conformers such as a cone. The <sup>1</sup>H NMR chemical shift for the OH group of **2<sub>n</sub>** in CDCl<sub>3</sub> suggested formation of intramolecular hydrogen bonding, the strength of which seems to be weaker than that of the corresponding *p*-*tert*-



**Figure 2.** X-ray structures of **24** (a) and **26** (b). Protons are not shown for clarity.

butylcalix[*n*]arenes **3<sub>n</sub>** (*n* = 4, 6, and 8), respectively.<sup>12,13,18</sup> This may be ascribed to the enlarged skeleton of the thiacalix[*n*]arene ring to separate OH groups further away from each other.

Ohba et al. carried out detailed measurements of the <sup>1</sup>H NMR spin–lattice relaxation time *T*<sub>1</sub> to estimate the rate of inversion between the cone–cone conformations. The results showed that the activation energy of the inversion of the **24** scaffold is 56.5 kJ/mol, which is smaller than that of **34** (64.9 kJ/mol), indicating an increase in mobility of the molecular framework of **24** due to the enlarged ring.<sup>10</sup>

### 3. Chemistry of Thiacalix[4]arenes

It is feasible for both thiacalix[*n*]arenes and calix[*n*]arenes to undergo chemical modifications intrinsic to phenols, that is, modifications at the phenolic hydroxy group and/or the *p*-position. Therefore, a variety of thiacalix derivatives corresponding to the methylene-bridged 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, the possibility for 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 from each other. Herein, the authors will concentrate on chemical modifications of the thiacalix[4]arenes.

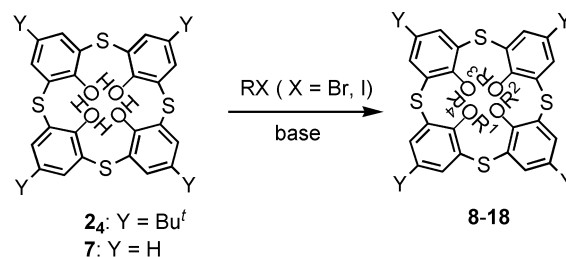
### 3.1. Modification of Lower Rim (Phenolic Hydroxy Group)

#### 3.1.1. Etherification by the Reaction with Alkyl Halides

Various functional groups can be introduced at the hydroxy groups by simple base-catalyzed etherification (the Williamson synthesis). Reaction products ranging from mono- to tetrasubstituted derivatives can be selectively synthesized using the appropriate reaction conditions for a given substituent.

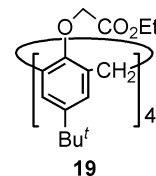
Reaction of **24** and **7** with simple alkyl halides (RI or RBr) in the presence of base generally gives the tetraalkylated products **8–15** in good yield (Scheme 6).<sup>20</sup> In the case of the reaction of **7** with MeI, a series of tetra- (**9**) and partially methylated compounds (**16–18**) were prepared by Lhoták et al.<sup>21</sup>

**Scheme 6.** Etherification of **24** and **7** with Alkyl Halides to Produce **8–18**



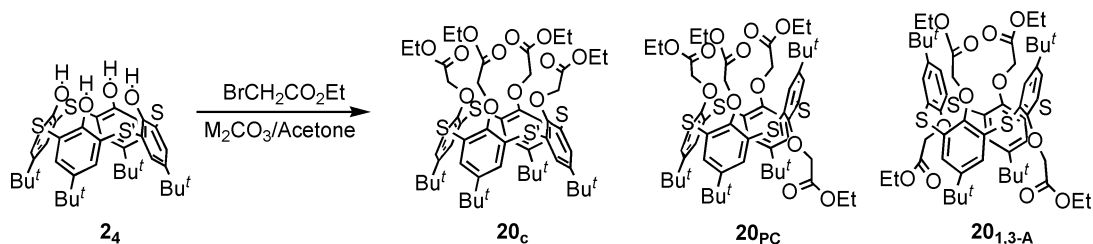
|                | <b>8</b>        | <b>9</b> | <b>10</b>       | <b>11</b> | <b>12</b>       | <b>13</b> | <b>14</b>       | <b>15</b> | <b>16</b> | <b>17</b> | <b>18</b> |
|----------------|-----------------|----------|-----------------|-----------|-----------------|-----------|-----------------|-----------|-----------|-----------|-----------|
| Y              | Bu <sup>t</sup> | H        | Bu <sup>t</sup> | H         | Bu <sup>t</sup> | H         | Bu <sup>t</sup> | H         | H         | H         | H         |
| R <sup>1</sup> | Me              | Me       | Et              | Et        | Pr              | Pr        | Bu              | Bu        | H         | H         | H         |
| R <sup>2</sup> | Me              | Me       | Et              | Et        | Pr              | Pr        | Bu              | Bu        | H         | Me        | Me        |
| R <sup>3</sup> | Me              | Me       | Et              | Et        | Pr              | Pr        | Bu              | Bu        | H         | H         | Me        |
| R <sup>4</sup> | Me              | Me       | Et              | Et        | Pr              | Pr        | Bu              | Bu        | Me        | Me        | Me        |

On the other hand, Shinkai et al. reported reaction of **34** with ethyl bromoacetate in the presence of alkali carbonate as base to produce the corresponding tetraacetate **19** in a cone or partial cone conformation.<sup>22</sup> The conformational stereoselectivity of these etherifications was readily controlled by choosing a suitable alkali carbonate. These tetraacetates are one of the most versatile compounds in calixarene chemistry because the acetate group is easily

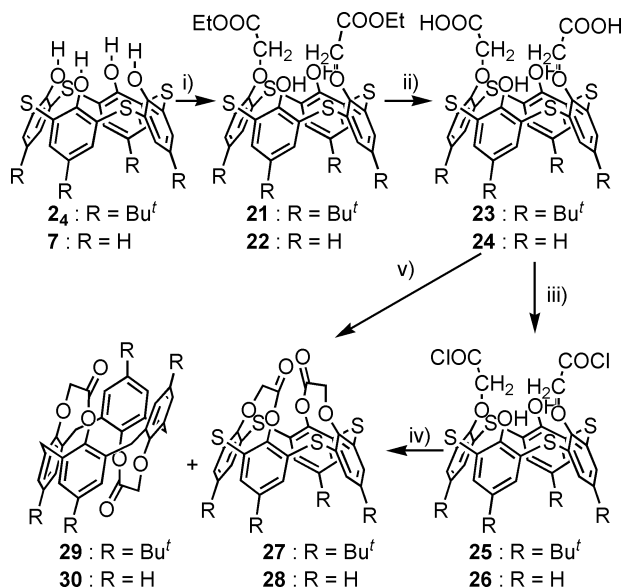


**Table 1.** Conformer Distribution for the Reaction of **24** to **20**

| base                            | time/h | yield % | conformer distribution/% |                        |                           |
|---------------------------------|--------|---------|--------------------------|------------------------|---------------------------|
|                                 |        |         | <b>20<sub>C</sub></b>    | <b>20<sub>PC</sub></b> | <b>20<sub>1,3-A</sub></b> |
| Li <sub>2</sub> CO <sub>3</sub> | 46     | 0       | 0                        | 0                      | 0                         |
| Na <sub>2</sub> CO <sub>3</sub> | 36     | 85      | 91                       | 9                      | 0                         |
| K <sub>2</sub> CO <sub>3</sub>  | 28     | 95      | 24                       | 61                     | 15                        |
| CS <sub>2</sub> CO <sub>3</sub> | 4      | 96      | 3                        | 16                     | 81                        |

Scheme 7. Etherification of **24** with Ethyl Bromoacetate Using the  $M_2CO_3$ /Acetone Reaction System ( $M = Li, Na, K,$  and  $Cs$ )

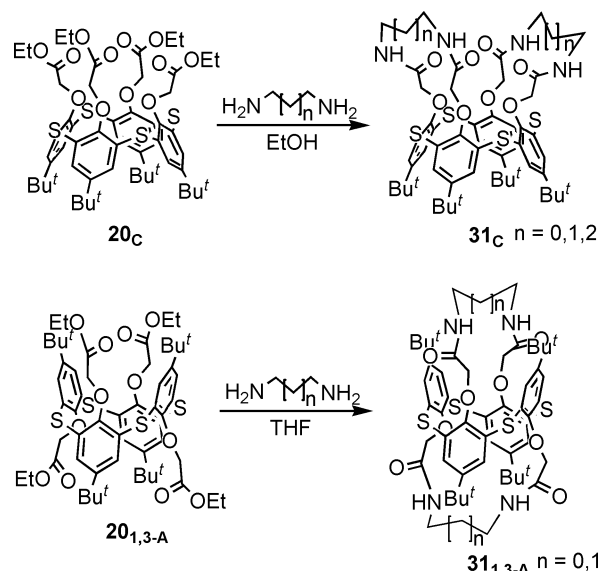
converted to carboxylic acid, amides, and another esters. Therefore, we and two other groups studied the synthesis of the corresponding tetraacetate of thiacalix[4]arene by reaction of **24** and **7** with ethyl bromoacetate using the acetone/ $M_2CO_3$  reaction system ( $M = Li, Na, K,$  and  $Cs$ ) (Scheme 7, Table 1).<sup>23</sup> It was found that etherification of **24** afforded **20** in three conformational isomers out of the possible four, i.e., cone **20<sub>c</sub>**, partial cone **20<sub>pc</sub>**, and 1,3-alternate **20<sub>1,3-A</sub>**, as unambiguously assigned by <sup>1</sup>H NMR and X-ray structure analysis. Table 1 lists the combined yield of isolated **20** and the isomer distribution.<sup>23a</sup> It is interesting to note that the alkali-metal carbonates had a distinct influence on the distribution of the conformers, suggesting that the template effect may be the main controlling factor as in the case of formation of **19**. Shinkai's results of direct tetra-etherification showed that  $Na_2CO_3$  and  $K_2CO_3$  gave cone-**19** selectively but  $Cs_2CO_3$  gave partial cone-**19**.<sup>22</sup> They needed the protection-deprotection technique to obtain 1,3-alternate-**19**. By contrast, **24** could conveniently be derivatized directly into **20<sub>1,3-A</sub>** by use of  $Cs_2CO_3$  as the base. This may be attributed to the size of the thiacalix skeleton being large enough to accommodate the  $Cs^+$  ion to form the intermediate which leads to **20<sub>1,3-A</sub>**, while the calix skeleton cannot form a similar intermediate because of steric congestion. Furthermore, reaction of **24** and **7** with a controlled amount of ethyl bromoacetate using  $K_2CO_3$  gave diether **21** and **22** in which distal ether groups adopt a syn orientation (Scheme 8).<sup>24</sup>

Scheme 8. Synthesis of Lactone Compounds<sup>a</sup>

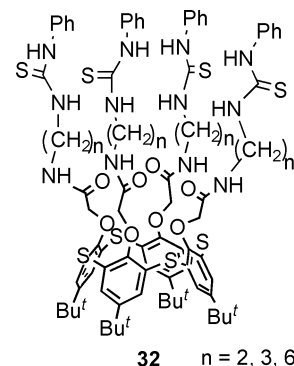
<sup>a</sup> Conditions: (i)  $BrCH_2COOEt$ , acetone- $K_2CO_3$ ; (ii)  $KOH$ ,  $H_2O-EtOH$ ; (iii)  $(COCl)_2$ ,  $CH_2Cl_2$ ; (iv)  $NEt_3$ ,  $CH_2Cl_2$ ; (v)  $P_2O_5$ ,  $CH_2Cl_2$ .

It is obvious that these acetate compounds can be easily converted to the corresponding carboxylic acid derivatives. For example, hydrolysis of diacetates **21** and **22** afforded

the corresponding bis(carboxymethoxy) derivatives **23** and **24** quantitatively (Scheme 8). Interestingly, Lhoták et al. found that **23** and **24** undergo an unprecedented intramolecular cyclization via bis-acid chloride **25** and **26** or directly to yield lactone compounds **27–30**, which have inherent chirality as demonstrated by separation on a chiral HPLC.<sup>24</sup> Furthermore, novel types of proximally bridged *p*-tert-butylthiacalix[4]arenes **31<sub>c</sub>** and **31<sub>1,3-A</sub>** at the lower rim have been recently prepared by direct aminolysis of tetraacetate **20<sub>c</sub>** and **20<sub>1,3-A</sub>** with aliphatic diamines (Scheme 9).<sup>25</sup> On the

Scheme 9. Aminolysis Reaction of **20** with Aliphatic Diamines

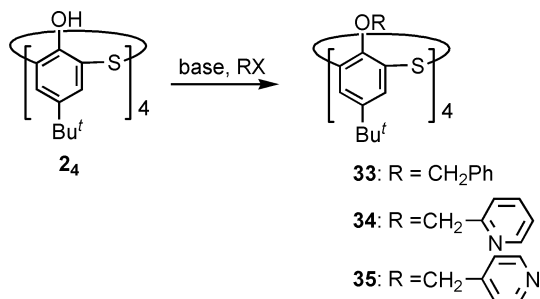
other hand, several amides such as **32** derived from **20<sub>c</sub>** were synthesized and applied to anion receptor.<sup>26</sup> These results indicate that the acetate derivatives of thiacalix[4]arenes are also as versatile as the methylene-bridged counterparts for derivatization.



Calix[4]arene *O*-benzyl ethers of defined conformation have commonly been used as the starting material for the

preparation of calix[4]arenes of the desired conformation. Therefore, it is highly desirable to have a set of all four conformational isomers of tetra-*O*-benzyl ethers **33**. We succeeded in the preparation of the four conformational isomers of **33** (Scheme 10).<sup>27</sup> Among these isomers, cone

#### Scheme 10. Synthesis of Tetra-*O*-benzyl Ethers from **24**



and 1,3-alternate isomers could be selectively synthesized directly from **24** in 68% and 70% using NaH and Cs<sub>2</sub>CO<sub>3</sub> as base, respectively. On the other hand, it required three- and four-step sequential benzylation of **24** for the synthesis of partial cone and 1,2-alternate isomers, respectively. Similarly, the cone and 1,2-alternate conformers of tetrakis(pyridylmethoxy)-thiacalix[4]arene **34** and **35** were synthesized by reaction of **24** with 2- and 4-(chloromethyl)pyridine in the presence of Cs<sub>2</sub>CO<sub>3</sub> as base.<sup>28</sup>

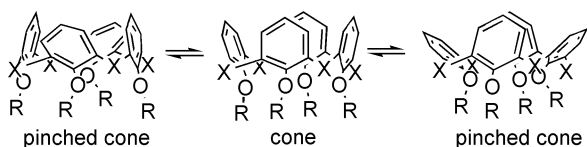
#### 3.1.2. Conformational Behavior of Alkylated Derivatives

Introduction of a sulfur atom into the calix[4]arene skeleton induces considerable changes in the conformational behavior of the thiacalix[4]arene derivatives because the cavity of thiacalixarenes is larger than that of classical calixarenes. Lhoták et al. studied the details of conformational preferences of lower rim alkylated thiacalix[4]arenes using a combination of NMR spectroscopy and X-ray crystallography.

Whereas the parents **24** and **7** adopt the cone conformation both in solution and in the solid state, the <sup>1</sup>H NMR study showed that tetramethyl ether **9** was in a thermodynamic equilibrium of at least three different conformations.<sup>29</sup> It is noteworthy that X-ray diffraction of this compound revealed unique molecular packing. The whole unit cell consists of 16 molecules of **9**, where 12 molecules adopt the cone conformation and the remaining 4 molecules are in the 1,3-alternate conformation.

On the other hand, the <sup>1</sup>H NMR spectrum of tetraethyl ether **11** reveals the presence of all four possible conformers in CDCl<sub>2</sub>/CDCl<sub>2</sub> solution at room temperature.<sup>30</sup> The conformer distribution at 303 K (cone:partial cone:1,2-alternate:1,3-alternate = 17:55:2:26) should be compared with that of the methylene-bridged counterpart, which is mobile only above ca. 130 °C and possesses the corresponding equilibrium ratio of 7:47:44:3.

In the case of alkylated derivatives of methylene-bridged calix[4]arene, the pinched cone–pinched cone interconversion as shown in Figure 3 is usually unobservable by <sup>1</sup>H



**Figure 3.** Schematic representation of pinched cone–pinched cone interconversion.

NMR spectroscopy due to the very low coalescence temperature. However, introduction of sulfur atoms leads surprisingly to a dramatic change in conformational behavior. Thus, the pinched cone–pinched cone interconversion of tetraalkylated thiacalix[4]arenes is relatively slow and easily observable by NMR spectroscopy at normal temperature, and the thermodynamic activation parameters of the interconversion could be determined.<sup>31</sup>

Furthermore, Koèa et al. compared the conformational properties of **11** in detail with those of the methylene-bridged counterpart by means of molecular dynamics and quantum mechanics.<sup>32</sup>

As stated before, the *O*-propyl substituent is bulky enough to retard rotation of a phenol unit of the classical calix[4]arenes. Interestingly, however, it was found that the *O*-propylated phenol nucleus of **13** still retains the freedom to rotate, though very slowly, because **24** has a larger ring size than **34**.<sup>33</sup> Thus, the 1,3-alternate conformer of **13** (the major product isolated from direct alkylation of **7** with propyl iodide) approached a conformational mixture of thermodynamic equilibrium containing four isomers after heating at 120 °C in CDCl<sub>2</sub>/CDCl<sub>2</sub> solution for 4 months. On the contrary, all attempts to achieve thermal equilibration of tetra-*O*-butylthiacalix[4]arene **15** failed. The starting 1,3-alternate conformer was the only detectable product after heat treatment, indicating that the butyl group is just bulky enough to prevent rotation of the alkylated phenolic rings through the annulus of thiacalix[4]arene, at least at temperatures up to 413 K.

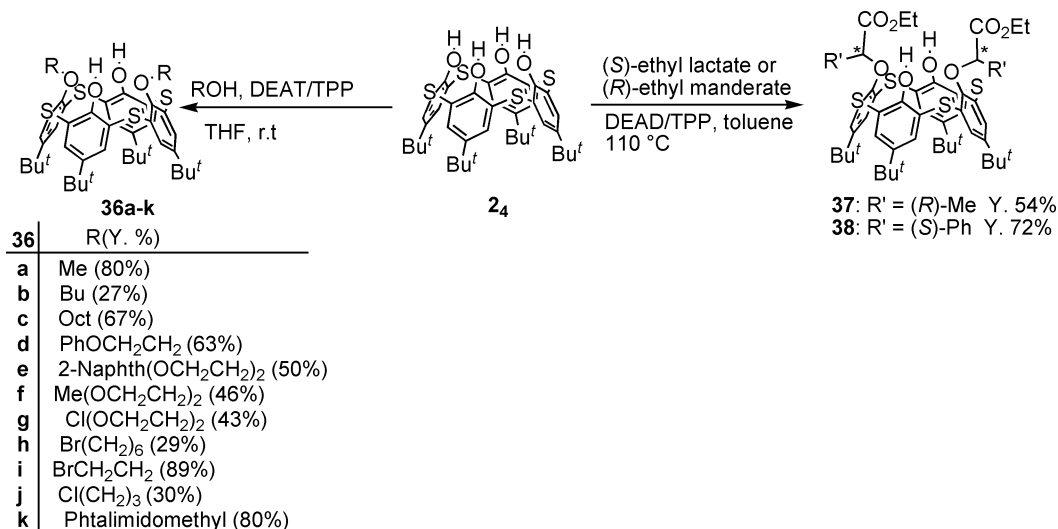
#### 3.1.3. Formation of 1,3-Diethers via the Mitsunobu Reaction

Bitter et al. reported regioselective distal dialkylation of **24** with alcohols under the Mitsunobu protocol using diethyl azodicarboxylate/triphenylphosphine (DEAD/TPP) system.<sup>34</sup> For example, treatment of **24** with a 10-fold excess of MeOH using 3.0 equiv of DEAD/TPP in THF at ambient temperature afforded 1,3-diether **36a** in 80% yield (Scheme 11). The reaction was repeated with a series of primary alcohols, resulting in formation of 1,3-diethers **36b–k**. Under these conditions the reaction generally stopped at the disubstitution stage and the tri- or tetraethers could not be isolated. The Mitsunobu protocol provides a convenient route for the synthesis of chiral thiacalix[4]arenes (see section 4.1.5); reaction of **24** with (*S*)-ethyl lactate and (*R*)-ethyl mandelate cleanly afforded the chiral diethers **37** and **38** in good yields with possible inversion of configuration.

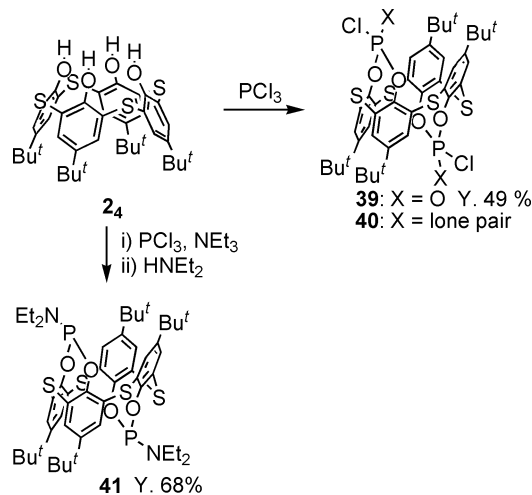
#### 3.1.4. Formation of Phosphoryl Ethers and Silyl Ether

Reaction of **24** with an excess of PCl<sub>3</sub> gave bis-chlorophosphate compound **39**, which adopts the 1,2-alternate conformation (Scheme 12).<sup>35</sup> Formation of chlorophosphate **39** instead of the expected compound **40** indicates that the initially formed chlorophosphite readily undergoes oxidation by air. X-ray data indicated the existence of a weak P–S interaction in **39** because the P–S distance of 3.22(1) Å is shorter than the sum of the van der Waals radii for sulfur and phosphorus of 3.65 Å. However, reaction of **24** with 2 equiv of PCl<sub>3</sub> in the presence of Et<sub>3</sub>N and subsequent condensation with diethylamine led to isolation of the diester amide **41** in high yield without oxidation.<sup>36</sup> Compound **41** was investigated by temperature-dependent <sup>1</sup>H NMR and <sup>31</sup>P NMR spectroscopy in a range from –80 to 120 °C. In this range no conformational changes could be detected.

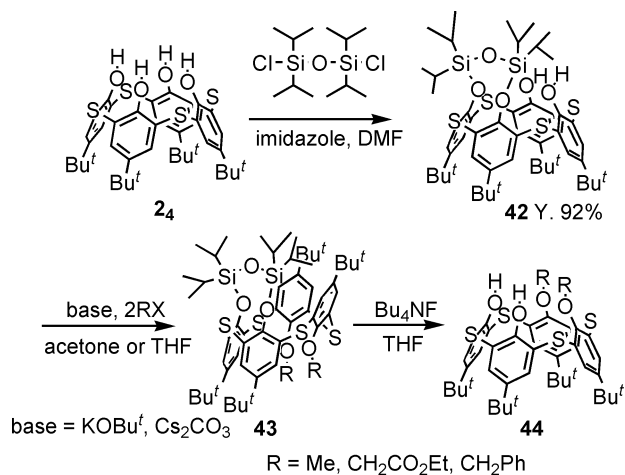
## Scheme 11. Synthesis of Thiacalix[4]arene 1,3-Diethers via the Mitsunobu Reaction



## Scheme 12. Synthesis of Phosphorus Thiacalix[4]arenes

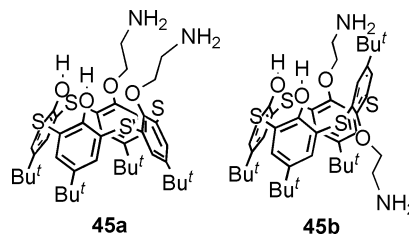


## Scheme 13. Formation of Proximally Disiloxane-Bridged Compound 42 and Application to the Synthesis of 1,2-Diethers



In the calix[4]arene chemistry regioselective *O,O'*-difunctionalization at the neighboring phenolic hydroxy groups had not yet been sufficiently explored, and development of a general method for such transformations was highly desired. In this regard, it is of great significance that treatment of **24** with 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane provides

the proximally disiloxane-bridged compound **42** in 92% yield (Scheme 13).<sup>37</sup> Treatment of **42** with alkyl halide in the presence of a base gave 1,2-alternate *O'',O'''*-dialkylated products **43** in high yield.<sup>37</sup> Subsequent desilylation of **43** by Bu<sub>4</sub>NF eventually gave *O,O'*-dialkylated products **44** quantitatively. Therefore, it is obvious that compound **42** is a highly useful synthetic intermediate for 1,2-disubstitution of thiacalix[4]arene **24** at the lower rim. For example, both *syn*- and *anti*-1,2-bis(*O*-2-aminoethyl)ethers **45a** and **45b** can be stereoselectively prepared by reaction of **42** with chloroacetamide followed by reduction.<sup>38</sup> Furthermore, it should be noted that this method can be applied to methylene-bridged calix[4]arene.<sup>37,39</sup>



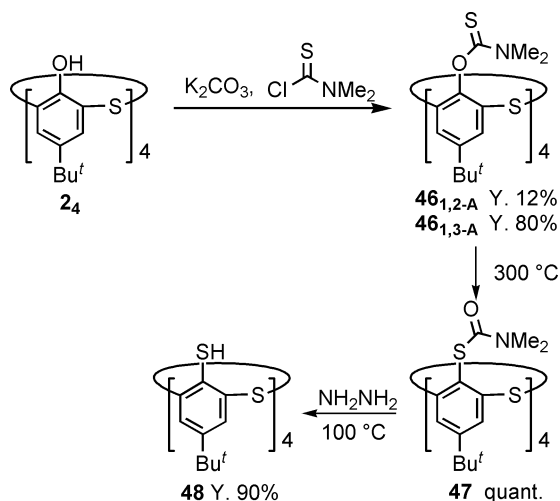
## 3.1.5. Synthesis of Mercaptothiacalix[4]arenes

It is well known in basic organic chemistry that phenolic OH groups highly resist displacement by other substituents. Therefore, it is not surprising that there are few examples of calixarenes bearing substituents other than those of -OR types at the lower rim.<sup>40</sup> One of the rare examples of phenolic OH substitution relies on the classical Newman-Kwart reaction, where the OH group is eventually converted to SH. This methodology was applied to **34** for conversion of four OH to SH.<sup>41</sup> Then, synthesis of *p*-tert-butyltetramercaptothiacalix[4]arene **48** bearing eight sulfur atoms was also achieved by a series of similar treatments.<sup>42</sup> Acylation of **24** with *N,N*-dimethylthiocarbamoyl chloride produced a conformational mixture of *O*-thiocarbamoyl derivative **46**, which was thermally converted into *S*-carbamoyl derivative **47** (Scheme 14). Finally, deprotection with hydrazine hydrate gave **48** in good yield. In contrast to parent **24**, the mercapto derivative **48** adopts the 1,3-alternate conformation in the solid state as revealed by X-ray crystallography.

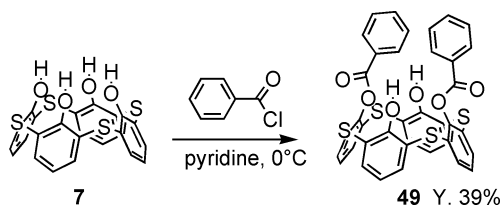
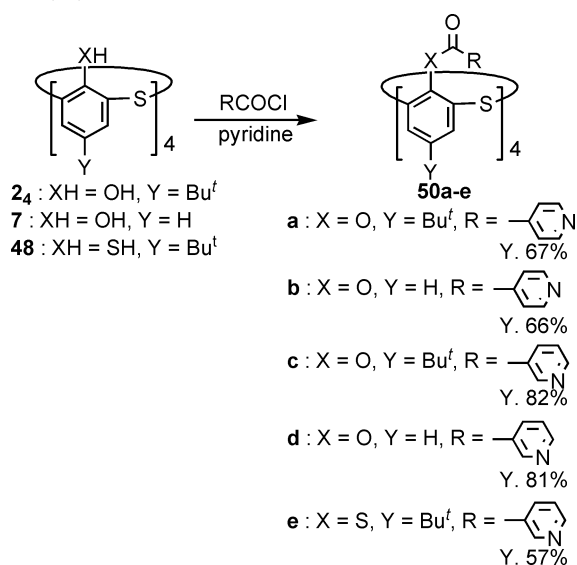
## 3.1.6. Acylation of Phenolic OH Group

Compared to etherification, acylation at the lower rim (or more generally ester formation) has been rather rare in



**Scheme 14. Synthesis of Mercaptothiacalix[4]arene 48 from 2<sub>4</sub>**

thiacalix[4]arene chemistry. Reaction of **7** with benzoyl chloride at low temperature afforded only dibenzoylated derivative **49** in a moderate yield (Scheme 15).<sup>43</sup> On the other hand, treatment of **2<sub>4</sub>**, **7**, and **48** with isonicotinoyl or nicotinoyl chloride afforded derivatives **50a–e** bearing four pyridine units (Scheme 16).<sup>44</sup> From each condensation a series of tetrasubstituted conformers was isolated. In the case of **50a** and **50b**, the most abundant was the 1,2-alternate conformer, whereas in the case of **50c** and **50d**, the 1,3-alternate conformer was the major component. Finally, in the case of **50e**, the cone conformer was the exclusive product.

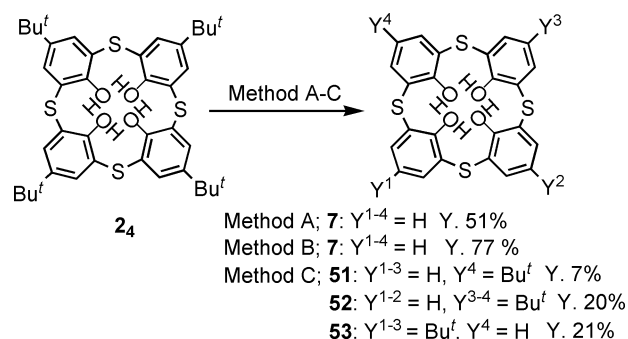
**Scheme 15. Reaction of 7 with Benzoyl Chloride****Scheme 16. Synthesis of Tetrabenzoyl-Type Derivatives from 2<sub>4</sub>, 7, and 48**

## 3.2. Modification at the Upper Rim (*p*-Position)

Electrophilic aromatic substitution (S<sub>E</sub>Ar) reaction provides the most general method for modification of calixarenes at the *p*-position of the phenol residue, which basically stands for thiacalixarenes.<sup>45</sup>

### 3.2.1. Friedel–Crafts Dealkylation

*p*-*tert*-Butylthiacalix[4]arene **2<sub>4</sub>** can be converted into the fully de-*tert*-butylated compound **7** in 51% yield using AlCl<sub>3</sub>/phenol/toluene under reflux conditions, according to the established procedure in the classical calixarene chemistry (Scheme 17).<sup>16</sup> In the solid state, **7** adopts a cone conformation similar to **2<sub>4</sub>**. This procedure, however, sometimes tended to give rather varying results, especially on large-scale reactions. Hamada et al. improved this procedure to be more reliable for the large-scale preparation of **7**; treatment of **2<sub>4</sub>** with 10.5 equiv of AlCl<sub>3</sub> at 80 °C with phenol gave **7** in 80% yield.<sup>46</sup> Furthermore, partial dealkylation of **2<sub>4</sub>** was achieved using 7.1 equiv of AlCl<sub>3</sub> and a shorter reaction time to produce mono-, di-, and tri(*p*-*tert*-butyl)thiacalix[4]arene **51–53** in 7%, 20%, and 21% yield, respectively. X-ray structure analysis revealed that **51–53** adopt the cone conformation and form dimeric self-inclusion units in such a manner that phenol moieties are inserted into the cavity of each other molecule, indicating that the number of *tert*-butyl groups determines the solid-state structure of thiacalixarenes.<sup>47</sup>

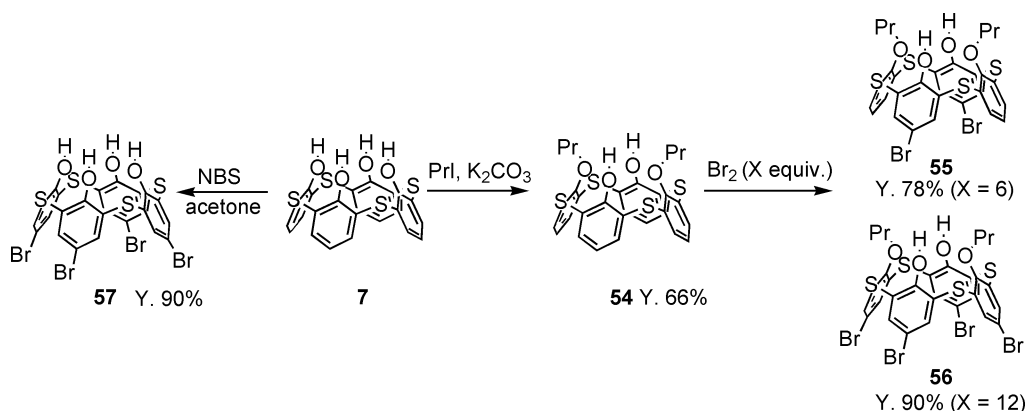
**Scheme 17. Synthesis of De-*tert*-butylated Compounds from 2<sub>4</sub><sup>a</sup>**

<sup>a</sup> Method A: AlCl<sub>3</sub> (40 mol equiv), phenol (10 mol equiv), toluene, reflux, 7 days. Method B: AlCl<sub>3</sub> (10.5 mol equiv), phenol (5 mol equiv), toluene, 80 °C, 2 h. Method C: AlCl<sub>3</sub> (7 mol equiv), phenol (5 mol equiv), toluene, 80 °C, 30 min.

### 3.2.2. Bromination and Nitration

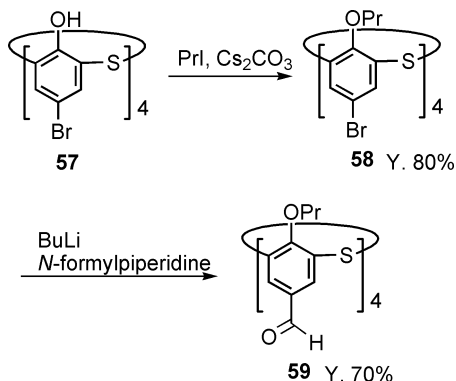
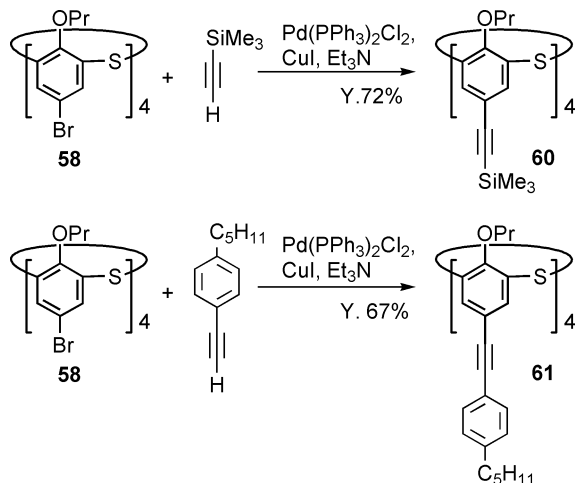
Thiacalixarenes have significant advantages over classical calixarenes in that the former are viable to additional modification by oxidation of the sulfide linkage as will be discussed in section 3.3.1. This oxidizability, however, sometimes requires exploration of alternative transformation methods other than those used in the methylene-bridged calixarenes. For instance, although *p*-bromo and *p*-nitro derivatives of **7** should be a potential starting material for various derivatizations, attempted bromination and nitration of **7** by conventional methods including the ones used for the synthesis of *p*-bromo- and *p*-nitrocalix[4]arenes resulted in formation of complex mixtures due to concomitant oxidation of the sulfide linkage.<sup>48</sup> It is interesting to note that the dibromo (**55**) and tetrabromo derivatives (**56**) were successfully obtained in high yields by Lhoták et al. by bromination of 1,3-diether **54** (Scheme 18).<sup>48a</sup> Later, Kal-

## Scheme 18. Bromination of Thiacalix[4]arene

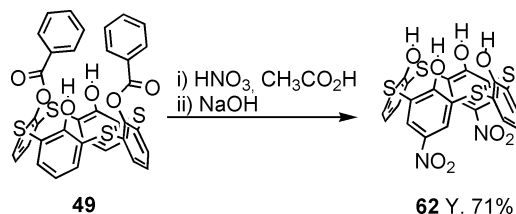


chenko et al. and Parola et al. reported the synthesis of tetrabromo derivative **57** in high yield by direct NBS bromination of **7**.<sup>49</sup> Treatment of **57** with PrI/Cs<sub>2</sub>CO<sub>3</sub> gave tetra-*O*-propylthiacalix[4]arene **58** in good yield, which in turn was treated with BuLi and *N*-formylpiperidine to give *p*-formyl derivative **59** (Scheme 19).<sup>50</sup> Obviously, the formyl function of **59** should be a useful starting point for the upper rim functionalization. Furthermore, **58** was coupled with both trimethylsilylacetylene and 4-pentylphenylacetylene using dichlorobis(triphenylphosphane)palladium(II) as a catalyst (Scheme 20). The resulting adducts **60** and **61** have potential to be used in nonlinear optical applications.<sup>49b</sup>

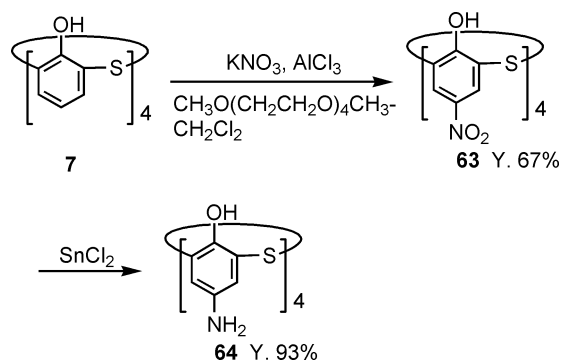
Selective synthesis of dinitro derivative **62** was attained by nitration of dibenzoyl derivative **49** followed by debenzoylation in aq. NaOH (Scheme 21).<sup>43</sup> The acid–base

Scheme 19. Formylation of *p*-Bromothiocalix[4]areneScheme 20. Synthesis of *p*-Alkynylthiacalix[4]arenes

properties of **62** in water were studied by UV–vis spectroscopy, and its pK<sub>a</sub> values were determined. On the other hand, it was found that nitration of **7** proceeded without oxidation of sulfur by reacting with KNO<sub>3</sub>/AlCl<sub>3</sub> in tetraglyme/CH<sub>2</sub>Cl<sub>2</sub> to give tetranitrothiacalix[4]arene **63** in 67% yield (Scheme 22).<sup>51</sup> Choice of solvent is crucial for this reaction; THF, acetonitrile, or toluene did not afford the described nitration product. It is said that the key step of the reaction is in situ formation of N<sub>2</sub>O<sub>4</sub>, which forms active electrophilic species NO<sup>+</sup>NO<sub>3</sub><sup>−</sup> stabilized by the complexing ether. X-ray structural analysis revealed that **63** adopts the 1,2-alternate conformation. Reduction of **63** with SnCl<sub>2</sub> gave tetraamino compound **64** almost quantitatively, whose acid–base property was studied by UV spectroscopy.<sup>52, 53</sup>

Scheme 21. Selective Synthesis of Dinitro Derivative **62** from **49**

## Scheme 22. Synthesis of Tetranitrothiacalix[4]arene and Its Reduction to Tetraamino Derivative



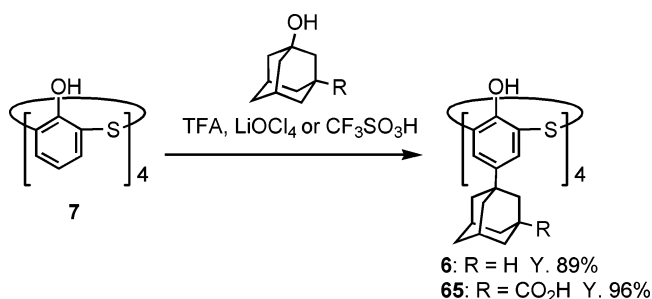
## 3.2.3. Friedel–Crafts Alkylation and Diazo Coupling

Friedel–Crafts alkylation of **7** was carried out by heating at reflux for 3 days with 1-adamantanol in trifluoroacetic acid in the presence of a catalytic amount of LiClO<sub>4</sub> to give *p*-(1-adamantyl)thiacalix[4]arene **6** in 89% yield (Scheme 23).<sup>15</sup> 3-Carboxy-1-adamantanol reacted in the same way to give the analogous derivative **65** almost quantitatively (96%). A chloromethyl group was introduced to the upper rim by

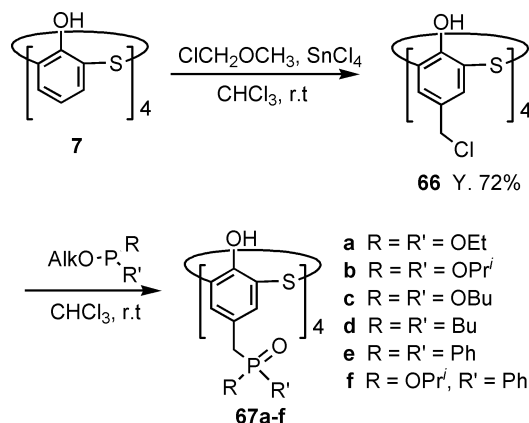
reaction of **7** with an excess amount of chloromethyl methyl ether and  $\text{SnCl}_4$  in chloroform to afford **66** in 72% yield (Scheme 24).<sup>49a</sup> The synthetic potential of **66** was demonstrated by an Arbuzov reaction with esters of phosphorous acids at ambient temperature to give tetraphosphorylated derivatives **67a–f** in good yield. This transformation shows that the chloromethyl group at the calixarene upper rim possesses high reactivity toward nucleophilic reagents. On the other hand, various *p*-phenylazo derivatives **68a–f** were synthesized by reaction of **7** with the corresponding diazonium salts (Scheme 25).<sup>54</sup> *p*-Aminothiocalix[4]arene **64** was obtained by reductive cleavage the diazo-coupling products **68b**.<sup>54b</sup>

### 3.2.4. Sulfonation

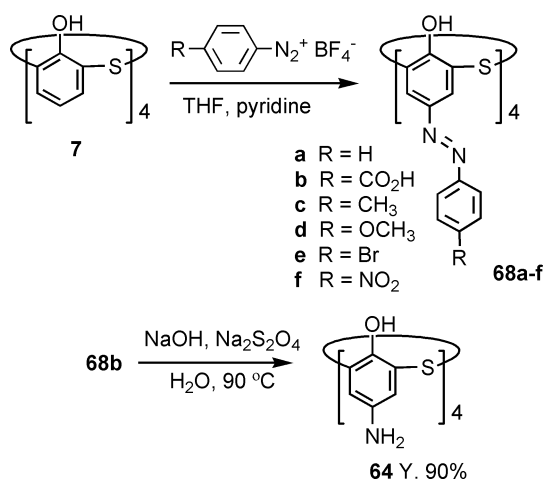
Although thiacalix[*n*]arenes are essentially insoluble in water, introduction of a sulfo function onto the upper rim Scheme 23. Synthesis of *p*-(1-Adamantyl)thiacalix[4]arenes from **7**



Scheme 24. Introduction of Chloromethyl Group into **7** and Its Reaction with Esters of Phosphorous Acid

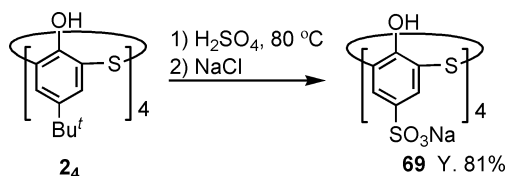


Scheme 25. Reaction of **7** with Diazonium Salts



would expand their chemistry into aqueous solutions. Interestingly, direct sulfonation of **7** has not yet been described, but ipso-sulfonation of **24** has been successfully accomplished. Treatment of **24** with concentrated sulfuric acid (80 °C) followed by salting out with sodium chloride gave the 4-sulfonic acid salt **69** in good yield (Scheme 26).<sup>55</sup>

Scheme 26. Sulfonation of **24** to **69**



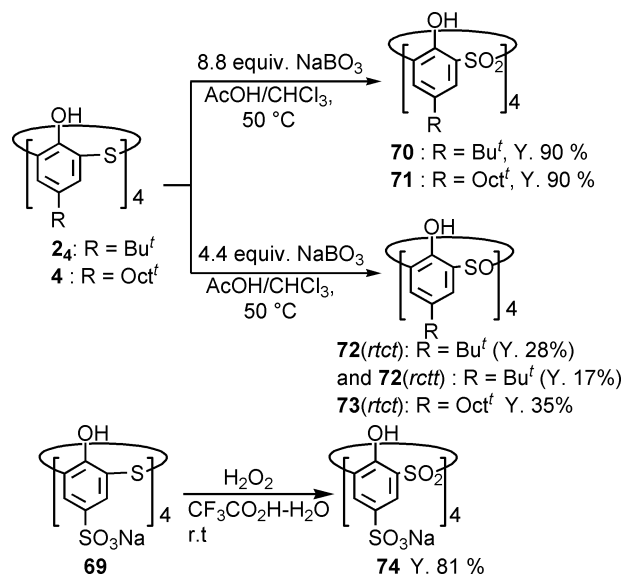
## 3.3. Modification Unique to Thiacalixarenes

By virtue of the sulfide function, thiacalixarenes can undergo unique transformations that are not applicable to methylene-bridged calixarenes, the most important of which is oxidation to sulfinyl and sulfonyl function.

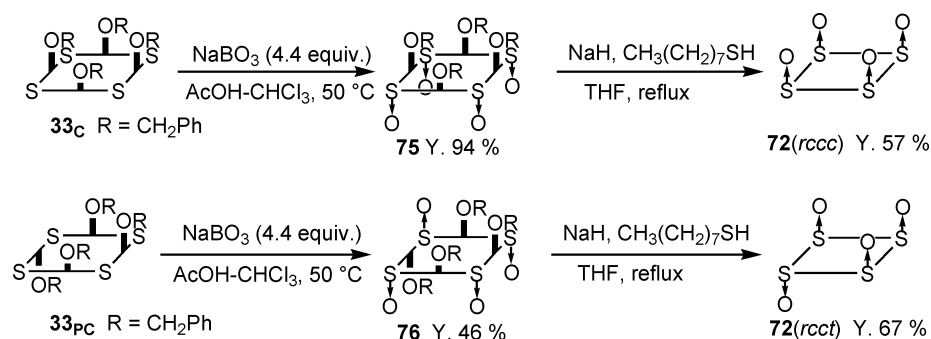
### 3.3.1. Reaction on Bridging Sulfur

Treatment of **24** 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 **70** almost quantitatively (Scheme 27).<sup>56</sup> Similar treatment of **4** and **69** gave the corresponding sulfones **71**<sup>57</sup> and **74**,<sup>58</sup> respectively, in high yields. X-ray structural analysis by Hosseini et al. showed that sulfonyl derivative **70** has the 1,3-alternate conformation due to hydrogen bonding between phenolic hydroxy groups and sulfonyl oxygens, in contrast to the cone conformation of **24** and **34**.<sup>56a,59</sup>

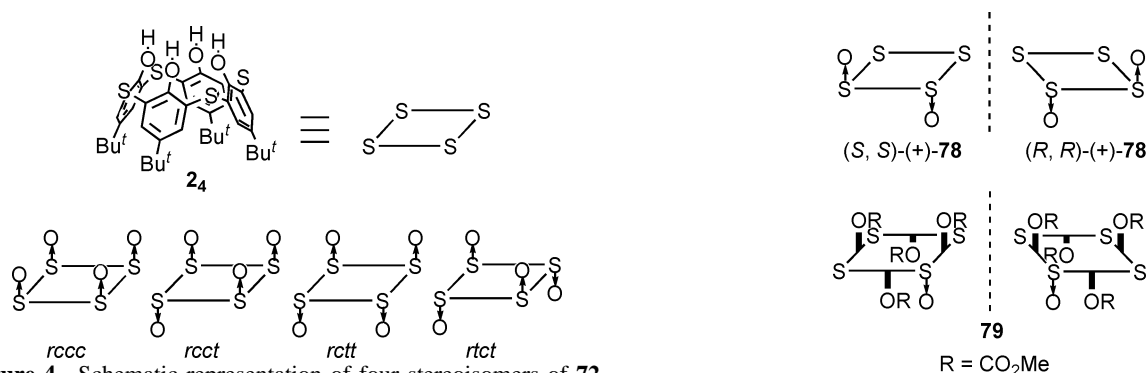
Scheme 27. Oxidation of Thiacalix[4]arenes to Sulfinyl- and Sulfonylcalix[4]arenes



Sulfonylcalix[4]arenes, in which all four bridging groups are sulfinyl function, can theoretically have four stereoisomeric forms (*recc*, *rcct*, *rtct*, and *rtct*) due to the disposition of the tetrahedral sulfinyl moiety, and their synthesis and studies on the characteristics stimulated the authors' and other's interest (Figure 4).<sup>27,57,60</sup> Actually, all four isomers were obtained as follows: Direct oxidation of **24** affords *rtct* and *rcct* stereoisomers of **72** in 27% and 17% yield,

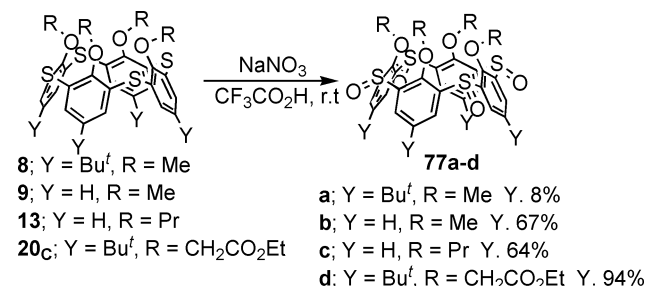
Scheme 28. Stereocontrolled Oxidation of **33** to Produce *rccc* and *rcct* Isomers of **72**

respectively (Scheme 27). On the other hand, the *rccc* and *rcct* isomers were obtained by stereocontrolled oxidation of tetrabenzyl ether **33** of defined conformations (cone and partial cone, respectively) to give **75** and **76**, respectively, followed by debenzoylation (Scheme 28).<sup>27</sup> It can be seen that the stereochemistry of the oxidation was completely controlled by the disposition of the benzyl groups. Lhoták et al. reported another stereocontrolled oxidation in which  $\text{NaNO}_3$ - $\text{CF}_3\text{CO}_2\text{H}$  was effective for oxidation of the sulfide to sulfoxide function to give **77** (Scheme 29).<sup>61</sup>



**Figure 4.** Schematic representation of four stereoisomers of **72**. Herein the term *cis* (*c*) or *trans* (*t*) is used to denote the disposition of sulfoxide oxygen toward reference oxygen with respect to the mean plane containing four sulfur atoms. The isomer notation proceeds around in a clockwise direction from the reference oxygen, which should be chosen to maximize the number of *cis*, where *cis* is preferable to *trans*.

## Scheme 29. Stereocontrolled Oxidation of Tetraethers of Cone Conformation



Construction of chiral host compounds is one of the major interests in calixarene chemistry. The most feasible synthetic strategy for chiral calixarenes is to anchor chiral residues at the lower or upper rim of the calixarene skeleton. On the other hand, introduction of at least two kinds of achiral substituents provides a more sophisticated way to create chiral calixarenes owing to generation of dissymmetry or asymmetry within the molecule. In addition to these strategies, the thiacalix-

[4]arene scaffold possesses inherent advantages to create chirality due to oxidation of the bridging sulfide to generate (1) *S*-centered chirality and/or (2) molecular asymmetry.<sup>62</sup> As an example of case 1, disulfinyldithiacalix[4]arenes (*S,S*)-(+)-**78** and (*R,R*)-(-)-**78** were prepared by simple oxidation of tetramethyl ether **8** with 2-fold excess of  $\text{NaBO}_3$  followed by optical resolution on chiral HPLC.<sup>62a</sup> In case 2, tetraacetate fixed in 1,3-alternate was oxidized to chiral monosulfoxide **79**, which was resolved using *L*-menthol.<sup>62b</sup>

Sulfilimines (sulfimides) are the nitrogen analogues of sulfoxides. It is known that an *N*-sulfonylhaloamide such as chloramine T **80** easily reacts with sulfides to give the corresponding sulfilimines.<sup>63</sup> Recently, we studied reaction of thiacalix[4]arenes with **80**; thiacalix[4]arene **24** was converted to tetramethyl ether **8**, which in turn was treated with **80** and then  $\text{BBr}_3$  to give **81** having a sulfilimine group (Scheme 30).<sup>64</sup> However, it was very difficult to convert the other three sulfides to sulfilimine under our conditions. X-ray analysis revealed that **81** adopts a cone conformation in the solid state in which the sulfilimine group is directed toward the axial orientation to take part in circular hydrogen bonding with four OH groups (Figure 5). Although direct treatment of **24** with **80** did not afford any sulfilimine products, to our pleasure it was a new efficient method for the preparation of novel thiacalix[4]arene monospirodienones **82**. In classical calixarene chemistry similar spirodienone derivatives are very attractive intermediates to prepare varying derivatives by use of the strained spiro structure and the presence of diene, hydroxy, and carbonyl functions.<sup>65</sup>

During the study of the synthesis of intra- and intermolecular bridged thiacalix[4]arenes (see section 4.2.2), Bitter et al. found unprecedented, interesting cyclizations of thiacalix[4]arenes **24** with glycols under the Mitsunobu protocol

to produce *O,S*-bridged thiacalix[4]arenes **83** and **84**, Scheme 31.<sup>66</sup>

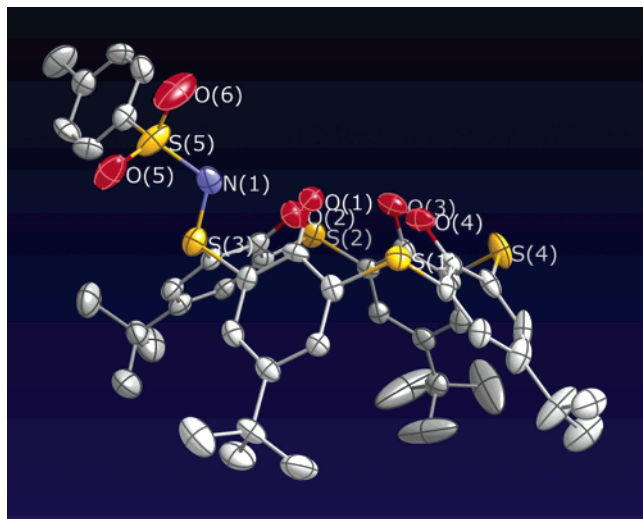
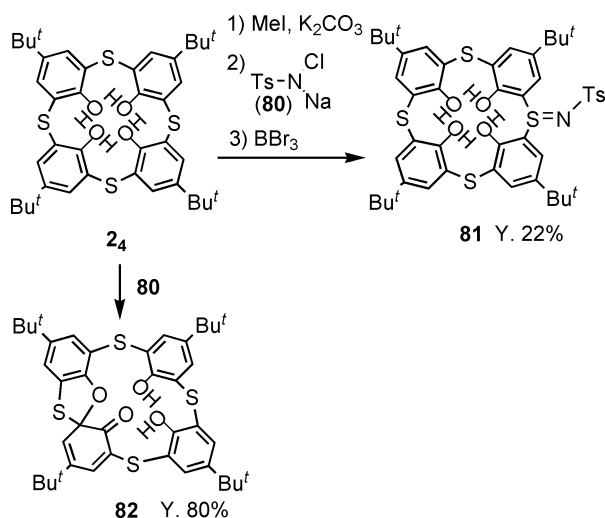
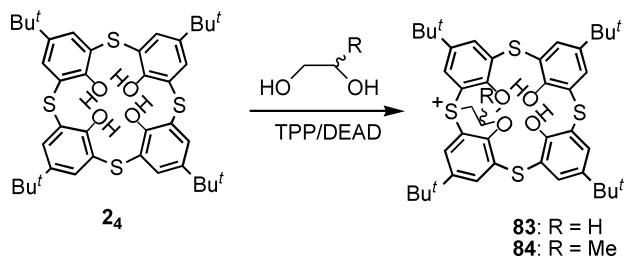


Figure 5. X-ray structure of **81**. Protons are not shown for clarity.

### Scheme 30. Reaction of Thiacalix[4]arenes with Chloramine T **80**



### Scheme 31. Synthesis of *O,S*-Bridged Thiacalix[4]arenes



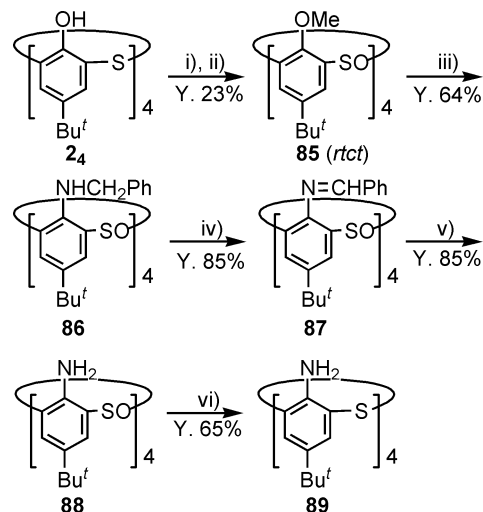
#### 3.3.2. Displacement of OH with NH<sub>2</sub> Group

As mentioned in section 3.1.5, there have been very few examples of calixarenes bearing substituents other than those of -OR types at the lower rim, which means that conventional calixarene chemistry has essentially relied on phenol chemistry. Therefore, development of the methodology for substitution of the lower rim OH with other groups would open a new world in calixarene chemistry. In this context, development of a method for introducing an amino substituent to the lower rim is highly desirable because the amino

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 from **34** were reported by Shinkai et al.,<sup>67</sup> there is no precedent for those comprised of only aniline units.

The authors developed the chelation-assisted nucleophilic aromatic substitution (S<sub>N</sub>Ar) protocol in which carbonyl, sulfinyl, phosphinyl, and the like highly activate an *o*-alkoxy group toward nucleophiles containing a cationic center that can form a chelate complex with the substrate.<sup>68</sup> As an extension of the principle, treatment of tetramethyl ether of sulfinylcalix[4]arene **85** (*rtct*) with lithium benzylamide displaced all the methoxy groups with a benzylamino moiety to give 1,3-alternate **86** with high stereoselectivity (Scheme 32).<sup>69</sup> Subsequent debenzoylation via **87** gave aminosulfinylcalix[4]arene **88**, reduction of the sulfinyl function of which afforded aminothiocalix[4]arene **89**, providing the first example of a calix derivative comprised of only aniline units. X-ray crystallographic analysis revealed that **89** adopts the 1,3-alternate conformation in which intramolecular NH...S bondings are observed between an amino group and ortho sulfides (Figure 6). It should be stressed here that calixarene chemistry based on aniline chemistry has now emerged in addition to that based on phenol chemistry.

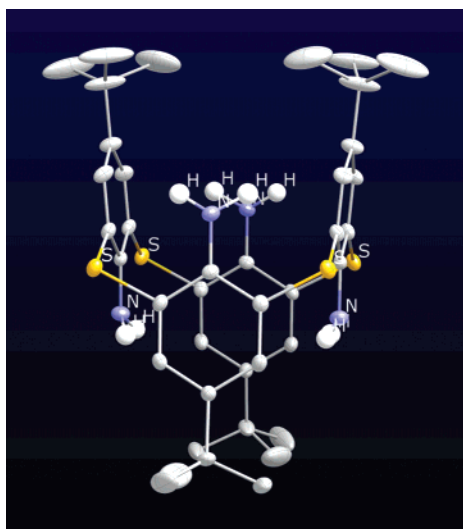
### Scheme 32. Synthesis of *p*-*tert*-Butylaminothiacalix[4]arene **89**<sup>a</sup>



<sup>a</sup> Conditions: (i) NaBO<sub>3</sub>, CH<sub>3</sub>CO<sub>2</sub>H-CHCl<sub>3</sub>; (ii) K<sub>2</sub>CO<sub>3</sub>, MeI, acetone, reflux; (iii) PhCH<sub>2</sub>NHLi, THF, room temperature; (iv) NBS, BPO, benzene, reflux; (v) conc. HCl, CHCl<sub>3</sub>, reflux; (vi) LiAlH<sub>4</sub>-TiCl<sub>4</sub>, THF, room temperature.

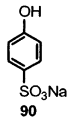
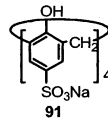
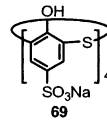
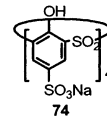
## 3.4. Acidity of Sulfonic Acid Derivatives

It is essential to know the acidity of the relevant phenol residues for development of novel functions of calixarenes. Calixarenes having *p*-sulfonate functions are highly water soluble. The acidity of the phenolic hydroxy groups of **69** and **74** were measured to compare them with those of monomeric **90** and methylene-bridged **91** (Table 2).<sup>70</sup> It was found that the phenolic OH of **69** is more acidic than that of **91**, an especially large difference being observed in pK<sub>a2</sub>. These differences may be ascribed to the electronic effect of the sulfur moiety as well as changes in hydrogen bonding due to enlargement of the ring. It was also seen that conversion of the sulfide to sulfone further strengthened the acidity.



**Figure 6.** X-ray structure of **89**. Protons on carbon atoms are not shown for clarity.

**Table 2.** Comparison of  $pK_a$  Values of *p*-Sulfonated Compounds Determined by Spectrophotometric Titration

|           |  |  |  |  |
|-----------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| $pK_{a1}$ | 8.9                                                                               | $3.08 \pm 0.05$                                                                   | $2.18 \pm 0.05$                                                                   | — <sup>b)</sup>                                                                   |
| $pK_{a2}$ |                                                                                   | $12.02 \pm 0.02$                                                                  | $8.45 \pm 0.01$                                                                   | $1.28 \pm 0.09$                                                                   |
| $pK_{a3}$ |                                                                                   | — <sup>a)</sup>                                                                   | $11.19 \pm 0.15$                                                                  | $4.60 \pm 0.11$                                                                   |
| $pK_{a4}$ |                                                                                   | — <sup>a)</sup>                                                                   | $11.62 \pm 0.12$                                                                  | $4.42 \pm 0.13$                                                                   |

<sup>a</sup> The  $pK_{a3}$  and  $pK_{a4}$  values are not measurable; estimated to be  $> 13$ .

<sup>b</sup> The  $pK_{a1}$  value is not measurable; roughly estimated to be in the range from  $-2$  to  $0$ .

## 4. Function of Thiocalixarenes

Thiocalixarenes have intrinsic features due to the sulfide function which allow various transformations unique to them in addition to those common to conventional calixarenes. These merits have been advantageously utilized for development of new functions of thiocalixarene class compounds, among which are recognition of organic molecules as well as metal ions, synthesis, and utilization of metal complexes. Herein, these new functions of thiocalixarenes will be discussed with regard to the role of the sulfur function.

### 4.1. Recognition of Organic Molecules

#### 4.1.1. Inclusion of Organic Molecules by Crystallization

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 of thiocalix $[n]$ arenes has actually been substantiated by X-ray structural analysis of several host–guest complexes.<sup>13,16,18</sup> Ohba et al. and the authors studied the inclusion behavior of calixarenes (**3<sub>4</sub>**, **2<sub>4</sub>**, and **2<sub>6</sub>**) by measuring the amount of solvent molecule retained in the crystals formed upon crystallization from the solvent (Table 3).<sup>10c,13,18</sup> In the cases where crystals were obtained, methylene-bridged calixarene **3<sub>4</sub>** gave 1:1 host–guest complexes with all the solvents but acetone, while sulfur-bridged **2<sub>4</sub>** afforded crystals of somewhat different composition ranging from 2:1 to 1:2 host-to-guest ratio. Com-

pound **2<sub>6</sub>**, which has six phenol units, formed stable inclusion complexes with many of the solvents examined. Although these crystallization experiments could not definitely tell whether the guest molecules were really included in the cavity or retained among the crystal lattice, the results in Table 3 indicate that the type of bridging group and number of ring members bring about rather different crystal structures.

Although **2<sub>4</sub>** is essentially insoluble in water, Zhu et al. found an interesting phenomenon that a water molecule could also be included into the hydrophobic cavity of **2<sub>4</sub>**.<sup>71</sup> Single crystals suitable for X-ray analysis were prepared by addition of water to a solution of **2<sub>4</sub>** in  $\text{CH}_2\text{Cl}_2$ –MeOH followed by slow evaporation. X-ray crystallographic analysis and density functional calculation confirmed that dimeric water is embedded within a hydrophobic cavity of **2<sub>4</sub>** and stabilized by hydrogen bonding of aromatic  $\pi \cdots \text{H}_2\text{O}(1)$  and methyl- $\cdots \text{H}_2\text{O}(2)$  in the complex with binding energies of 1.4 and 0.9 kcal mol<sup>-1</sup>, respectively.

**Table 3.** Host versus Guest (H:G) Ratio of the Calix $[n]$ arene Complexes Formed from Crystallization

| solvent            | <b>3<sub>4</sub></b><br>H:G | <b>2<sub>4</sub></b><br>H:G | <b>2<sub>6</sub></b><br>H:G |
|--------------------|-----------------------------|-----------------------------|-----------------------------|
| acetone            | 1:2                         | 3:2                         | 1:1                         |
| chloroform         | a                           | 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       | a                           | b                           | 1:1                         |
| cyclohexane        | a                           | 1:1                         | 1:1                         |
| aniline            | a                           | c                           | 1:3                         |
| 1,4-dioxane        | 1:1                         | 1:1                         | 1:1                         |
| octane             | a                           | c                           | 2:1                         |
| <i>m</i> -xylene   | a                           | c                           | 1:1                         |
| <i>o</i> -xylene   | 1:1                         | c                           | 1:1                         |
| <i>p</i> -xylene   | a                           | c                           | 1:2                         |
| decaline           | a                           | 1:1                         | 1:1                         |
| dichloromethane    | 1:1                         | a                           | a                           |
| 1,2-dibromoethane  | 1:1                         | a                           | a                           |

<sup>a</sup> Not examined. <sup>b</sup> Inclusion complex does not form. <sup>c</sup> Host-to-guest ratio is not clear.

#### 4.1.2. Complexation with Water-Soluble Thiocalix[4]arene

It is well known that hydrophobic interaction is the major driving force for inclusion of organic guests into the calix cavity. The complexation behavior of *p*-sulfonatothiocalix- $[4]$ arene **69** with organic molecules was studied by NMR titration method or salting out of the complexes from aqueous solutions.<sup>55</sup> It was found that **69** showed size and shape selectivity to bind small chlorinated organic molecules in its hydrophobic cavity in a 1:1 or 1:2 manner in aqueous solution. On the other hand, detailed inclusion behavior of *p*-sulfonatothiocalix $[4]$ arene **69** toward monosubstituted benzenes in water was compared with that of the methylene-bridged **91**.<sup>72</sup> Both hosts encapsulated almost all the guest examined into the cavity from the side of the aromatic moiety. Stability of the inclusion complexes increased with electron-withdrawing ability of the substituent on the guest, suggesting  $\pi$ – $\pi$  electronic interaction between the host and guest for inclusion. Comparing the two hosts, thiocalix $[4]$ arene **69** showed higher inclusion ability than calix $[4]$ arene **91**. Considering the lower electron density on the aromatic ring of **69** than that of **91**, the size rather than the electron density of the calix framework seems to be more operative in determining the inclusion ability.

Interestingly, **69** can form inclusion complexes with even water-miscible organic molecules such as alcohols, ketones,

cyclic ethers, etc.<sup>73</sup> X-ray crystallographic analysis of **69** with acetone suggested that the guest is retained with the aid of cation coordination and hydrogen bonding (Figure 7). Similarly, the structures and thermodynamics of complexes of **69** and **91** with dipyrindinium ions,<sup>74</sup> diazacycloalkanes,<sup>75</sup> dipyrindines,<sup>76</sup> phenanthroline,<sup>76</sup> and metal complexes<sup>77</sup> were reported.

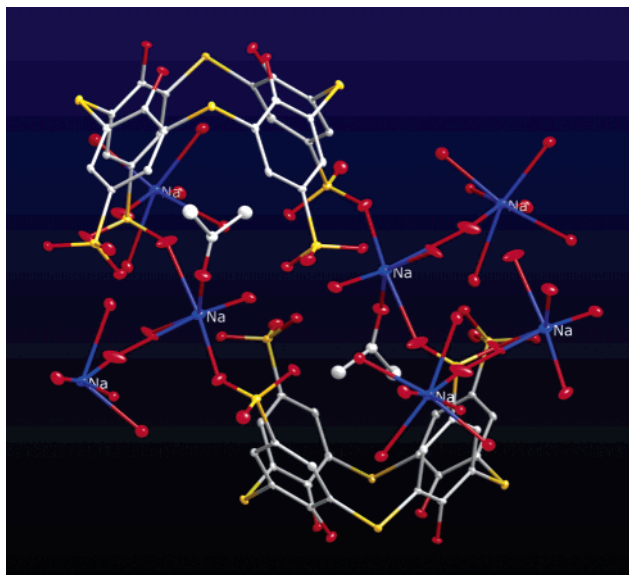


Figure 7. X-ray structure of **69** complex including acetone.

The inclusion behavior of **69** with  $C_{60}$  in water was investigated by photoluminescence (PL) and quantum-chemical methods.<sup>78</sup> The stoichiometry of calixarene/ $C_{60}$  complex was found to be 2:1, in which  $C_{60}$  fullerene is included in a cavity composed of two-half-bowl molecules of **69**.

#### 4.1.3. Removal of Organic Halides from Water

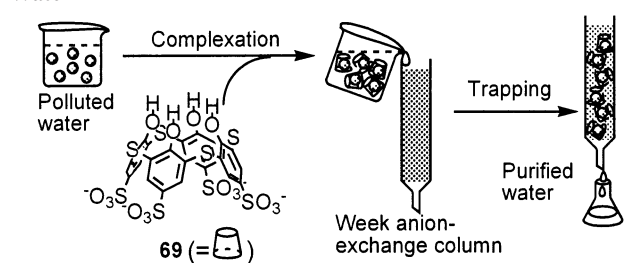
As mentioned above, water-soluble thiacalix[4]arene **69** can form inclusion complexes with small chlorinated organic molecules, which was advantageously utilized for removing organic halides of environmental concern from water.<sup>79</sup> Thus, **69** was added to an aqueous solution containing halogenated organic molecules 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 complexes were trapped onto the resin by electrostatic interactions between the sulfonate function of the complex and the cationic center of the resin (Table 4). It should be noted that the inclusion ability of **69** toward organic halides is far more superior to that of the corresponding methylene-bridged analogue **91**.

#### 4.1.4 Recognition of Organic Molecules by Thiacalix[4]-arene Derivatives

Lhoták et al. synthesized calix[4]arene derivatives **92** and **93** which had two zinc–porphyrin residues attached to distal two phenolic oxygens.<sup>80</sup> Their recognition ability toward 1,4-diazabicyclo[2.2.2]octane (DABCO) as organic guest was studied. It was revealed that **92** trapped one DABCO molecule by pinching with the two porphyrin rings to give a 1:1 complex, while each of the porphyrins of **93** independently caught the guest molecules to form a 1:2 complex. This difference was ascribed to the difference in the ring size of the

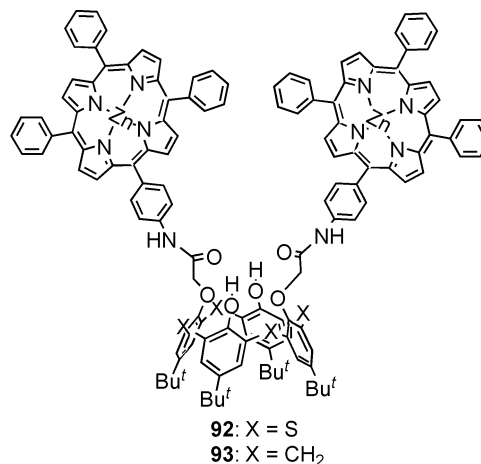
two hosts and the degree of preorganization by hydrogen bonding.

Table 4. Removal of Halogenated Organic Compounds from Water<sup>a</sup>



| guest                               | $C_{\text{initial}}/\text{ppm}$ | $C_{\text{final}}/\text{ppm}$ | 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%      |
| $\text{CH}_2\text{ClCH}_2\text{Cl}$ | 198                             | $4.08 \times 10^{-2}$         | 99.9794%      |
| $\text{CH}_2\text{ClCHCl}_2$        | 267                             | $1.35 \times 10^{-1}$         | 99.9495%      |

<sup>a</sup> Conditions are as follows. Sample solution:  $C_{\text{initial}} = 2.0 \text{ mmol dm}^{-3}$ ,  $[\mathbf{69}]_{\text{Total}} = 5.0 \text{ mmol dm}^{-3}$ . Column:  $20 \text{ cm}^3$  of weak anion-exchange resin having dimethylamino groups. Flow rate:  $2 \text{ cm}^3/\text{min}$ .



Hosoya et al. studied the applicability of thiacalix[4]arene **24** as a selector for high-performance liquid chromatography (HPLC).<sup>81</sup> First, uniformly sized polymer particles were prepared by using a multistep swelling and polymerization method with ethylene glycol dimethacrylate as a cross-linker. Methacrylic acid (MAA) was introduced onto the surface of the resulting polymer particles through a new modification method. Then, **24** was chemically bonded through the MAA group using 1,4-dibromobutane as a spacer. The performance of the prepared polymer-based thiacalix[4]arene-modified stationary phase was evaluated with HPLC. Specific chromatographic retention behavior was observed for catechol relative to positional isomers. Separation factors ( $\alpha_{\text{xy/ylene}}$ ) for respective compounds are shown in Table 5.

#### 4.1.5. Chiral Recognition by Optically Active Thiacalix[4]-arenes

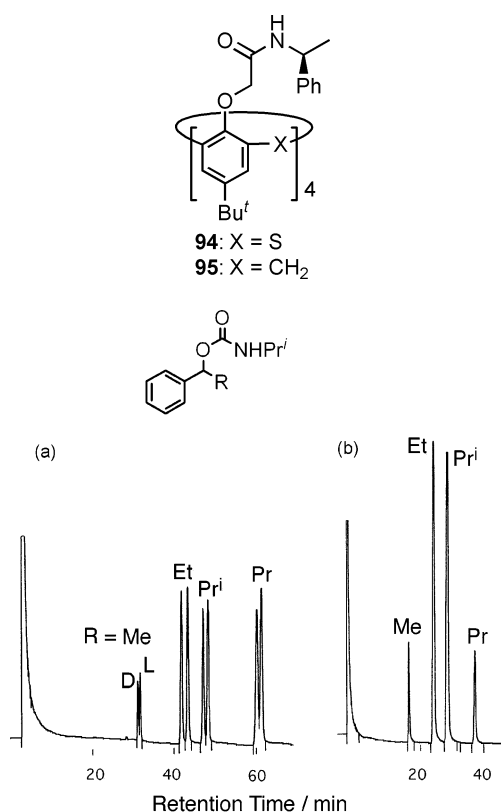
Optically active thiacalix[4]arenes having chiral amines were synthesized from tetraacetate **20c** and applied to chiral selectors of chiral stationary phases (CSPs), the enantioselectivity of which was assessed by GC for various chiral analytes such as alcohol, amine, and amino acid derivatives.<sup>82</sup> For example, CSP **94** having four (*S*)-1-phenethylamide groups exhibited chiral separation for the samples tested

**Table 5. Separation Factor ( $\alpha_{\text{xylene}} = k'(\text{solute})/k'(\text{xylene})$ ) of Prepared Polymer-Based Stationary Phase Modified with **2<sub>4</sub>** for Catechol-Related Compounds by Reversed-Phase HPLC<sup>a</sup>**

|              | <i>o</i> | <i>m</i> | <i>p</i> |
|--------------|----------|----------|----------|
| xylene       | 1.00     | 1.00     | 1.00     |
| cresol       | 0.86     | 0.92     | 0.90     |
| benzene-diol | 2.02     | 1.22     | 0.84     |

<sup>a</sup> HPLC conditions: mobile phase, methanol/water (90:10 v/v); flow rate, 150 L min<sup>-1</sup>; column, stainless steel column (150 mm L × 2.0 mm i.d.); detection, UV 210 nm; temperature, 30 °C.

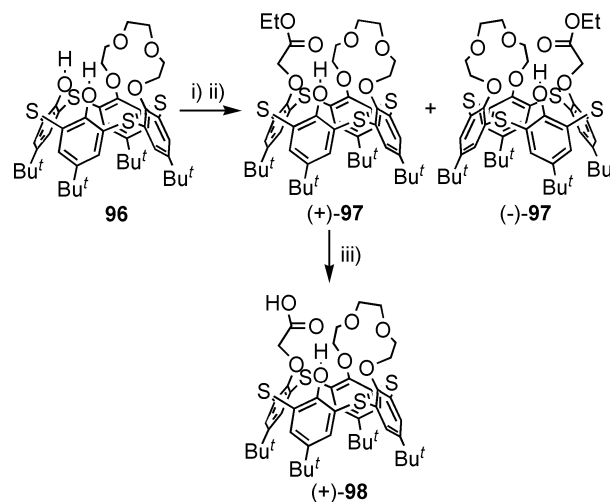
(Figure 8). On the contrary, calix[4]arene (**95**) based CSP could not discriminate chirality of the same samples. Although the difference of the performance of the two CSPs may partly be due to the high melting point of **95** to inhibit sufficient interaction between the selector and an analyte, the flexibility of the thiacalix platform may play an important role in making strong hydrogen bonding with the analyte to show the chiral discrimination ability.



**Figure 8.** Gas chromatograms of alcohol enantiomers derivatized to isopropyl carbamates on chiral stationary phases containing **94** (a) and **95** (b). Carrier gas, He (15 cm<sup>3</sup>/s); column temperature, 140 °C.

As mentioned in section 3.3.1, introduction of at least two kinds of achiral substituents into the upper and/or lower rims may create molecular dissymmetry or asymmetry to form inherently chiral calixarenes because of the cyclic structure of calix class compounds. In fact, synthesis and optical resolution of inherently chiral thiacalix[4]arenes have been reported.<sup>24,83</sup> For example, it is readily conceivable that 1,2-bridged thiacalixcrowns (see section 4.2.2) having only one symmetry plane are desymmetrized to inherently chiral derivatives by introducing an achiral substituent at one of the two remaining hydroxy groups. Actually, mono-*O*-alkylation of **96** with ethyl bromoacetate gave (±)-**97**, which were optically resolved by chiral HPLC. Subsequent hydrolysis of the

(+)-ester moiety gave inherently chiral 1,2-bridged thiacalix[4]crown carboxylic acid (+)-**98** (Scheme 33).<sup>83a</sup> Its chiral recognition ability as a chiral solvating agent was studied by <sup>1</sup>H NMR spectroscopy. It was shown that (+)-**98** clearly discriminated enantiomeric primary amines as well as amino esters.

**Scheme 33. Synthesis of Inherently Chiral Thiacalix[4]crown Carboxylic Acid **98**<sup>a</sup>**

<sup>a</sup> Conditions: (i) BrCH<sub>2</sub>CO<sub>2</sub>Et, Na<sub>2</sub>CO<sub>3</sub>, THF; (ii) optical resolution by chiral HPLC [column, Daicel CHIRALPAK AD, 20 mm i.d. × 25 cm; mobile phase, hexane-2-propanol (98:2); flow rate, 6.0 mL min<sup>-1</sup>]; (iii) KOH, EtOH-H<sub>2</sub>O.

## 4.2. Recognition of Metal Ions

### 4.2.1. Complexation with Thiacalix[4]arenes Modified at Lower Rim

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. Although thiacalix[4]arenes by themselves have varying metal-recognition ability, the ability is also improved by applying similar methodology. Along this line, various thiacalix[4]arene-based ligands have been prepared by introducing functional groups such as ether,<sup>84</sup> ester,<sup>23,85</sup> ketone,<sup>86</sup> carboxylic acid,<sup>87</sup> amide,<sup>86a,c,88</sup> phosphine oxide,<sup>89</sup> etc. Generally, the coordination ability of these thiacalix[4]arenes was investigated by a solvent extraction study. For example, Lamartine et al. compared the extraction ability of compounds **99–101** for various metal-ion picrates (Table 6).<sup>86a</sup> The percent extraction *E* % was calculated by eq 1

$$E \% = [(A_0 - A_1)/A_0] \times 100\% \quad (1)$$

where *A*<sub>1</sub> and *A*<sub>0</sub> are the absorbances of the aqueous phase measured at 355 nm before and after extraction. The results listed in Table 6 show that compound **101** containing amide groups shows significant complexation ability toward all cations examined with maximal levels for K<sup>+</sup>, Rb<sup>+</sup>, and Ag<sup>+</sup>, while the corresponding methylene-bridged compound **102**

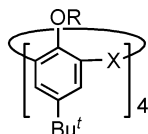


Table 6. *E* % of Metal Ions by 99–101

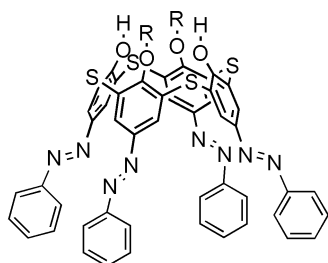
| extractant | Li <sup>+</sup> | Na <sup>+</sup> | K <sup>+</sup> | Rb <sup>+</sup> | Cs <sup>+</sup> | Ca <sup>2+</sup> | Ba <sup>2+</sup> | Mg <sup>2+</sup> | Al <sup>3+</sup> | Pb <sup>2+</sup> | Fe <sup>3+</sup> | Ni <sup>2+</sup> | Cu <sup>2+</sup> | Ag <sup>+</sup> |
|------------|-----------------|-----------------|----------------|-----------------|-----------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|-----------------|
| <b>99</b>  | 1.1             | 1.4             | 0.6            | 0.6             | 0.6             | 1                | 0.6              | 0.9              | 0                | 1                | 2.5              | 1.4              | 1.3              | 2.4             |
| <b>100</b> | 1.2             | 2.8             | 8.6            | 8.3             | 3.2             | 2.4              | 2.8              | 3.1              | 3.9              | 3.1              | 8.2              | 2.7              | 3.6              | 35.3            |
| <b>101</b> | 22.9            | 55              | 80.1           | 78              | 56.4            | 29.8             | 24.1             | 39.7             | 42.8             | 32.6             | 50.9             | 32.7             | 40.5             | 95.9            |

showed a somewhat different behavior.<sup>90</sup>

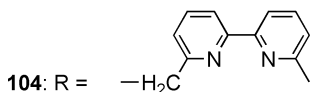
On the other hand, it was found that compound **34** having pyridyl groups shows high affinity to Ag<sup>+</sup> ion.<sup>28</sup> Similarly, compounds **103** and **104** having bithiazoyl and bipyridyl groups have the best efficiency for Cu<sup>2+</sup> and Ag<sup>+</sup> ions.<sup>91</sup>



- 99:** X = S, R = CH<sub>2</sub>COMe  
**100:** X = S, R = CH<sub>2</sub>COC<sub>6</sub>H<sub>5</sub>  
**101:** X = S, R = CH<sub>2</sub>CONEt<sub>2</sub>  
**102:** X = CH<sub>2</sub>, R = CH<sub>2</sub>CONEt<sub>2</sub>



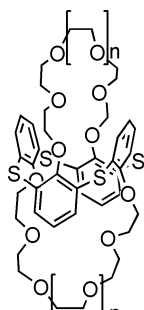
- 103:** R = -H<sub>2</sub>C



- 104:** R = -H<sub>2</sub>C

#### 4.2.2. Complexation with Intra- and Intermolecular Bridged Thiacalix[4]arenes

Among the calixarene derivatives, calixcrowns are those in which any two of the phenolic hydroxy groups are bridged with a polyether chain. It has been proved that this class of ligands has high metal-recognition ability. Therefore, the corresponding sulfur analogues of these calixcrowns, thiacalixcrowns have also been prepared. Lamare et al. reported the first example of thiacalixcrowns; 1,3-alternate thiacalix[4]-bis(crown-5) **105a** and -bis(crown-6) **105b** were synthesized by reaction of **7** with tetra- and pentaethylene glycol ditosylate in the presence of potassium carbonate.<sup>92</sup> Bitter et al.



- 105a** (n = 0)  
**105b** (n = 1)

reported similar transformation for the synthesis of bis- and monocrowns.<sup>93,94</sup> Biscrowns **105**–**106** were synthesized by cyclocondensation of **24** and **7** with tetraethylene glycol ditosylate and 1,14-diiodo-3,6,9,12-tetraoxatetradecane (Scheme 34). On the other hand, previous formation of 1,3-diethers **36a** and **107** from **24** was followed by reaction with tetraethylene glycol ditosylate or 1,14-diiodo-3,6,9,12-tetraoxatetradecane to afford monocrowns **108a–d**.<sup>93b</sup> Reinhoudt et al. studied in detail the reaction of **24** with oligoethylene glycol ditosylates catalyzed by alkali-metal carbonates to give three types of thiacalix[4]crowns **106**, **109**, and **110** and found that any of these could be obtained selectively by choice of the base catalyst and the number of ethylene glycol units (Scheme 35, Table 7).<sup>94</sup> Furthermore, the Mitsunobu protocol using the DEAD/TPP system for selective synthesis of 1,3-diethers (see section 3.1.3) was also applied to the synthesis of thiacalixcrowns.<sup>95</sup> As expected, treatment of **24** with 1.5 equiv of various ethylene glycol derivatives using 3.0 equiv

#### Scheme 34. Synthesis of Bis- and Monocrowns from 24 and 7

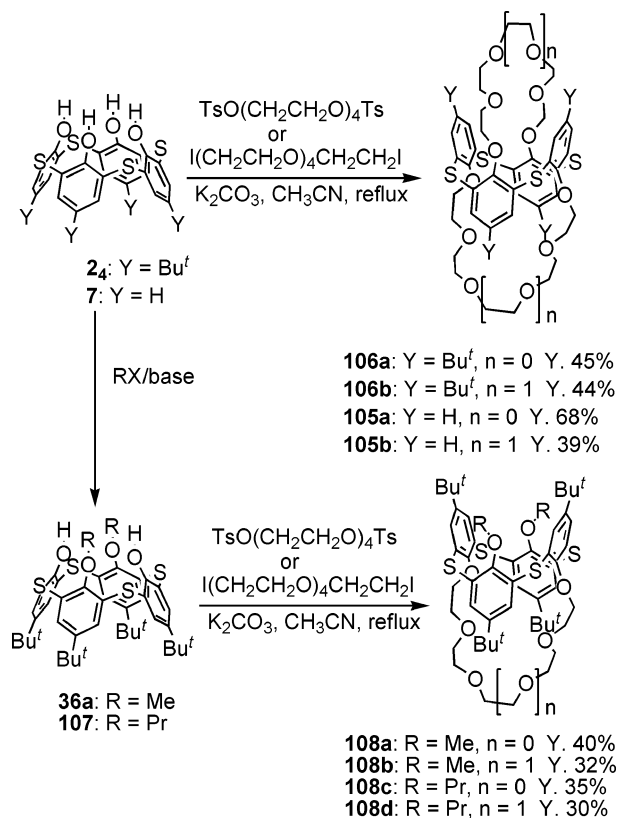
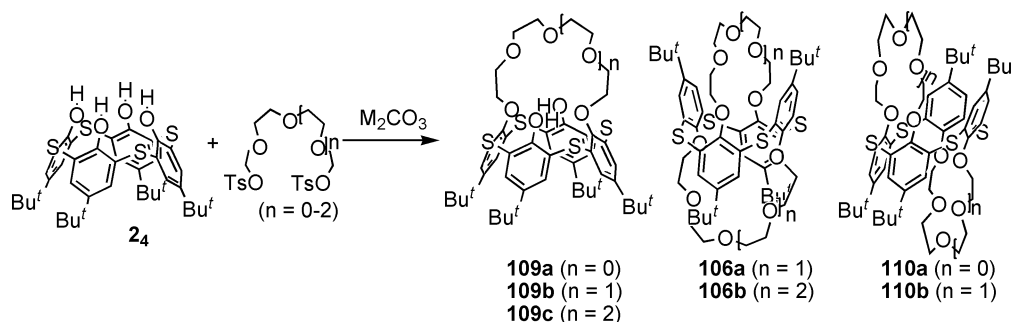
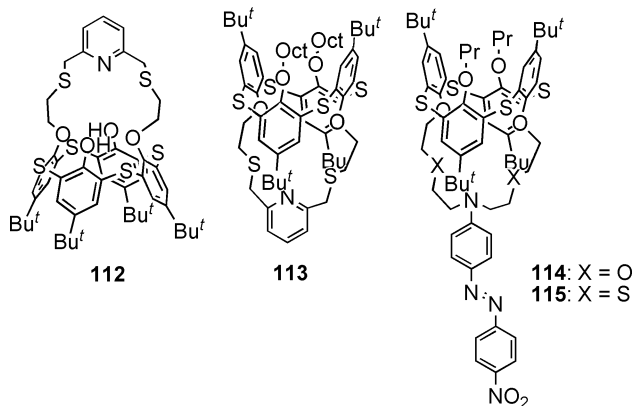
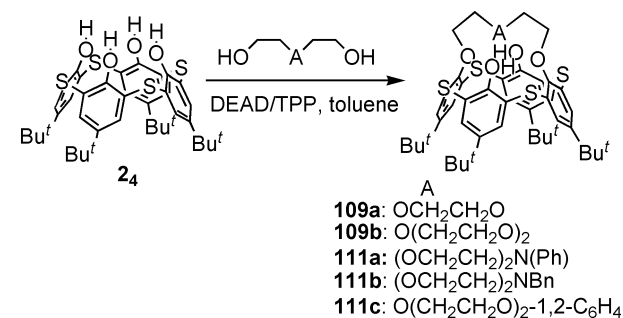
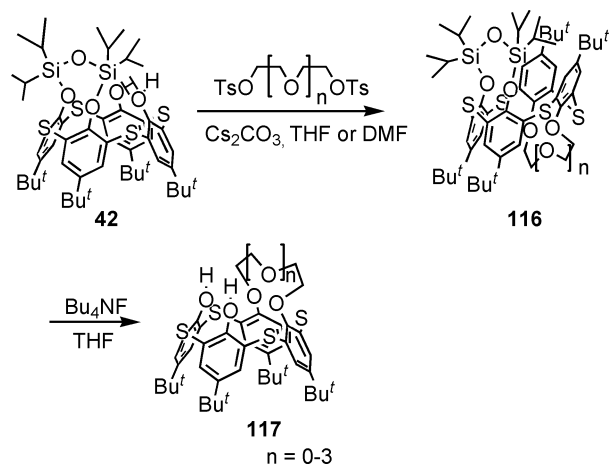


Table 7. Synthesis of Thiacalix Mono- and Biscrowns

| entry | n | base (equiv)                          | time | conv. of 24 (%) | products formed (ratio) |
|-------|---|---------------------------------------|------|-----------------|-------------------------|
| 1     | 0 | Na <sub>2</sub> CO <sub>3</sub> (12)  | 15 d | 50              | <b>109a</b>             |
| 2     |   | K <sub>2</sub> CO <sub>3</sub> (4)    | 2 d  | 40              | <b>110a</b>             |
| 3     |   | Cs <sub>2</sub> CO <sub>3</sub> (4)   | 6 h  | 100             | <b>110a</b>             |
| 4     | 1 | Na <sub>2</sub> CO <sub>3</sub> (12)  | 11 d | 50              | <b>109b</b>             |
| 5     |   | K <sub>2</sub> CO <sub>3</sub> (4)    | 12 h | 100             | <b>106a</b>             |
| 6     |   | Cs <sub>2</sub> CO <sub>3</sub> (4)   | 12 h | 100             | <b>110b/106a</b> (1:1)  |
| 7     | 2 | Na <sub>2</sub> CO <sub>3</sub> (1.2) | 15 d | 40              | <b>109c</b>             |
| 8     |   | K <sub>2</sub> CO <sub>3</sub> (4)    | 7 d  | 100             | <b>106b/109c</b> (1:4)  |
| 9     |   | Cs <sub>2</sub> CO <sub>3</sub> (4)   | 6 h  | 70              | <b>106b</b>             |

Scheme 35. Formation of Thiacalixcrowns from **24**

of DEAD/TPP in toluene at ambient temperature selectively afforded 1,3-bridged monocrowns **109a,b** and **111a–c** (Scheme 36). Furthermore, Mitsunobu cyclization of **24** with glycol was expanded to oligoethylene glycol analogues composed of O, S, and N atoms in the chain to produce

Scheme 36. Reaction of **24** with Oligoethylene Glycols under the Mitsunobu Conditions To Give 1,3-Bridged MonocrownsScheme 37. Synthesis of 1,2-Bridged Monocrowns from **42**

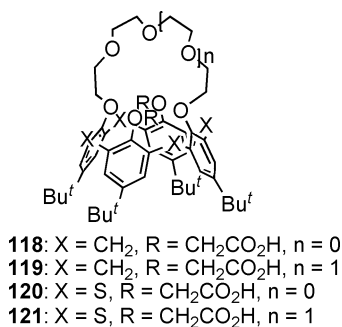
various monocrowns such as **112–115**.<sup>96</sup> On the contrary, reaction of disiloxane-capped **42** with several oligo(ethylene glycol) ditosylates using  $\text{Cs}_2\text{CO}_3$  as the base gave monocrowns **116**, which were desilylated by  $\text{Bu}_4\text{NF}$  to give only 1,2-bridged monocrowns **117** (Scheme 37).<sup>97</sup>

Then, the complexation ability of the synthesized thiacalixcrowns to metal cations was studied by performing a solvent extraction study<sup>92,93,98</sup> and dynamic  $^1\text{H}$  NMR experiments.<sup>94a,96,98a</sup> In almost all cases, thiacalixcrowns as well as classical calixcrowns showed high affinity to alkali-metal cations. On the contrary, Reinhoudt et al. found that thiacalix[4]crowns **109b** and **110a,b** show a higher extraction ability toward  $\text{Ag}^+$  ion than alkali-metal ions, in sharp contrast to the corresponding methylene-bridged calix[4]crowns, such as  $\text{K}^+$  and  $\text{Cs}^+$  ions.<sup>94a</sup> The difference was ascribed to the presence or absence of coordination by bridging sulfurs in addition to crown ether oxygens of the thiacalix- or calixcrowns. Thiacalix[4]crown derivatives could be modified to show excellent selectivity for  $^{226}\text{Ra}^{2+}$  ion for use as extractant, which attracted some interest because the ion is found as trace amounts of naturally occurring radioactive materials in aqueous waste streams of non-nuclear industries, e.g., coal mining.<sup>99</sup> For example, the extractability of the thiacalix- and calix[4]crown dicarboxylic acid were investigated for  $^{226}\text{Ra}^{2+}$  ion in the presence of a large excess of the common alkali and alkaline-earth cations. Selective extraction of  $^{226}\text{Ra}^{2+}$  ( $2.9 \times 10^{-8}$  M) was observed even at an extremely high  $\text{M}^{n+}/^{226}\text{Ra}^{2+}$  ratio of  $3.5 \times 10^7$  [ $\text{M}^{n+} = \text{Na}^+, \text{K}^+, \text{Rb}^+, \text{Cs}^+, \text{Mg}^{2+}, \text{Ca}^{2+}, \text{and Sr}^{2+}$  (1 M)] at extractants concentration of  $10^{-4}$  M. Furthermore, the selectivity for  $\text{Ra}^{2+}$  ion was evaluated in terms of the selectivity coefficients [ $\log(K^{\text{Ra}}_{\text{ex}}/K^{\text{M}}_{\text{ex}})$ ], in which  $K^{\text{Ra}}_{\text{ex}}$  and  $K^{\text{M}}_{\text{ex}}$  are extraction constants for  $\text{Ra}^{2+}$  and  $\text{M}^{2+}$  ions, respectively (Table 8). Compounds **118–121** show high selectivity for  $^{226}\text{Ra}^{2+}$ , with  $\log(K^{\text{Ra}}_{\text{ex}}/K^{\text{M}}_{\text{ex}})$  of  $\sim 4.2$  ( $\text{Mg}^{2+}$ ),  $\sim 3.5$  ( $\text{Ca}^{2+}$ ), and  $\sim 3.4$  ( $\text{Sr}^{2+}$ ). It is known that  $\text{Ba}^{2+}$  has very similar properties to  $\text{Ra}^{2+}$ , and then it is noteworthy that onlythiacalix[4]crown derivative **121** showed substantial selectivity toward  $^{226}\text{Ra}^{2+}$ .

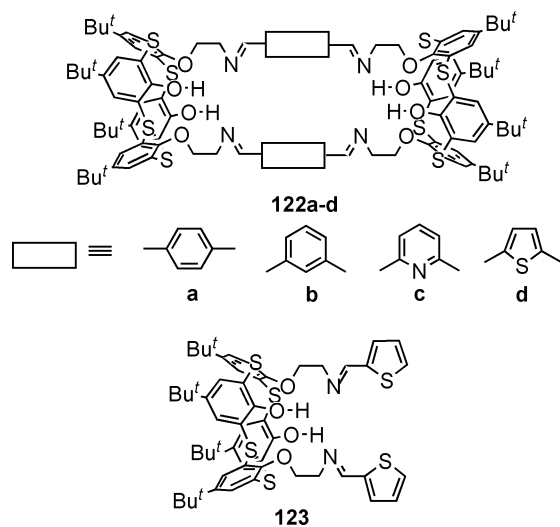
Recently, it became clear that those calixarenes which are bridged intermolecularly often show superior functions to

Table 8. Selectivity Coefficients ( $\log(K^{\text{Ra}}_{\text{ex}}/K^{\text{M}}_{\text{ex}})$ ) of Calix[4]crowns **118–121** for  $^{226}\text{Ra}^{2+}$

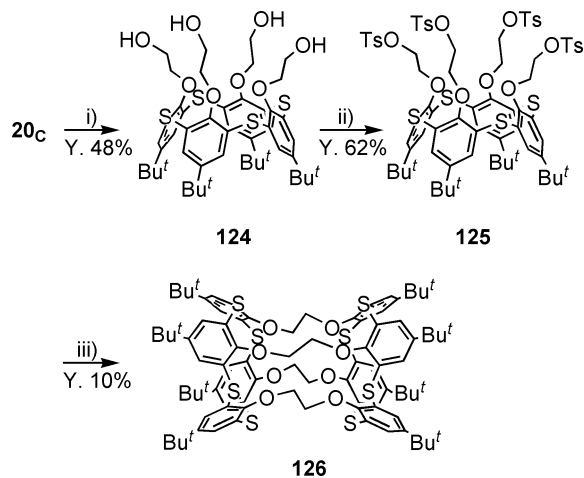
| ionophores | $\log(K^{\text{Ra}}_{\text{ex}}/K^{\text{Mg}}_{\text{ex}})$ | $\log(K^{\text{Ra}}_{\text{ex}}/K^{\text{Ca}}_{\text{ex}})$ | $\log(K^{\text{Ra}}_{\text{ex}}/K^{\text{Sr}}_{\text{ex}})$ | $\log(K^{\text{Ra}}_{\text{ex}}/K^{\text{Ba}}_{\text{ex}})$ |
|------------|-------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|
| <b>118</b> | 3.7                                                         | 1.1                                                         | 0.3                                                         | -1.3                                                        |
| <b>119</b> | 4.2                                                         | 3.4                                                         | 2.6                                                         | -0.5                                                        |
| <b>120</b> | 4.2                                                         | 3.5                                                         | 1.7                                                         | -0.5                                                        |
| <b>121</b> | 3.8                                                         | 3.5                                                         | 3.4                                                         | +0.9                                                        |



those of the corresponding monomeric entities. Actually, the authors synthesized bisthiacalix[4]arenes **122**, which quantitatively and selectively extracted silver ion from the aqueous phase into an organic one.<sup>100</sup> These extraction behaviors were much better than those reported for the analogues having conventional calix[4]arene units.<sup>101</sup> Monomeric thiacalix podand **123** did not extract any of the metal ions under the same conditions. On the other hand, thiacalix[4]tube **126** was



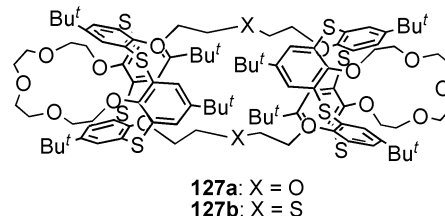
Scheme 38. Synthesis of Thiacalix[4]tube **126**<sup>a</sup>



<sup>a</sup> Conditions: (i) LiAlH<sub>4</sub>, Et<sub>2</sub>O; (ii) tosyl chloride, Et<sub>3</sub>N; (iii) **2**, K<sub>2</sub>CO<sub>3</sub>, xylene, reflux.

prepared by starting from tetraacetate **20c** (Scheme 38).<sup>102</sup> Reduction of **20c** gave **124**, which was subsequently treated with tosyl chloride to give tetratosylate **125**. This precursor was treated with thiacalix[4]arene **2** to give the desired product **126**, though in low yield. Preliminary studies on the

binding of **126** with alkali metals were undertaken using <sup>1</sup>H NMR and ESI MS. On the other hand, Bitter et al. reported various intermolecular bridged derivatives such as **127a,b** using the Mitsunobu protocol.<sup>83b</sup>



It should be noted that the above-mentioned strategies were used for preparation of thiacalix[4]arene derivatives potentially applicable to segments of nanotubes and cores of dendrimers.<sup>103</sup>

#### 4.2.3. Extraction by Thiacalix[4]arenes without Coordinating Auxiliaries

The authors found that the sulfur-containing calixarenes can extract various metal ions without requiring introduction of coordinating auxiliaries, which is one of the most advantageous characteristics of the thiacalixes as compared to the corresponding classical methylene-bridged counterparts.<sup>56b,57,104</sup> Thus, the metal extraction abilities of *p*-*tert*-octylthiacalix[4]arenes **4**, **71**, **73**, and **128** toward as many as 40 metal ions were investigated under varying pH conditions (Table 9).<sup>57</sup> As known for calixarene chemistry, methylene-bridged **128** hardly extracted any metal ions while **4**, **71**, and **73** extracted soft, hard, and both soft and hard metal ions, respectively. These extraction behaviors can be reasonably explained based on the HSAB principle in which compound **4** can ligate to soft metal ions with the bridging sulfur in addition to the phenoxide oxygen and **71** to hard metal ions with sulfonic oxygen, while **73** alters its coordination site between the sulfur atom and the oxygen atom of the SO function depending on the softness and hardness of the relevant metal ion (Figure 9).

*p*-*tert*-Butylthiacalix[6]arene **26** extracted soft to intermediate metal ions to the same extent as the [4]counterpart did, indicating that the O<sup>-</sup>, S, O<sup>-</sup> tridentate binding manner rather than the effect of the ring extension is critical to determine the complexing ability.<sup>105</sup> On the other hand, it is interesting

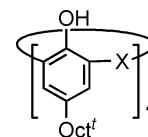
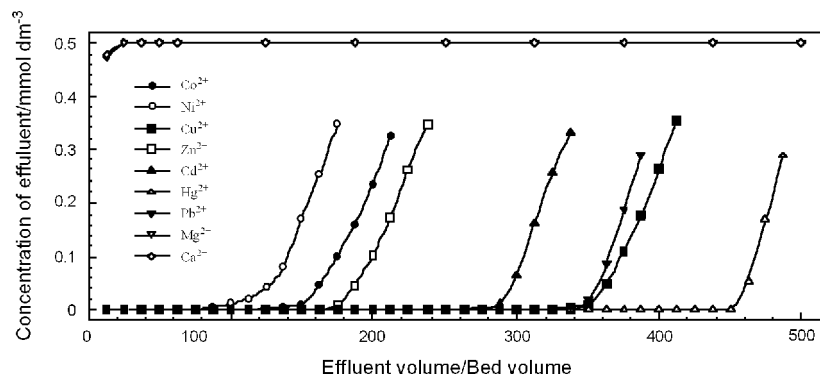


Table 9. Periodic Table of Extracted Metal Ions by **4**, **71**, and **73**

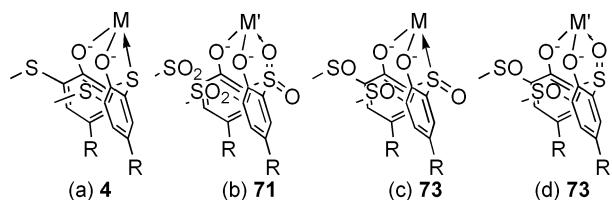
|   | 1 | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 |
|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 1 |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 2 |   | Li | Be |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 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 |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

M Extracted by **4**  
M Extracted by **4** and **73**  
M Extracted by **71** and **73**  
M Not extracted by **4**, **71**, **73**



**Figure 10.** Column breakthrough profile for the adsorption of metal ions by **69**-loaded resin. Resin bed: 0.80 cm<sup>3</sup> (5.0 mm i.d. × 40 mm high). Concentration of metal ions in feed solution: 0.50 mmol dm<sup>-3</sup>. Solution pH: 6.5. Feed rate: 0.10 cm<sup>3</sup> min<sup>-1</sup> (7.5 beds h<sup>-1</sup>).

to note that aminothiocalix[4]arene **89** selectively extracts noble-metal palladium and gold ions from a mixture containing several heavy metal ions.<sup>106</sup> Furthermore, complexation thermodynamics of water-soluble thiocalix[4]arene **69** with lanthanoid(III) ions in aqueous solution was investigated.<sup>107</sup>



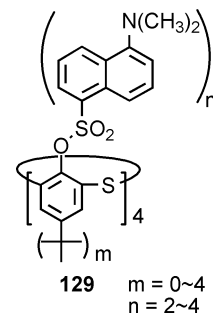
**Figure 9.** Schematic representation of the coordination manners of (a) *p*-*tert*-octylthiocalix[4]arene **4**, (b) the sulfonyl **71**, and (c, d) sulfinyl **73** analogues. M and M' denote soft and hard metal ions, respectively. R = Oct'.

#### 4.2.4. Sensing of Metal Ions

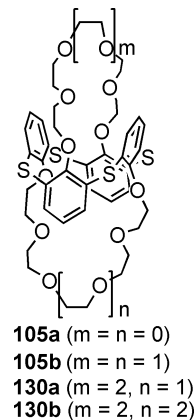
The remarkable complexation ability of thiocalixarenes toward metal ions has been utilized for the sensing of them. For example, J-Renault et al. and Lamartine et al. applied thiocalix[4]arene **24** to a component of thin films for electrolyte–insulator–semiconductor (EIS), ion-sensitive field effect transistor (ISFET), and gold microelectrodes, which allowed detection of Cu<sup>2+</sup> at a level of as low as 10<sup>-7</sup> M.<sup>108</sup> Needless to say, phenols are electroactive functional groups. Therefore, voltammetric recognition of metal ions using **24** was examined.<sup>109</sup> In pH 8 solution, voltammograms of **24** dramatically changed in the presence of transition-metal ions such as Cd<sup>2+</sup>, Co<sup>2+</sup>, and Ni<sup>2+</sup>, while alkali-metal ions and alkaline-earth-metal ions caused only negligible changes to that of **24** even at high concentrations. It was demonstrated that the voltammetry was applicable to the analysis of Cd<sup>2+</sup> ion.

On the other hand, modified thiocalix[4]arenes were also applied for sensing of metal ions. Hamada et al. modified the phenolic function of **24** and its *de-tert*-butylated compounds **7** and **51–53** with a dansyl moiety to the corresponding derivatives **129**, which were used as host molecules for the fluorescent sensing of metal ions in aqueous solutions.<sup>46,110</sup> It was found that the number of *tert*-butyl moieties significantly affected the fluorescent intensity, increasing with decreasing number of *tert*-butyl groups.

Furthermore, Kim et al. reported the potentiometric responses of thiocalix[4]biscrowns with 1,3-alternate conformation **105a,b** and **130a,b** in poly(vinyl chloride) membrane electrodes.<sup>111</sup> Their potentiometric measurement by the fixed interference method showed selectivities toward K<sup>+</sup> and Cs<sup>+</sup> ions over other alkali-, alkaline-earth-, and transi-



tion-metal ions examined. Among the ionophores, biscrown-**6** **130b** (*m*, *n* = 2) showed a high selectivity for Cs<sup>+</sup> over K<sup>+</sup> ion and could be applied to a Cs<sup>+</sup> ion-selective electrode.



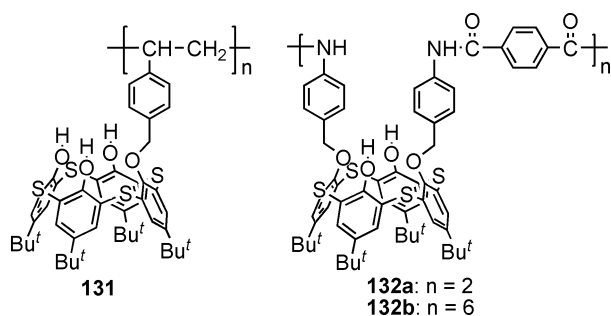
#### 4.2.5. Removal and Separation of Metal Ions

The high complexation ability of thiocalixarenes to metal ions was applied for the component of adsorbent for removal and preconcentration of heavy-metal ions in water and pre-column chelating reagent for HPLC.<sup>112</sup> For example, a chelating adsorbent was prepared by loading an anion-exchange resin with water-soluble **69** having a sulfo function.<sup>112b</sup> This resin strongly retained the heavy-metal ions tested (Co<sup>2+</sup>, Ni<sup>2+</sup>, Cu<sup>2+</sup>, Cd<sup>2+</sup>, Zn<sup>2+</sup>, Hg<sup>2+</sup>, and Pb<sup>2+</sup>) in a slightly acidic to neutral pH region, while no adsorption was observed for alkaline-earth-metal ions, Mg<sup>2+</sup> and Ca<sup>2+</sup>, in this pH region, which is in good accordance with the result of the solvent extraction study by **24**. A continuous column adsorption system with the present resin allowed the selective and almost quantitative (more than 99.98%) removal of heavy-metal ions until a given capacity volume of the column (Figure 10).

On the other hand, Kikuchi et al. prepared ion exchangers by impregnating a polyformylstyrene–divinylbenzene-coated

silica column supported with **24** and sulfonyl analogue **70** to investigate their adsorption performance for  $^{241}\text{Am}^{3+}$  and lanthanide ions.<sup>113</sup> Interestingly, the distribution coefficient of **70** for  $^{241}\text{Am}^{3+}$  is  $5000\text{ cm}^3/\text{g}$  at pH 4, whereas that for  $\text{Nd}^{3+}$  or  $\text{Eu}^{3+}$  is only  $10\text{ cm}^3/\text{g}$ .<sup>113a</sup> Therefore, the separation factor of  $^{241}\text{Am}^{3+}/\text{lanthanides}$  becomes 500, suggesting that selective separation of  $\text{Am}^{3+}$  is attainable in the weak acidic solution.

Yilmaz et al. reported the synthesis of polymeric thiacalix-[4]arene **131** and **132a,b** and their complexation properties toward alkali- and heavy-metal ions by liquid–liquid and solid–liquid extraction study.<sup>114</sup>

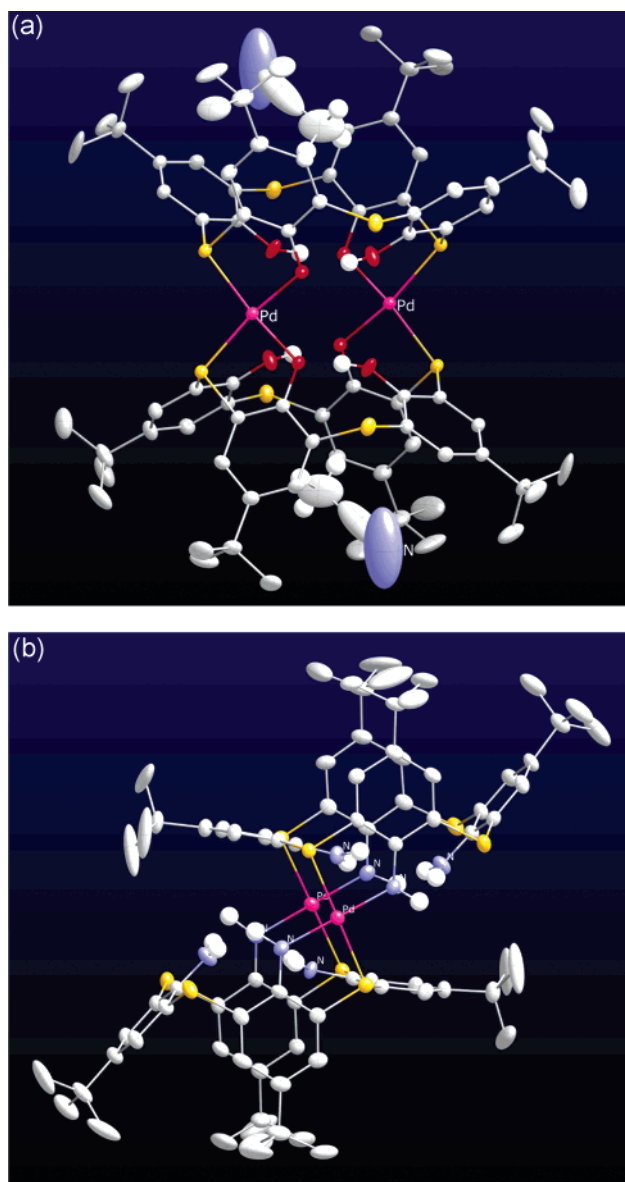


#### 4.2.6. Preparation of Metal Complexes Using Thiacalixarenes as Ligand

**Table 10. Ratio of Ligands and Metal Ions in Metal Complexes Based on Thiacalix[n]arenes**

| ligand                                                                                | metal species                                                                        | ligand:metal | ref |
|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------|-----|
| <b>24</b>                                                                             | $\text{LiClO}_4 \cdot 3\text{H}_2\text{O}$                                           | 1:2          | 115 |
|                                                                                       | $\text{NaO}_3\text{SCF}_3$                                                           | 1:1          | 115 |
|                                                                                       | KOH                                                                                  | 2:2          | 115 |
|                                                                                       | RbOH                                                                                 | 4:4          | 115 |
|                                                                                       | $\text{CsClO}_4$                                                                     | 4:3          | 115 |
|                                                                                       | $\text{MnCl}_2$                                                                      | 2:4          | 116 |
|                                                                                       | $\text{FeCl}_2$                                                                      | 1:4          | 117 |
|                                                                                       |                                                                                      | 4:10         | 117 |
|                                                                                       | $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$                                   | 2:4          | 118 |
|                                                                                       | $\text{ZnCl}_2$                                                                      | 3:4          | 119 |
|                                                                                       | $[\text{M}(\text{DMSO})_6](\text{ClO}_4)_2$ (M = Zn, Co)                             | 2:3          | 120 |
|                                                                                       | <i>cis</i> - $[\text{M}(\text{N}_2)_2(\text{PMe}_2\text{Ph})_4]$ (M = Mo, W)         | 1:1          | 121 |
|                                                                                       | $[\text{CpMCl}_2]_2$ (M = Rh, Ir)                                                    | 1:1          | 122 |
|                                                                                       | $\text{Pd}(\text{OAc})_2$                                                            | 2:2          | 123 |
| $\text{Nd}(\text{dmsO})_4(\text{NO}_3)_3$                                             | 2:4                                                                                  | 124          |     |
| $[\text{UO}_2(\text{dmsO})_5](\text{ClO}_4)_2$                                        | 1:1                                                                                  | 125          |     |
| $\text{CpTiCl}_3$ , <i>cis</i> - $[\text{Mo}(\text{N}_2)_2(\text{PMe}_2\text{Ph})_4]$ | 1:1(Ti):1(Mo)                                                                        | 126          |     |
| <b>26</b>                                                                             | $\text{Cu}(\text{OAc})_2$                                                            | 2:10         | 127 |
|                                                                                       | $\text{Co}(\text{OAc})_2$                                                            | 1:5          | 128 |
|                                                                                       | $\text{Ni}(\text{OAc})_2$                                                            | 1:4          | 128 |
| $\text{Ni}(\text{OAc})_2 + \text{M}(\text{OAc})_2$ (M = Co, Mn, Cu)                   | 1:4(Ni):1(M)                                                                         | 128          |     |
| <b>48</b>                                                                             | $[\text{CpMCl}_2]_2$ (M = Rh, Ir)                                                    | 1:2          | 128 |
|                                                                                       | $\text{MnCl}_2 \cdot 2\text{H}_2\text{O}$                                            | 1:2          | 129 |
| <b>69</b>                                                                             | $\text{CuSO}_4 \cdot 2\text{H}_2\text{O}$                                            | 1:4          | 130 |
|                                                                                       | $\text{Co}(\text{OAc})_2$                                                            | 1:2          | 131 |
| <b>70</b>                                                                             | $\text{Ni}(\text{acac})_2$                                                           | 1:2          | 131 |
|                                                                                       | $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O} + 1,4,7\text{-triazacyclononane}$ | 1:1          | 132 |
|                                                                                       | $\text{M}(\text{OAc})_3 \cdot 3\text{H}_2\text{O}$ (M = Gd, Nd)                      | 4:8          | 133 |
|                                                                                       | $\text{Pd}(\text{OAc})_2$                                                            | 3:2          | 134 |
| <b>72(rtct)</b>                                                                       | $\text{Pd}(\text{OAc})_2$                                                            | 3:2          | 134 |
| <b>72(rccc)</b>                                                                       | $\text{MnCl}_2$                                                                      | 2:4          | 117 |
| <b>89</b>                                                                             | $\text{Pd}(\text{OAc})_2$                                                            | 2:2          | 123 |

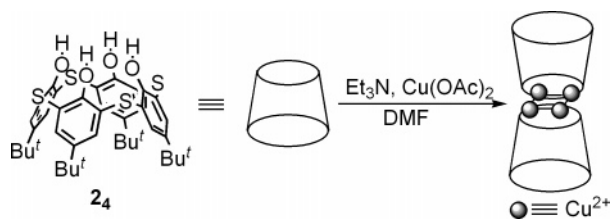
As mentioned above, thiacalix[n]arenes and their derivatives have high affinity to various metal ions by virtue of the coordination of the bridging groups. Actually, a variety of metal complexes have already been prepared, many of their structures being elucidated by X-ray crystal analysis.<sup>115–134</sup> It has been revealed that they frequently assemble to form multinuclear complexes using many ligating sites. The ratio



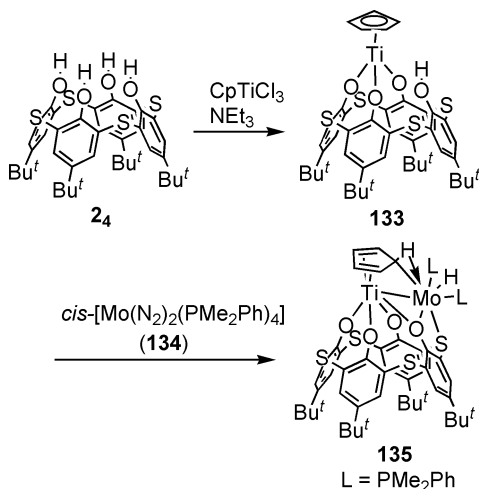
**Figure 11.** X-ray structure of **24**– $\text{Pd}^{2+}$  complex (a) and **89**– $\text{Pd}^{2+}$  complex (b). Protons on carbon atoms are not shown for clarity.

of thiacalix[n]arenes (ligand) and metal ions of the reported metal complexes is summarized in Table 10.

For example, *p*-*tert*-butylthiacalix[4]arene **24** formed a 2:4 complex with  $\text{Cu}^{2+}$  (Scheme 39), while  $\text{Pd}^{2+}$  afforded a 2:2 complex (Figure 11a).<sup>118,123</sup> Similarly, aminothiocalix[4]arene **89** formed stable complexes with soft metal ions by coordination of the bridging sulfur and amine nitrogen. For example, a **89**– $\text{Pd}^{2+}$  complex of 2:2 composition was prepared and its structure elucidated (Figure 11b).<sup>123</sup> Recently, Hidai et al. reported an example of a heterobimetallic complex incorporating a thiacalixarene ligand (Scheme 40).<sup>126</sup> The preparation involves incorporation of a cyclopentadienyl titanium fragment into the thiacalix[4]arene ligand to obtain a partially *O*-metalated Ti complex **133**, followed by reaction with molybdenum complex **134** to give Ti–Mo complex **135**. The Ti–Mo distance in this complex is  $2.730(9)\text{ \AA}$ , indicating the presence of some bonding interactions between these metals. In these structurally elucidated complexes coordination of the phenolic oxygens as well as the bridging moieties to the metal centers has been proved.

Scheme 39. Synthesis of  $2_4$ - $\text{Cu}^{2+}$  Complex

## Scheme 40. Synthesis of Ti–Mo Heterobimetallic Thiacalix[4]arene Complex



On the other hand, a ternary complex of sulfonylcalix[4]-arene **70** with  $\text{Zn}^{2+}$  and 1,4,7-triazacyclononane shows a unique dynamic behavior. That is, variable-temperature NMR of the complex indicated that  $\text{Zn}^{2+}$  is freely going around among the eight oxygen atoms including four sulfonyl oxygens and four phenolic oxygens of the thiacalix **70** arranged on a plane as shown in Scheme 41.<sup>132</sup>

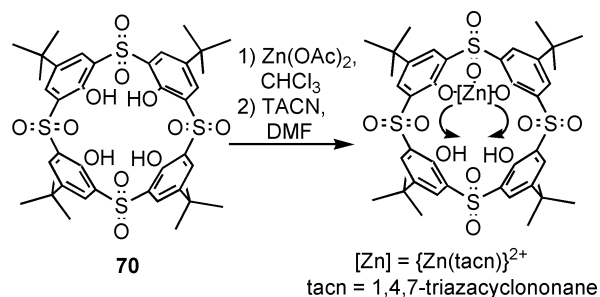
It has been revealed that thiacalix[*n*]arenes also serve as cluster-forming ligands. For example, reaction of  $\text{Cu}(\text{OAc})_2$  and thiacalix[6]arene **2<sub>6</sub>** gave ferromagnetically coupled decacopper cluster sandwiched by two hexaanionic **2<sub>6</sub>**.<sup>127</sup> On the other hand, lanthanides formed wheels using sulfonylcalix[4]arene **70** (Scheme 42).<sup>133</sup> For example,  $\text{Gd}(\text{OAc})_3 \cdot 4\text{H}_2\text{O}$  gave a complex possessing a wheel-like core involving eight  $\text{Gd}^{3+}$  ions supported by four ligands and eight  $\text{AcO}^-$  groups.

## 4.3. Function of the Metal Complexes

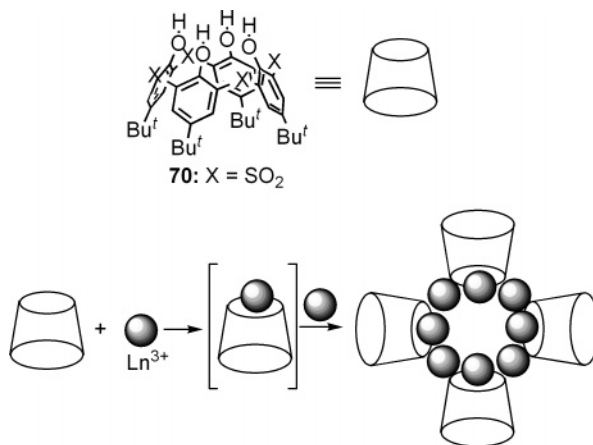
As stated above, thiacalixarenes form stable and unique complexes with various metal ions. Therefore, it is quite natural to expect the development of novel functional materials by combining a given metal of characteristic nature with a thiacalixarene of specific ligating ability.

## 4.3.1. Guest Absorption by Metal Complexes

Hamada et al. reported that potassium salts of **2<sub>6</sub>** and **2<sub>8</sub>** construct zeolitic structure, which can absorb several guest molecules.<sup>135</sup> For example, treatment of **2<sub>8</sub>** ( $\text{H}_8\text{L}$ ) with KH in THF, followed by recrystallization from methanol, afforded crystals of  $[\text{K}_4(\text{LH}_4)] \cdot 8\text{MeOH}$  of a zeolite structure because of the highly extensive coordination ability of the unit.<sup>135b</sup> Because of the zeolitic crystal structure, the crystal of adduct  $[\text{K}_4(\text{LH}_4)] \cdot 8\text{MeOH}$  gradually lost methanol to give eventually methanol-free apohost  $[\text{K}_4(\text{LH}_4)]$  when exposed to air. Surprisingly, the apohost could again absorb organic

Scheme 41. Synthesis of  $70$ - $\text{Zn}^{2+}$ -tacn Complex

## Scheme 42. Formation of a Lanthanide Wheel



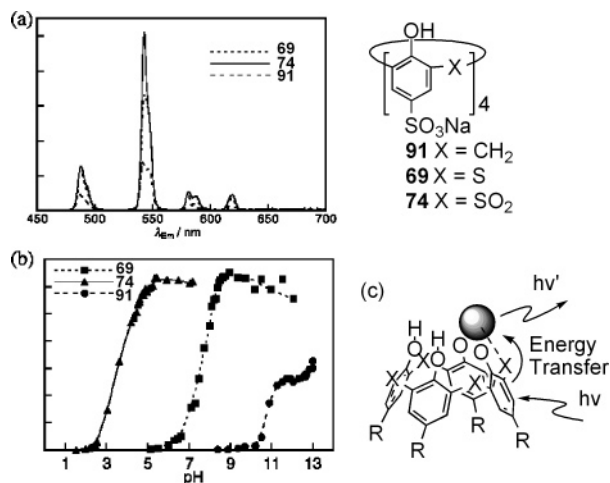
guest molecules such as methanol and benzene when kept in the vapor of the guest. Upon binding with methanol as the guest molecule, the apohost returned to the original structure.

## 4.3.2. 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. Therefore, efforts to develop effective ligands have been continuing to further improve the luminescent ability. Considering that the calixarenes are a potential ligand of lanthanoid metals, the authors compared **69** and **74** with methylene-bridged **91** in terms of the complexation ability with  $\text{Tb}^{3+}$  and then energy-transfer luminescent capability of the resulting complexes.<sup>58</sup> It was found that **69** as well as **74** are superior to **91** in both complexation ability toward  $\text{Tb}^{3+}$  and luminescent strength of the complex, with **74** giving somewhat better results than **69** (Figure 12). Thus, it was shown that **74** is a practical reagent for high-sensitivity detection of  $\text{Tb}^{3+}$  in aqueous solution (detection limit of 37 ppt).<sup>136</sup>

## 4.3.3. Peroxidase-like Catalysis

Odo et al. investigated the peroxidase-like catalytic activity of ion exchangers modified with some metal complexes of thiacalix[4]arenetetrasulfonate ( $\text{M-TCAS}$ ,  $\text{M} = \text{Fe}^{3+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ , and  $\text{Ni}^{2+}$ ).<sup>137</sup> The ion-exchanger modified with  $\text{Fe}^{3+}$ -**69** showed the highest catalytic activity among the metal complexes tested. The activity of this catalyst was then used for determination of hydrogen peroxide, quantitative determination of which is a subject of particular importance in the field of chemistry and food chemistry. Thus, determination of  $\text{H}_2\text{O}_2$  was carried out by measuring the fluorescence intensity of a fluorescent substrate



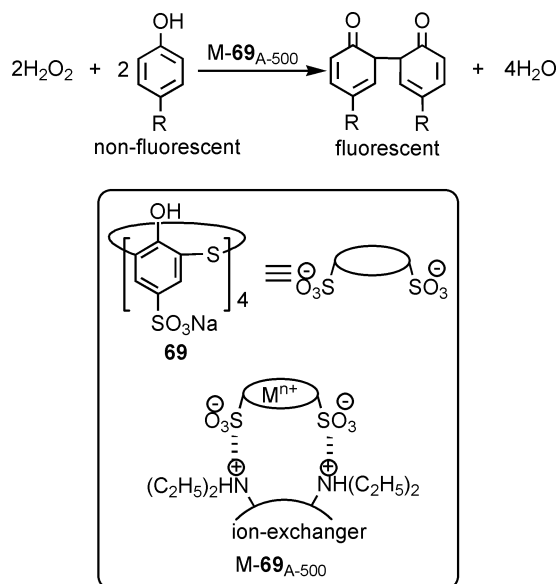
**Figure 12.** Emission spectra of  $\text{Tb}^{3+}$  complexes with calix[4]arenes **69**, **74**, and **91**(a), effect of pH on the luminescence intensity (b), and schematic mechanism for energy-transfer luminescence of  $\text{Tb}^{3+}$  complex (c). [**69**, **74**, or **91**] $_{\text{Total}} = 4.0 \times 10^{-6} \text{ mol dm}^{-3}$ , [ $\text{Tb}^{3+}$ ] $_{\text{Total}} = 2.0 \times 10^{-7} \text{ mol dm}^{-3}$ , [buffer] =  $1.0 \times 10^{-3} \text{ mol dm}^{-3}$ . (a)  $\lambda_{\text{Ex}} = 314$  ( $\text{Tb}^{3+}$ -**69**), 330 ( $\text{Tb}^{3+}$ -**74**), and 290 nm ( $\text{Tb}^{3+}$ -**91**). The pHs are 9.7 ( $\text{Tb}^{3+}$ -**69**), 6.5 ( $\text{Tb}^{3+}$ -**74**), and 12.0 ( $\text{Tb}^{3+}$ -**91**). (b)  $\lambda_{\text{Ex}} = 261$  ( $\text{Tb}^{3+}$ -**69**), 330 ( $\text{Tb}^{3+}$ -**74**), and 263 nm ( $\text{Tb}^{3+}$ -**91**).  $\lambda_{\text{Em}} = 543$  nm.

produced through an oxidative reaction of *p*-substituted phenol by the ion exchanger modified with  $\text{Fe}^{3+}$ -**69** (Scheme 43). The calibration curve of this method was linear over a concentration range from 0.1 to 5.0  $\mu\text{g}$  of  $\text{H}_2\text{O}_2$  in a 10 mL of sample solution. Furthermore, this method was applied to the spectrofluorometric determination of uric acid and glucose.<sup>137e</sup>

#### 4.3.4. Catalyst for Organic Synthesis

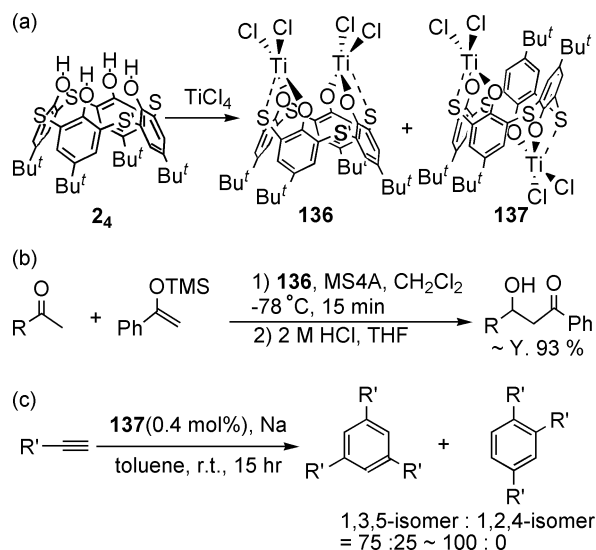
As mentioned above, thiacalixarenes have a characteristic ability to form stable polynuclear metal complexes by virtue of the many ligation sites. The authors then studied the synthesis of metal complexes which are useful for synthetic organic chemistry. Treatment of **24** with  $\text{TiCl}_4$  afforded two binuclear metal complexes, one of which was subjected to

#### Scheme 43. Detection of Hydrogen Peroxide Using Ion-Exchanger Modified Metal Complexes of **69** as Peroxidase-like Catalyst



X-ray crystallographic analysis to show that the calixarene ligand adopted a cone conformation **136**, forcing the two metal centers to reside in close vicinity with a syn arrangement with respect to the mean plane defined by the macrocycle (Scheme 44a).<sup>138</sup> The other one was assigned to be an anti dinuclear titanium(IV) complex **137** based on  $^1\text{H}$  NMR spectroscopy. Syn complex **136** showed high catalytic activity in the Mukaiyama–aldol reaction of aromatic aldehydes with silyl enol ethers, suggesting the double-activation ability of the bidentate Lewis acid toward the aldehydes (Scheme 44b). On the other hand, anti complex **137** was found to be an effective catalyst for cyclotrimerization of terminal alkynes, preferentially giving 1,3,5-trisubstituted benzenes (Scheme 44c).<sup>139</sup> These functions were rationalized in terms of the steric effect of the thiacalixarene skeleton and coordination of the bridging sulfur atom to the titanium center.

#### Scheme 44. Synthesis of Titanium Complexes of **24** (a), the Mukaiyama Aldol Reaction Using **136**, and Regioselective [2 + 2] Cycloaddition of Terminal Alkynes Using **137** (c)



These examples clearly show that thiacalixarenes are a very hopeful candidate for obtaining high-performance catalysts for organic transformation, and studies in this area are now in progress in the authors' group.

## 5. Conclusion

Since the discovery of a practical method for the synthesis of sulfur-bridged calixarenes, studies on their modification and development of the functions are now vividly progressing. These new members of the calix family are open to oxidation of the bridging sulfur moiety and chelation-assisted  $\text{S}_{\text{N}}\text{Ar}$  substitution of the phenolic hydroxy groups in addition to the common transformations applicable to the 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 development of a wide range of functional materials. In other words, thiacalixarenes are novel host molecules having almost boundless potential to be developed.

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