Chemistry of Thiacalixarenes

Pavel Lhoták[a]

Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday

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Thiacalixarenes — new members of the calixarene family — are very promising molecules with many potential applications in supramolecular chemistry. The presence of four sulfur atoms in the place of methylene groups imparts many novel features and properties to these molecules. This review deals with the chemistry of thiacalixarenes, and by comparison with "classical" calixarenes, emphasizes their differences in reactivity, unusual conformational preferences and modified complexation abilities.

Contents

1. Introduction

Thiacalixarenes **1** have recently emerged as new members of the calixarene family,[1] and from the beginning they have attracted considerable interest in the broad field of supramolecular chemistry.[2] The presence of sulfur atoms in place of the usual CH_2 bridges makes thiacalix[4]arenes very interesting molecules, with many features that are not present in the chemistry of "classical" calixarenes. Until recently, the employment of thiacalix[4]arenes as receptors, building blocks, and molecular scaffolds (platforms) in supramolecular chemistry — applications which are well-explored in the chemistry of classical calixarenes — was restricted by the lack of knowledge about these compounds and the absence of any general methods for their derivatization. As research continues, it is now obvious that these compounds possess some very uncommon features, different conformational preferences, and special complexation properties, and thus have many potential applications.

Pavel Lhoták was born on April 5, 1963, in Pilsen, Czech Republic. He studied organic chemistry at the Prague Institute of Chemical Technology (MS degree in 1986), where, in 1991, he obtained his doctorate (on the "Synthesis and Study of New Organic Luminophores") under the supervision of Professor Kuthan. From 1994 to 1996 he spent two years on a postdoctoral stay with Prof. Seiji Shinkai (Kyushu University, Fukuoka, Japan). After coming back to Prague he became an Assistant Professor and since 2001 (after his habilitation) he has been working as an Associate Professor in the Department of Organic Chemistry, PICT. In 1997 he was awarded the "Alfred Bader Prize", which is given by the Czech Chemical Society and the Alfred Bader Foundation to young scientists under 35 years. His research interests include synthetic organic chemistry, supramolecular chemistry, especially chemistry of calixarenes and noncovalent interactions.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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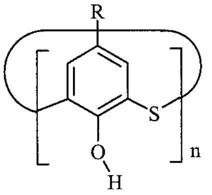

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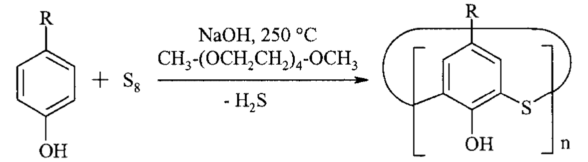


	2	**3**	**4**	**5**	**6**	**7**	**8**
n	4	5	6	8	4	4	4
R	*t*Bu	*t*Bu	*t*Bu	*t*Bu	1,1,3,3-tetramethylbutyl	1-adamantyl	phenyl

Scheme 1. Direct synthesis of thiacalix[4]arenes

2. Nomenclature of Thiacalixarenes

The official nomenclature used in Chemical Abstracts is clearly unsuitable for standard writing and discussion of these compounds. For example, the parent thiacalix[4]arene (**1**, $n = 4$, R = H) has the somewhat cumbersome name 2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetrol. Therefore, not surprisingly, the well-established nomenclature, numbering, and rules for "classical" calixarenes[1] have also been accepted for the thiacalixarene family. For example, the most common thiacalixarene (containing four phenolic rings) is considered to be the calix[4]arene which is substituted in positions 2, 8, 14, and 20 by four sulfur atoms, namely 2,8,14,20-tetrathiacalix[4]arene-25, 26, 27, 28-tetraol, or more simply thiacalix[4]arene (Figure 1).

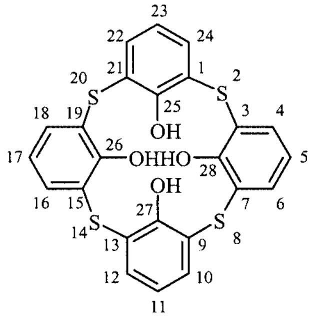


Figure 1. Numbering of thiacalix[4]arene

Consequently, the representation of conformational isomers is the same as in the calix[4]arene series (Figure 2).

3. Synthesis of Thiacalixarenes

As shown by Miyano,[3] the parent *p-tert*-butylthiacalix[4]arene **2** is easily prepared by the reaction of *p-tert*-butylphenol with elemental sulfur and NaOH in tetraethylene glycol dimethyl ether (Scheme 1) with the concomitant removal of H_2S. This reaction is a one-step, one-pot procedure that can be carried out on a large scale. Moreover, purification of the product can be accomplished using only simple precipitation and/or crystallization steps, leading to **2** in good yields (about 50 %). A similar procedure has been used for the preparation of the corresponding *tert*-octyl derivative **6**,[4] but unfortunately the yield of this compound was much lower (14 %). Very recently, thiacalix[4]arenes **7** and **8** were prepared in 20−28 % yields under similar reaction conditions, starting from *p*-(1-adamantyl)phenol[5] and biphenyl-4-ol,[6] respectively. Whereas four-membered thiacalixarenes are now accessible in multi-gram amounts, the higher thiacalixarenes **3** and **4** have only been isolated as by-products (trace amounts and 0.03 %, respectively) from a direct condensation procedure.[7]

Another approach to the synthesis of thiacalixarene derivatives is based on a stepwise procedure that could be described as non-convergent strategy.[1] This method enables the preparation of compounds possessing both -CH_2- and -S- junctions.[8] Although the individual steps usually proceed quite well, the overall yields of the reactions, outlined in Scheme 2, are very low and the whole process is rather complicated and tedious. On the other hand, this linear stepwise approach has produced derivatives **9**−**11**, which are unobtainable by direct condensation methods.

Very recently, a similar synthetic strategy based on the sulfur-bridged linear dimer **12** was described.[9] The starting compound can be prepared in high yield (75 %) in a one-step procedure from *p-tert*-butylphenol. Cyclization is effected by reaction with elemental sulfur under basic conditions (NaOH) in diphenyl ether. This procedure leads to the even-membered thiacalixarenes **2**, **4**, and **5** in reasonable yields (83 %, 5.3 %, and 4.3 %, respectively, depending on the reaction conditions and the ratios of reactants).

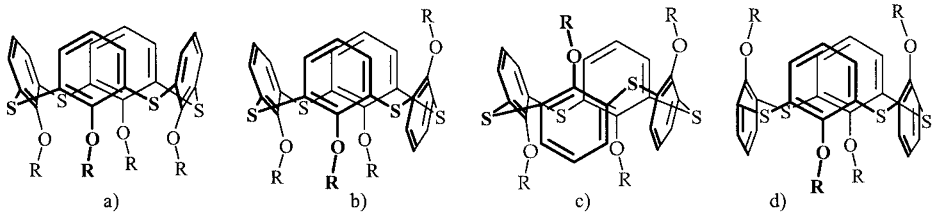
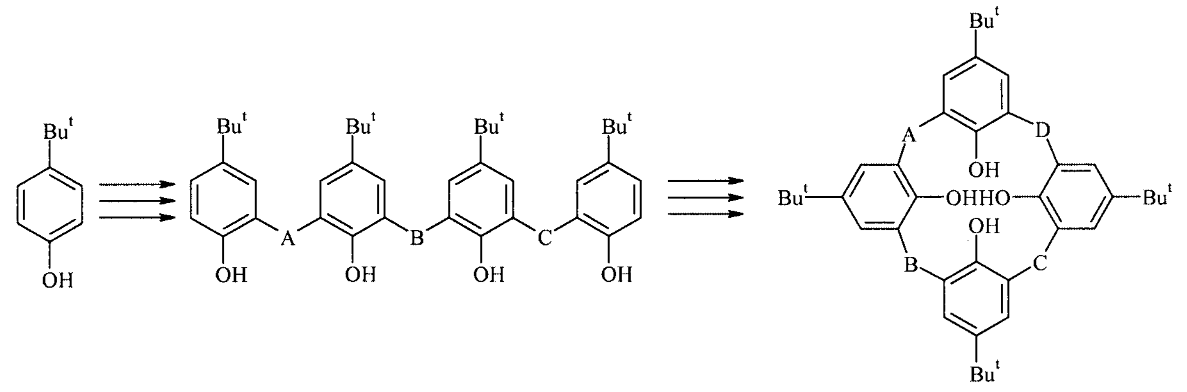
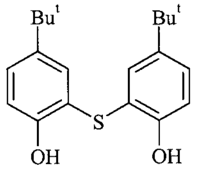


Figure 2. The four basic conformations of thiacalix[4]arenes: a) *cone*, b) *partial cone*, c) *1,2-alternate*, and d) *1,3-alternate*



	9	10a	10b	11
A	S	S	S	S
B	CH_2	S	CH_2	S
C	CH_2	CH_2	S	S
D	CH_2	CH_2	CH_2	CH_2

Scheme 2. Linear stepwise synthesis of thiacalix[4]arenes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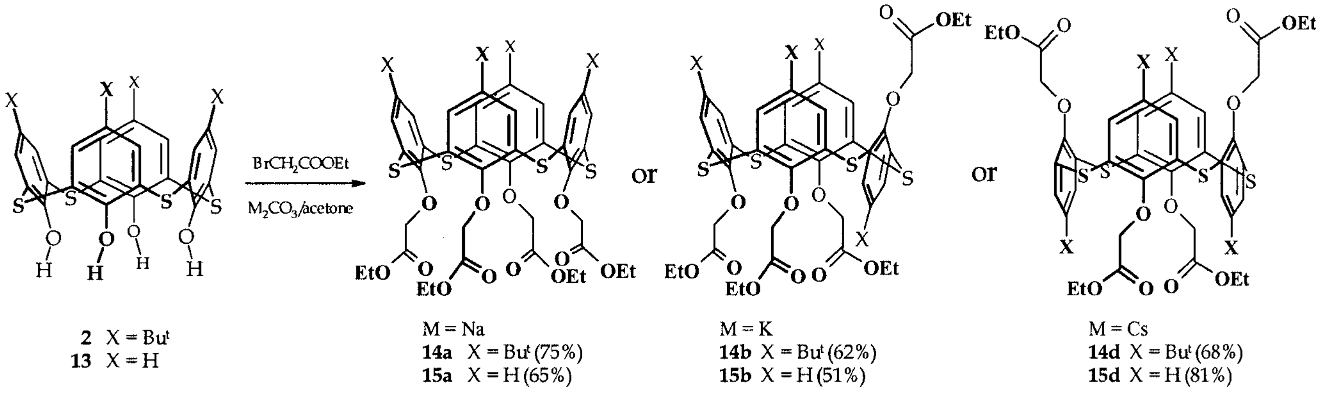
4. Reactions of Thiacalixarenes

4.1. Lower Rim Derivatization — Shaping of the Molecular Skeleton

Tetraalkylation of the lower rim (the phenol functions) is a standard method by which to modify the calix[4]arene skeleton.[1] Accordingly, several groups have studied[10,11,12] the alkylation of thiacalixarenes **2** and **13** with ethyl bromoacetate using the acetone/M_2CO_3 reaction system (M = Li, Na, K, and Cs). This reaction (Scheme 3) exhibits a surprisingly pronounced template effect, and leads to high yields of the corresponding tetraacetates **14** and **15** in various conformations (*cone*, *partial cone*, *1,3-alternate*). The products are easily accessible in multi-gram amounts without chromatographic purification. Very recently, the distribution of conformers from the alkylation reaction of the thiacalixarene **2** with α-bromoacetophenone was studied in detail.[13]

Tetraacetates **14** and **15**, which have precisely defined three-dimensional structures, are valuable building blocks for the construction of more sophisticated thiacalixarene systems. However, they are not compatible with common organometallic reagents (due to the presence of the ester groups), which partly hinders their utilization in subsequent chemical transformations.

As a part of our ongoing research into the derivatization of thiacalix[4]arene, we carried out a systematic study[14] into the tetraalkylation of this compound using simple alkyl halides which are bulky enough to immobilize the products in specific conformations that are isolable at room temperature. The conformer distribution of products **16** and **17** indicates that the behaviour of thiacalixarenes **2** and **13** is significantly different from classical calix[4]arenes. Theoretically, four basic conformations are accessible for thiacalix[4]arene (Figure 2). In the classical calix[4]arene series, method A (Table 1) yields a mixture of *1,3-alternate* and *partial cone* conformations in various ratios, depending on the alkylating agent (*partial cone* being always the major



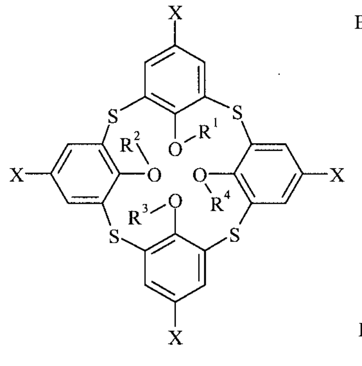
Scheme 3. Alkylation of thiacalix[4]arenes with ethyl bromoacetate

product). On the other hand, method B is known to yield preferentially the *cone* conformation.[1] The results obtained in the thiacalixarene series are summarized in Table 1.

The alkylation of **2**, carried out by Method A, leads to the corresponding *1,3-alternate* **16d** accompanied by small amounts of **16b** and **16c**. Similarly, **13** yields *1,3-alternate* **17d** and *partial cone* **17b**. Hence, this method is suitable for large-scale (multi-gram) preparation of the *1,3-alternate* conformers **16d** and **17d**, which can be obtained in high yields (about 60 %) by simple precipitation from the crude reaction mixture with $CHCl_3$/methanol.[15] Surprisingly, using Method B, **2** did not give the expected *cone* conformer **16a**. After two days, almost one half of the starting material remained unchanged and only small amounts of **16b**, **16c**, and **16d** were isolated from the reaction mixture. The same reaction with **13** gave the desired *cone* conformer **17a** (in only 19 % yield) accompanied by the *partial cone* derivative **17b**. Substitution of NaH with KH (Method C) does not bring any improvement in the yield of the *cone* conformers **16a** (0 %

Table 1. Alkylation of thiacalix[4]arenes **2** and **13** with PrI; A: PrI/K_2CO_3 in refluxing acetone, B: PrI/NaH in DMF at room temperature, and C: PrI/KH in DMF at room temperature

Compound	Alkylation method	Isolated yields of **16** and **17** (%) **a** (*cone*)	**b** (*partial cone*)	**c** (*1,2-alternate*)	**d** (*1,3-alternate*)
2	A	–	5	9	66
2	B	–	7	9	12
2	C	–	–	21	50
13	A	–	17	–	61
13	B	19	16	–	–
13	C	2	25	–	10



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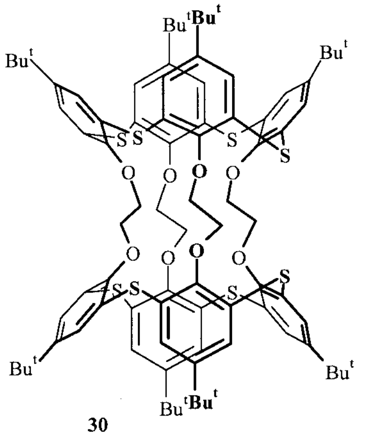

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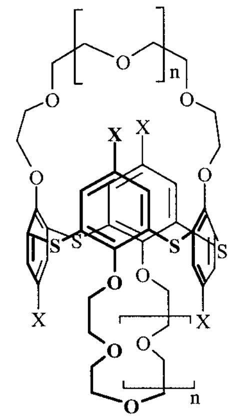
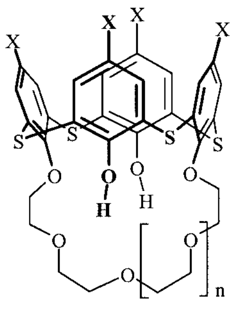
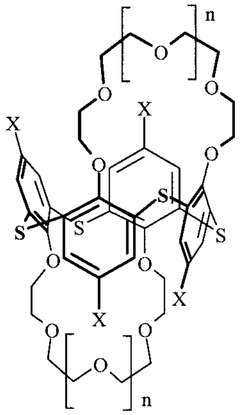


29a, X = H, Bu^t, n = 1, 2



29b, X = H, Bu^t, n = 1, 2



29c, X = H, Bu^t, n = 1, 2

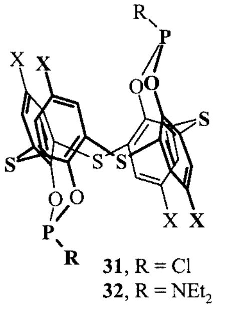
	16	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
X	*t*Bu	H	*t*Bu	H	*t*Bu	H	*t*Bu	H	H	*t*Bu	H	H	H
R^1	*n*Pr	*n*Pr	Me	Me	Et	Et	*n*Bu	*n*Bu	$-CH_2CH_2COCH_3$	$-CH_2COCH_3$	H	H	H
R^2	*n*Pr	*n*Pr	Me	Me	Et	Et	*n*Bu	*n*Bu	$-CH_2CH_2COCH_3$	$-CH_2COCH_3$	H	Me	Me
R^3	*n*Pr	*n*Pr	Me	Me	Et	Et	*n*Bu	*n*Bu	$-CH_2CH_2COCH_3$	$-CH_2COCH_3$	H	H	Me
R^4	*n*Pr	*n*Pr	Me	Me	Et	Et	*n*Bu	*n*Bu	$-CH_2CH_2COCH_3$	$-CH_2COCH_3$	Me	Me	Me

yield) and **17a** (2 %). However, the *1,2-alternate* conformer (the least accessible in the classical calix[4]arene series) **16c** formed in unexpectedly high yield (21 %).

It is surprising that neither Method B nor C is suitable for the synthesis of the *cone* conformer. By comparision, using Method B, calix[4]arene gives the *cone* conformer in 82 % (for X = H), and 88 % yield (for X = *t*Bu). Consequently, the *cone* conformers in the thiacalixarene series bearing four alkyl groups on the lower rim have so far been hardly available for derivatization.[16] This is another example of how the conformational behaviour of thiacalix[4]arenes differs from that of classical calixarenes.

Alkylation of the parent calixarenes **2** and **13** using the RI or RBr/M_2CO_3 system (M = Na, K, Cs) in acetone or acetonitrile generally gives the tetraalkylated products in good yields. For the systematic study of the conformational behaviour of thiacalixarenes, a series of tetraalkylated and partially alkylated compounds **18**−**23** and **26**−**28** were prepared by this method.[16,17] The derivative **24** was synthesized[18] by the alkylation of **13** with the corresponding tosylate, and **25** was obtained by using chloroacetone as the alkylating agent.[19] Very recently, more sophisticated systems based on thiacalix[4]arene have been reported. Thiacalix[4]tube **30** was prepared from the starting tetraacetate **14a** by reduction and subsequent conversion into the tetratosylate. This precursor was treated with thiacalixarene **2** to give the desired product **30** in 10 % yield.[20] Similarly, thiacalixcrowns of general formula **29a** were synthesized by direct alkylation of **2** and **13** with tetra- and pentaethylene glycol ditosylates[21,22] or diiodides.[23] The alkali metal cation complexation abilities of these compounds were studied by dynamic ^1H NMR experiments,[24] ESI-MS[20] or by extraction experiments.[21,23] Similar dialkylation methods can be used for the synthesis of monobridged compounds **29b**.[25] Bridging of **2** with ethylene glycol ditosylates was recently studied in detail.[26] It was found that (depending on the length and the nature of metal carbonate used) either monocrowns **29b** or biscrowns **29a** and **29c** could be obtained in acceptable yields. These compounds are excellent chelators of the Ag^+ cation.

An alternative route to 25,27-diethers is the Mitsunobu reaction.[27] The reaction of **2** with the appropriate alcohol in the presence of triphenylphosphane and diethyl azodicarboxylate leads regioselectively to the distally dialkylated derivatives. The same reaction system was also used for the preparation of the corresponding crown derivatives **29a** and **29b**.[28]



31, R = Cl
32, R = NEt_2

So far, acylation of the lower rim (or more generally ester formation) has been quite a rare procedure in thiacalixarene chemistry. Among the few examples, we should mention the reaction of dansyl chloride with thiacalixarene **2**[29] or its partly de-*tert*-butylated analogues,[30] leading to water-soluble dansyl-modified thiacalix[4]arenes. These compounds were tested for their ability as fluorescent detectors of metals in aqueous solutions. Another example of ester formation is the phosphorylation of **2** with PCl_3 in boiling toluene in the presence of NEt_3, to give the double-bridged phosphonous diester **31** in 68 % yield. Subsequent condensation with diethylamine leads to a high yield of the diester amide **32**. It is noteworthy that the above esterification preferentially gives the *1,2-alternate* conformation, which is the least accessible in classical calixarene chemistry.[31,32] Accordingly, the reaction of **2** and **13** with isonicotinoyl chloride in pyridine gives the *1,2-alternate* compounds as the main products.[33] Analogously, treatment of **2** with $TiCl_4$ in dichloromethane led to a mixture of two novel dinuclear titanium(IV) complexes [Ti_2**2**Cl_4] in the *1,2-alternate* and *cone* conformations. These were used as bidentate Lewis acid catalysts in the Mukaiyama-aldol reaction.[34]

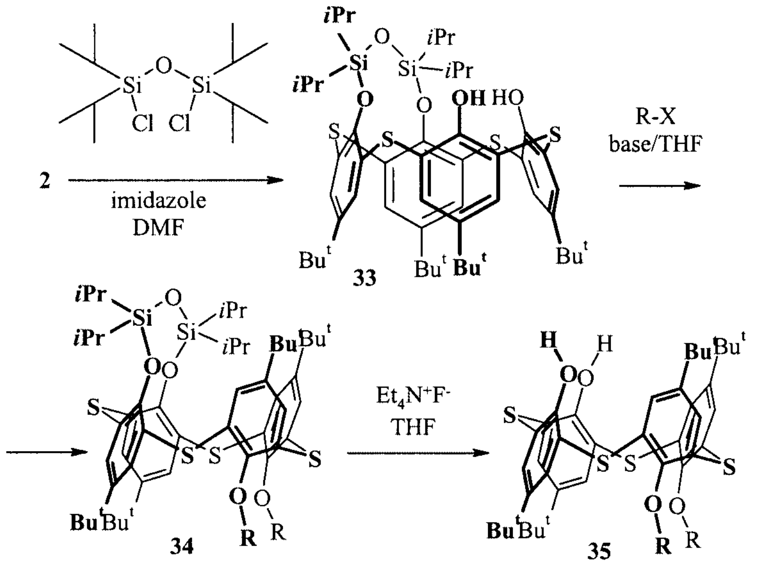
A similar strategy has been used[35] for the synthesis of proximally dialkylated thiacalixarenes **35** (Scheme 4). Treatment of **2** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane provides the proximally disiloxane-bridged compound **33** in 92 % yield. Reaction of this *O,O′*-disiloxane **33** with an alkyl halide in THF in the presence of a base (Cs_2CO_3 or *t*BuOK) gave the corresponding proximally dialkylated products **34** in excellent yields. Desilylation of this intermediate by treatment with tetrabutylammonium fluoride in THF yields the corresponding 25,26-dialkylated thiacalixarenes **35** quantitatively. The analogous 25,26-bridged derivatives were obtained using difunctional alkylating agents.[36]

To enhance the complexation ability of the thiacalixarenes, the lower rim hydroxyls were transformed into SH groups.[37] The acylation of **2** with *N,N*-dimethylcarbamoyl chloride produced the corresponding *O*-thiocarbamoyl derivative which was thermally converted into the *S*-carbamoyl derivative (the Newman−Kwart rearrangement). Deprotection with hydrazine hydrate gave the tetramercaptothiacalix[4]arene **36** in good yield.

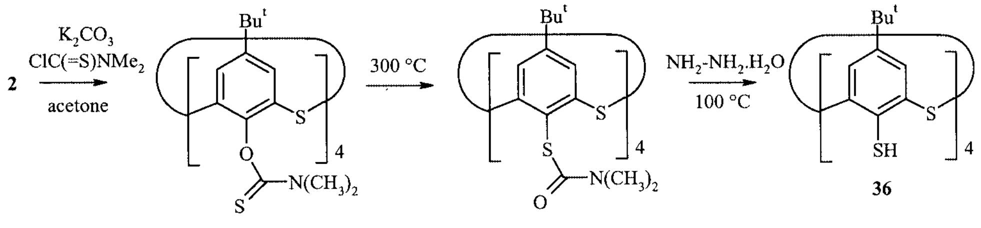
In contrast to the parent thiacalixarene **2**, the mercapto derivative **36** adopts the *1,3-alternate* conformation in the solid state.[38] (Scheme 5) This compound was transformed into the doubly bridged derivative by alkylation with 1,2-dibromoethane. In this case, X-ray single crystal diffraction proved the *1,2-alternate* conformation of the bridged product.[39]

During our attempts at derivatizing thiacalixarenes, we found that bis(carboxymethyloxy) derivatives **38a** and **38b** undergo an unprecedented intramolecular cyclization to yield the nine-membered lactone compounds **40a** and **40b**, respectively (Scheme 6).[40]

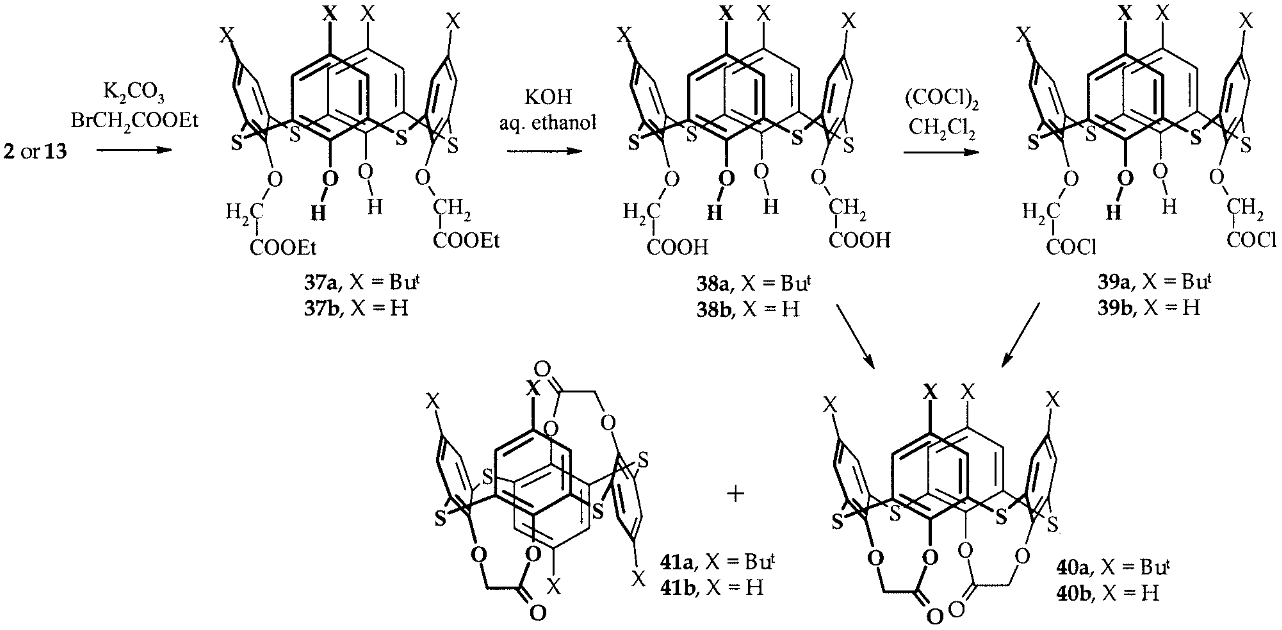
Thus, the treatment of a dichloromethane solution of **38a** with phosphorus pentoxide leads to a mixture of **40a** (66 %) and **41a** (10 %). The same type of compounds can be



Scheme 4. Proximal dialkylation of thiacalix[4]arene



Scheme 5. Preparation of tetramercaptothiacalix[4]arene **36**



Scheme 6. Synthesis of lactone derivatives of thiacalix[4]arene.

prepared in high yield from the corresponding acid chlorides **39a** or **39b** in the presence of triethylamine. For instance, stirring **39a** (prepared from **38a** by reaction with oxalyl chloride) with six equivalents of triethylamine in THF at room temperature yields **40a** in 69 % yield. The ^{1}H NMR spectrum of compound **40a** indicates that the molecule has C_2 symmetry, since it exhibits two singlets for the *t*Bu groups (δ = 0.88 and 1.40 ppm) and four doublets with a characteristic *meta* coupling (J = 2.2−2.7 Hz) in the aromatic part of spectrum. The inherent chirality of the new compounds was demonstrated by their ability to be separated on a chiral HPLC column.

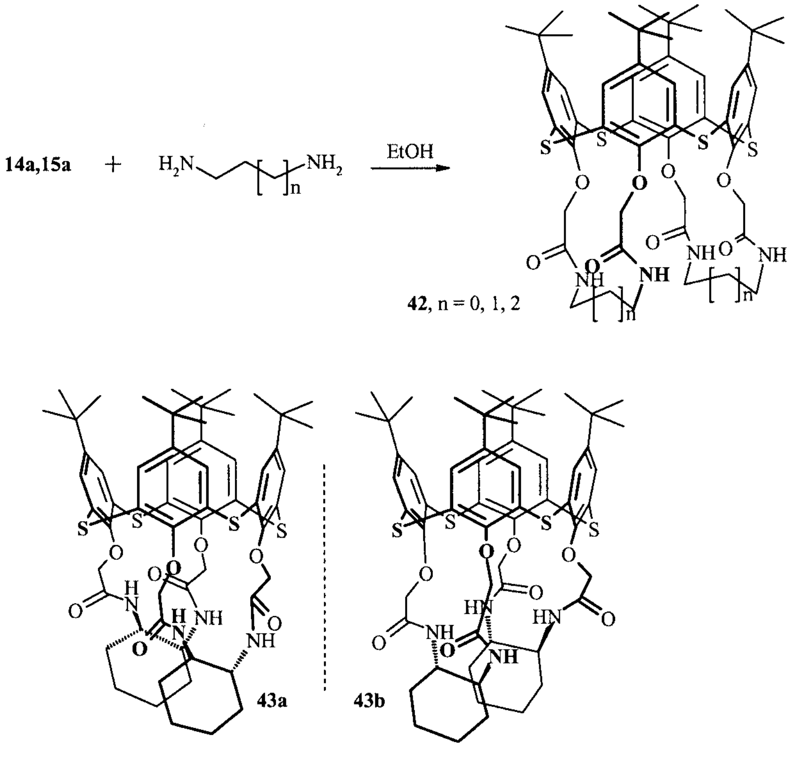
The bis(carboxymethyloxy) derivatives **39a** and **39b** adopt a *cone* conformation both in solution (as proved by NMR) and in the solid state (as shown by X-ray crystallography). Therefore, the formation of the *1,2-alternate* product **41a** is rather surprising and requires rotation of the -CH_2COOH substituent through the cavity. The formation of lactones of type **40** and **41** was only observed for thiacalix[4]arene derivatives; the same reactions, carried out with classical calix[4]arene derivatives, never give cyclic products of this type. Thiacalixarenes are probably better disposed for intramolecular cyclization because of their larger ring size.

Novel types of (lower rim) proximally bridged *p-tert*-butylthiacalix[4]arenes **42** have been recently prepared by direct aminolysis (Scheme 7) of the starting *cone* tetraacetates **14a** and **15a** with aliphatic α,ω-diamines.[41] The structures of the corresponding products were proved by X-ray analysis and display a cyclic array of binding sites (-NHCO-), potentially suitable for the complexation of selected substrates by means of hydrogen bonds. Aminolysis with chiral amines [(1*R*,2*R*)- or (1*S*,2*S*)-1,2-diaminocyclohexanes] leads to the isolation of chiral bridged products **43a** and **43b**.

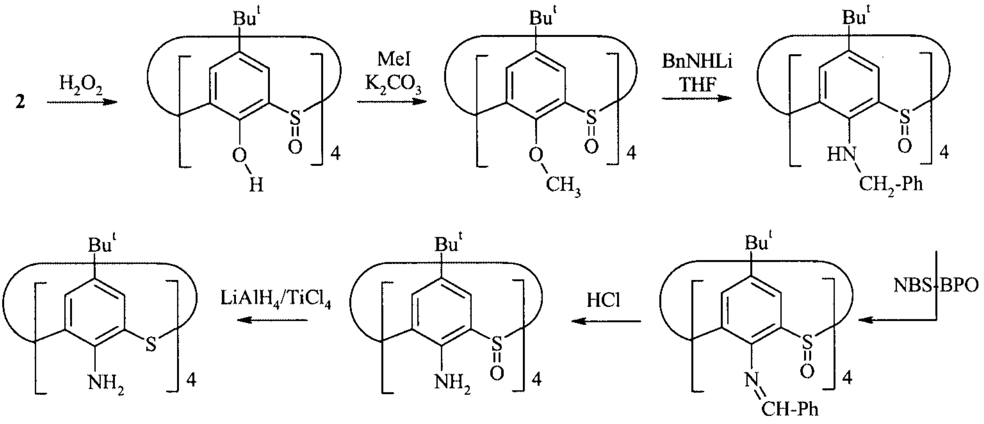
The substitution of the lower rim hydroxy groups with amino groups is a very difficult task in the classical calixarene series; hence only partly "aminated" calix[4]arenes have been reported.[42] However, an elegant strategy leading to fully aminated thiacalix[4]arenes has very recently appeared in the literature.[43] The route (Scheme 8) starts with preparation of the sulfoxide derivative of **2** (for more details on the oxidation of thiacalixarenes see later), which is then alkylated with methyl iodide. The key step of the synthesis is chelation-assisted nucleophilic aromatic substitution, in which the methoxy groups of the aromatic subunits are displaced by a nitrogen nucleophile (lithium benzylamide). The final thiacalixarene **44**, which possesses four amino groups on the lower rim, is then obtained by dehydrogenation, hydrolysis, and reduction. This compound proved to be highly specific for the extraction[44] of Au^{III} and Pd^{II} [45] ions, amongst the 40 transition metal ions tested.

4.2. Conformational Studies

Not surprisingly, the introduction of four sulfur atoms into the calix[4]arene skeleton induces considerable changes in the conformational behaviour of the thiacalixarenes. Because the cavity of thiacalix[4]arene is larger than classical calix[4]arenes, we were interested in the restrictions that govern the conformational behaviour of these compounds. To gain deeper insight into their conformational preferences, lower rim peralkylated and partly alkylated thiacalix[4]arenes were studied using a combination of NMR spectroscopy and X-ray crystallography. In general, the conformational analysis of thiacalix[4]arene derivatives is not a trivial task due to the absence of CH_2 bridges, the signals of which are used in classical calix[4]arene stereochemistry. Therefore, the assignment of conformers almost always requires more sophisticated methods, such as COSY, NOESY, EXSY and HMQC, amongst others.



Scheme 7. Aminolysis of thiacalix[4]arene tetraacetates



Scheme 8. Lower rim amination of the thiacalix[4]arene **2** — the sulfoxide pathway

Whereas the parent thiacalixarenes **2** and **13** adopt the *cone* conformation both in solution and in the solid state, the ^{1}H NMR spectrum of **21** reveals the presence of all four possible conformers in $Cl_2CDCDCl_2$ solution at room temperature.[46] 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 tetraethoxycalix[4]arene, which is mobile only at elevated temperatures (above about 130 °C) and possesses the corresponding equilibrium ratio 7:47:44:3.[47] This result highlights the different conformational preferences of thiacalixarenes. Some interesting behaviour was observed in the case of the *cone* conformer of **21** (Figure 3). The aromatic signals at δ = 6.60 and 6.95 ppm, indicating an average C_{4v} symmetry at 368 K, gradually broaden at lower temperatures, and almost disappear at 298 K. Finally, they reappear at 239 K with doubled multiplicity, indicating C_{2v} symmetry. This demonstrates the presence of an additional conformational movement with a free energy barrier only slightly lower than for a single aryl ring inversion. It is well-known[48] that the C_{4v} symmetry commonly observed in ^{1}H NMR spectra of calix[4]arene *cone* conformers is in fact the time-averaged signal of so called *pinched cone* conformations possessing C_{2v} symmetry (Scheme 9).

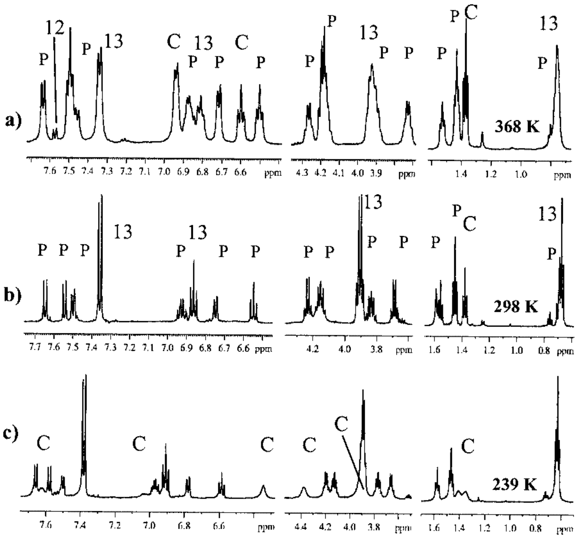
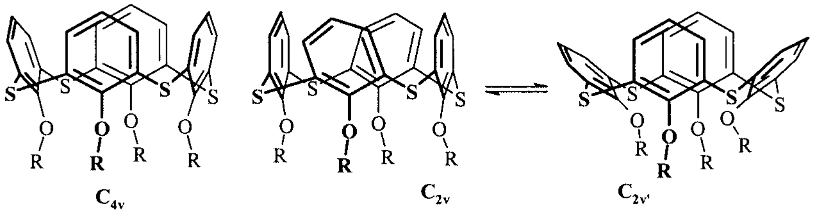


Figure 3. Temperature-dependent ^{1}H NMR spectra of **21** (500 MHz, $Cl_2CDCDCl_2$); P = *partial cone*, C = *cone*, 12 = *1,2-alternate*, 13 = *1,3-alternate*

In classical calix[4]arene derivatives, this *pinched cone* − *pinched cone* interconversion is usually unobservable by ^{1}H NMR spectroscopy, due to the very low coalescence temperatures. However, the introduction of sulfur atoms leads surprisingly to a dramatic change in conformational behaviour. The temperature-dependent ^{1}H NMR spectra of **21** were used for the quantitative determination[49] of the activation free energies $\Delta G^{\#}$ (Figure 4). The thermodynamic parameters of ring inversion in thiacalixarene **21** were found to be similar to those of the classical derivatives.[1] However, the barrier for the *pinched cone*−*pinched cone* interconversion (12.5 kcal mol^{-1}) is notably higher.

The dynamics and thermodynamics of *pinched cone* interconversion equilibria in peralkylated thiacalix[4]arenes have also been studied by Hartree−Fock and Density Functional methods in combination with temperature-dependent ^{1}H NMR spectroscopy. Theoretical calculations confirmed patterns observed in the stabilities of these systems, but the absolute values of the energy barriers were lower than found experimentally. The explanation could be related to the solvation of transition states (of C_4 or C_{4v} symmetry). Indeed, it was found that the coalescence temperature of the equilibrium process in **17a** depends on the solvent used for the measurement (Table 2), thus indicating a possible influence of the solvent on the energy of the transition state.[50]

The conformational behaviour of the tetramethoxy derivatives **18** and **19** was studied[51] in the temperature range 183−336 K in $CDCl_3$. The spectrum of **18** acquired at room temperature exhibits time-averaged signals caused by the fast chemical exchange of several conformers. The spectral pattern at lower temperatures is consistent with the presence of *partial cone* and *1,3-alternate* conformers, but unfortunately, extensive signal broadening did not allow us to prove the presence of these conformers by more sophisticated methods.



Scheme 9. *Pinched cone−pinched cone* interconversion of thiacalix[4]arenes

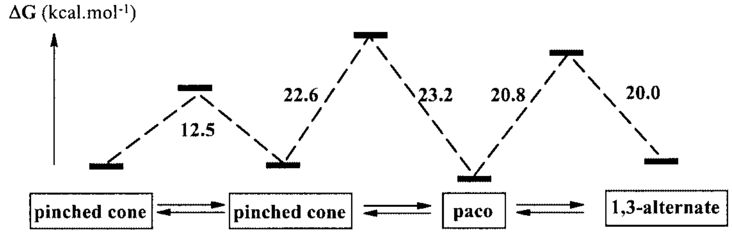


Figure 4. Activation free energies ΔG_0 for the interconversion processes of **2** (in $Cl_2CDCDCl_2$) (paco = *partial cone*)

Table 2. Coalescence temperatures (T_c) and corresponding activation free energies ($\Delta G^{\#}$) for the *pinched cone−pinched cone* interconversion of **17a**

Solvent	T_c/K	$\Delta G^{\#}$/kcal mol^{-1}
$Cl_2CDCDCl_2$	313	13.8
$CDCl_3$	298	13.3
CD_2Cl_2	293	12.9
[D$_7$]DMF	259	11.3
C_6D_5Cl	308	13.6

The temperature-dependent ^1H NMR spectra of **19** show rather complicated conformational dynamics (Figure 5). At 336 K, a simple set of three signals (a broad singlet and triplet in the aromatic region, and a methyl singlet at δ = 3.7 ppm) is observed, due to the fast interconversion of all four conformers. Lowering the temperature (to 220 K) leads to the appearance of new resonances. These can be assigned to the well-separated signals of the *pinched cone* conformations. Small signals due to the interconverting *alternate* and *partial cone* conformers are also visible.

The single-crystal X-ray analysis of conformationally mobile thiacalixarenes showed that the molecules adopt a *1,3-alternate* conformation. It should be noted that opposing phenyl rings are usually far from being coplanar. Thus, the two pairs of opposing aromatic subunits in **20**[15] are distorted, with interplanar angles of 30(3)° and 36(2)°. The square box-shaped cavities of *1,3-alternate* conformers are often packed parallel to each other in the crystal lattice to form beautiful infinite channels. These channels are always empty, but the free space outside can be occupied by solvent molecules. Such an arrangement was found in the cases of **20** and **18**,[52] in which molecules of dichloromethane are regularly spaced in the crystal lattice (Figure 6).

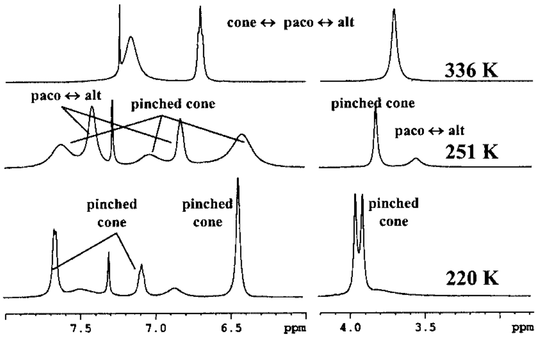


Figure 5. Temperature-dependent ^1H NMR spectra of **19** ($CDCl_3$, 500 MHz) (alt = *1,2-* and *1,3-alternate*, paco = *partial cone*)

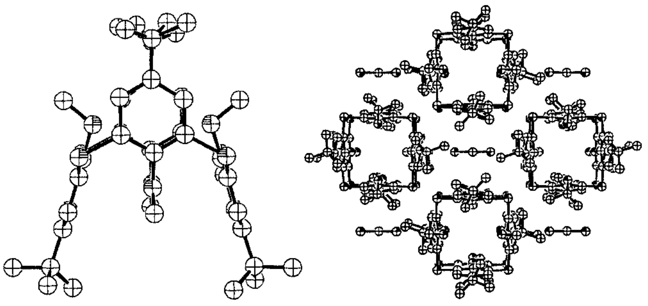


Figure 6. X-ray crystal structure of **18** showing CH_2Cl_2 molecules

X-ray analysis of **19** revealed unprecedented conformational behaviour[51] in the solid state. The unit cell contains 16 molecules of thiacalixarene **19**; 12 molecules adopt the *cone* conformation and the remaining 4 molecules prefer the *1,3-alternate* conformation (Figure 7). To the best of our knowledge, this is the first example of a solid-state structure in which two different calix[4]arene conformations coexist in a crystal lattice. The whole structure is held together by a complex array of CH−π and π−π interactions. The corridor-like structures consisting exclusively of the *cone* conformers (Figure 7, b) are filled with infinite lines of *1,3-alternate* conformers (Figure 7, a). The above phenomenon emphasizes the basic distinction between the

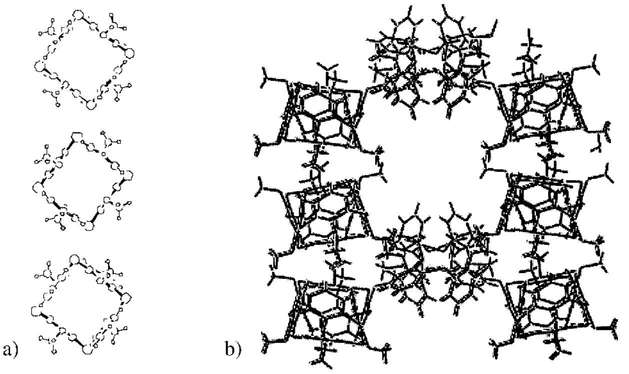


Figure 7. X-ray crystal structure of **19**

conformational behaviour of the thiacalix[4]arenes and classical calixarenes. At the same time, it clearly demonstrates the importance of weak non-covalent interactions (π−π and CH−π) in the solid state conformational preferences of thiacalixarene derivatives.

Another unique example of unusual thiacalixarene behaviour was found in the case of the partly alkylated derivatives. It is known from the chemistry of classical calix[4]arenes that distally dialkylated derivatives always prefer the *cone* conformation in the solid state. Surprisingly, **27** adopts an unusual *1,2-alternate* conformation, which is fixed by two hydrogen bonds (between the neighbouring methoxy and OH groups) on the opposite sites of the main molecular plane. The preference for the *1,2-alternate* conformation in thiacalixarenes seems to be more general. Recently, several other derivatives (namely, unsubstituted thiacalix[4]arenes bearing nitro- or arylazo- groups on the upper rim) were also found[53,54] to adopt this unexpected conformation in solid state. It indicates that the larger cavity of thiacalixarenes leads to a better energy minimization in the *1,2-alternate* conformation rather than the *cone* conformation. Moreover, compound **27** exhibits very interesting molecular packing.[17] The thiacalix[4]arene molecules are arranged along the *x* axis in such a way that they create infinite channels held together by intermolecular π−π interactions between the aromatic parts (upper rims) of the methoxy-substituted rings. The average distance between the two coplanar rings is 3.41 Å (Figure 8, a and b). Whereas the corresponding diethoxy derivative possesses almost exactly the same structural features, dipropoxythiacalix[4]arene prefers the *cone* conformation. In this case, however, the individual molecules form beautiful star-shaped assemblies bound together by a complex array of π−π interactions (Figure 8, c).

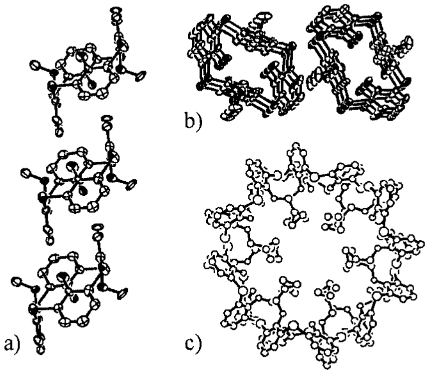


Figure 8. a) and b) X-ray crystal structure of **27**; c) Molecular packing of 25,27-dipropoxythiacalix[4]arene

It is well-known[1] that the introduction of propyl groups (or bulkier groups) onto the lower rim of calix[4]arenes hinders the interconversion of conformers, and consequently, leads to the formation of four stable isomers. However, in contrast to classical calix[4]arenes, the tetrapropoxy derivative **17** was found to be mobile at elevated temperatures. The *1,3-alternate* conformer **17d** (the major isolated product from the direct alkylation of **13** with propyl iodide) approached thermodynamic equilibrium after heating at 120 °C in $Cl_2CDCDCl_2$ solution for four months (Figure 9).[55] All four conformers **17a−d** could be identified in the ^1H NMR spectrum of the resulting mixture. The experimentally measured equilibrium distribution of conformers for **17** (31:58:4:7 = **a**:**b**:**c**:**d**) was, surprisingly, quite different from that for the above-mentioned tetraethoxythiacalixarene **21** (17:55:2:26 = **a**:**b**:**c**:**d** at 303 K). The *1,3-alternate* conformer **17d** is strongly disfavoured whereas the population of the *cone* conformer **17a** is significantly greater than for the ethoxy derivative **21**. The thermal equilibration of **17** reflects the fact that the cavity of thiacalix[4]arene is bigger than for calix[4]arene; the distances between the two distal and the two proximal sulfur atoms are approximately 7.8 Å and 5.5 Å, respectively,[15] whereas the typical distances between the corresponding CH_2 groups in the *1,3-alternate* conformer of calix[4]arene are 7.1 Å and 5.0 Å.

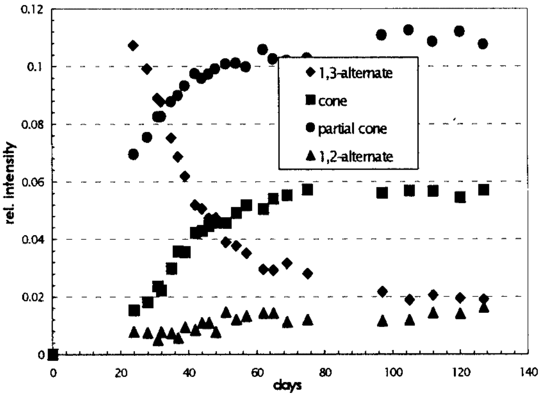
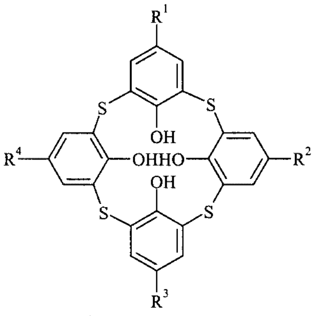


Figure 9. Thermal isomerization of **17d** (120 °C, $Cl_2CDCDCl_2$)

All attempts to achieve thermal equilibration of tetrabutoxythiacalix[4]arene **23** failed; only the starting *1,3-alternate* conformer could be isolated. This shows that the *n*-butyl groups are just bulky enough to prevent rotation of the alkylated phenolic rings through the main annulus of thiacalix[4]arene, at least at temperatures up to 413 K. Similarly, the tetrapropoxy derivative **16d**, bearing *tert*-butyl groups on the upper rim, did not interconvert under similar conditions. The above findings indicate that only the mechanism involving movement of the lower rim substituents through the annulus is possible in the thiacalix[4]arene series.

4.3. Upper Rim Derivatization

Since the thiacalix[4]arene **2** is easily available on a large scale, great attention has been devoted to the introduction of functional groups onto its upper rim. Modifications of the upper rim in the family of classical calixarenes are mainly carried out by two processes: (i) electrophilic substitution in the *para* position, and (ii) direct *ipso*-substitution of *tert*-butyl groups by electrophilic agents. In the thiacalixarene series, the Friedel−Crafts dealkylation of the upper rim substituents[56] is an example of the first approach. The starting material **2** was converted into the fully de-*tert*-butylated compound **13** in 51 % yield using an established procedure from classical calixarene chemistry ($AlCl_3$/phenol/toluene). However, we have found that this procedure sometimes gives very unsatisfying results, especially on a larger scale. To achieve complete removal of the *tert*-butyl groups, a lengthy reflux of the reaction mixture is needed, which seems to lead to partial decomposition of the starting material. Surprisingly, however, the dealkylation can be achieved smoothly at lower temperatures if phenol is not used.[30] This procedure was found to be more suitable for the large-scale preparation of **13**, and generally gives much better results (with yields about 80 %). Regioselective partial dealkylation of **2** was achieved using 7.1−7.4 equivalents of $AlCl_3$ and a shorter reaction time. This procedure leads to a mixture of **45**, **46**, and **47** in 6.5, 20, and 21 % yield, respectively.[30,57]



	13	45	46	47
R1	H	H	H	*t*Bu
R2	H	H	H	*t*Bu
R3	H	H	*t*Bu	*t*Bu
R4	H	*t*Bu	*t*Bu	H

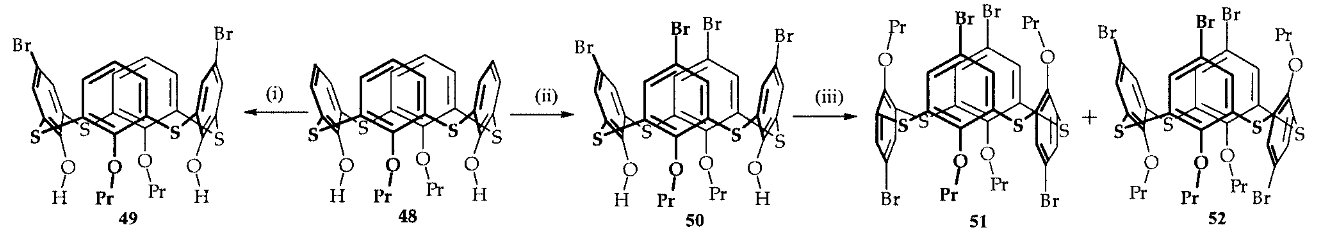
We found that the reactivity of these unsubstituted thiacalixarenes is very different from that of calix[4]arene. To our surprise, all attempts at nitration, halogenation, Friedel−Crafts acylation, and formylation of the tetra-*O*-alkylated thiacalixarenes **17**, **19**, and **21** using procedures known from classical calixarene chemistry[1] failed. Because dialkylated thiacalixarenes are easily accessible, we directed our attention to these compounds; one can envisage that bromination might lead to distally dibrominated derivatives.[58] The bromination of 25,27-dipropoxythiacalix[4]arene **48** was carried out by the addition of 6 equivalents of bromine, leading to the dibromo derivative **49** in 73 % yield (Scheme 10). However, the use of 12 equivalents of bromine under otherwise identical conditions smoothly gave the tetrabromo compound **50** in very high yield (90 %). This derivative **50** can be further alkylated with propyl iodide to give a mixture of the *1,3-alternate* conformer **51** and the *partial cone* conformer **52**. The ratio of these compounds depends on the reagent used (K_2CO_3 or NaH).

On the other hand, the unsubstituted starting thiacalixarene **13** smoothly reacts with *N*-bromosuccinimide in acetone[59,60] to yield the corresponding 5,11,17,23-tetrabromo derivative in 61 % yield. This compound was alkylated with propyl iodide/Cs_2CO_3 in acetone to give **51** (in 80 % yield), which was subsequently coupled to both trimethylsilylacetylene and 4-pentylphenylacetylene, with dichlorobis(triphenylphosphane)palladium(II) as a catalyst. The resulting adducts have the potential to be used in non-linear optical applications.[59]

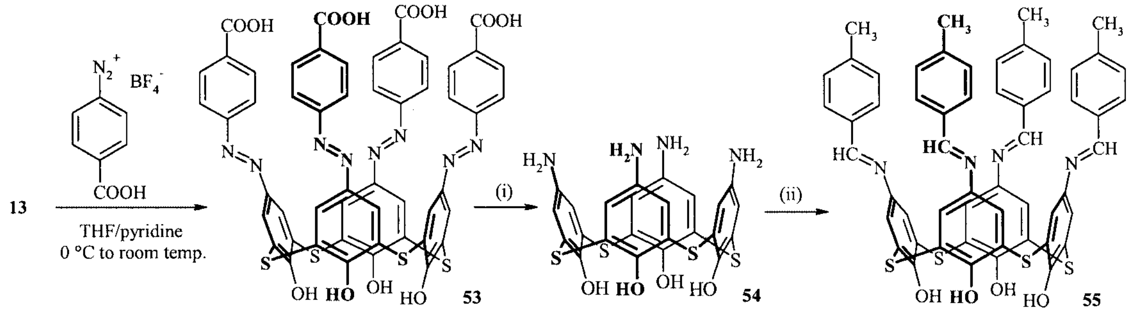
Amino-substituted calix[4]arenes are useful intermediates for the introduction of many other functionalities.[1] Commonly, their synthesis involves two steps: (i) nitration/*ipso*-nitration of the upper rim, and (ii) subsequent reduction of the resulting nitro compounds. Unfortunately, our attempts at nitrating thiacalixarenes, using the reaction conditions usually employed in calixarene chemistry, led exclusively to the oxidation of the bridging sulfur atoms. Starting from **2**, **13**, or their tetraalkylated derivatives, the formation of nitro compounds could not be achieved under any of the conditions tested [conc. HNO_3 (or 100 % HNO_3)/CH_2Cl_2 (or AcOH), 100 % HNO_3/CF_3COOH, $NaNO_3$/CF_3COOH]. On the other hand, these nitrating agents were shown to be excellent agents for the preparation of sulfones and sulfoxides.[61]

To achieve the introduction of amino groups to the upper rim of thiacalixarenes, we employed diazo coupling, which is a well-known reaction from classical calix[*n*]arene chemistry. The reaction between the thiacalixarene **13** and a diazonium salt proceeded efficiently to yield the corresponding tetraazo compound **53** (Scheme 11). The reaction can be carried out with a solution of the diazonium salt (usually the tetrafluoroborate) in THF, using pyridine as a catalyst.[62] The formation of an azo compound is easily detectable by the change of colour (from orange to dark red). Reduction of the azo compounds was most efficiently achieved using $Na_2S_2O_4$ and NaOH in an aqueous solution; the carboxy derivative **53** was found to be suitably soluble in the reaction medium (Scheme 11). Stirring the reaction mixture at elevated temperatures gave the expected product **54** in 90 % yield. Subsequent reaction with *p*-methylbenzaldehyde in toluene gave the Schiff base **55**, which is more soluble in organic solvents and is stable enough to be analysed using common techniques. The ^1H NMR spectrum of **55** indicates that it prefers the expected *cone* conformation. A similar reaction pathway was employed recently[53,54] for the synthesis of the azo derivatives of thiacalixarenes, which have potential for use in nonlinear optics.

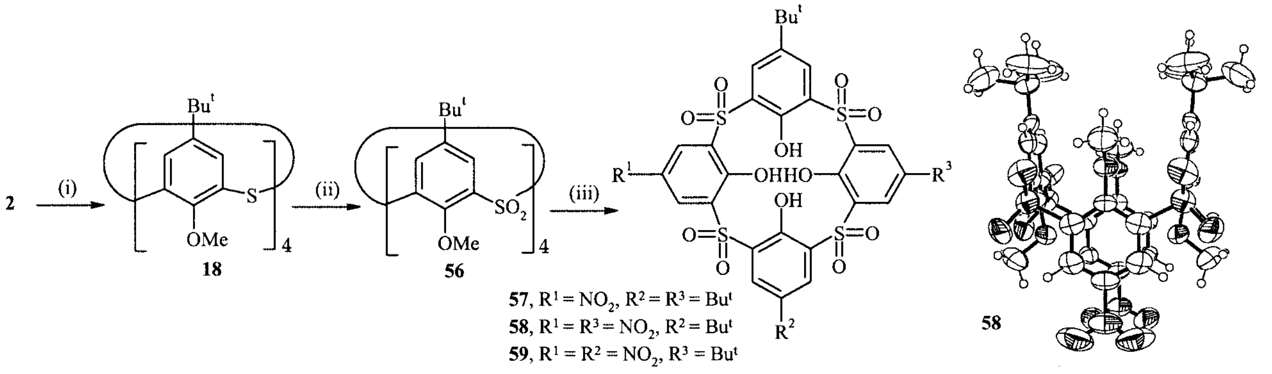
We realized that in order to avoid nonspecific oxidation of thiacalixarenes during nitration, derivatives which have



Scheme 10. Bromination of thiacalix[4]arene derivatives: (i) Br_2 (6 equiv.), $CHCl_3$, room temp. (73 %); (ii) Br_2 (12 equiv.), $CHCl_3$, room temp. (90 %); (iii) PrI/K_2CO_3, acetone, reflux, 48 h (56 %) or PrI/NaH, DMF, room temp., 48 h (73 %)



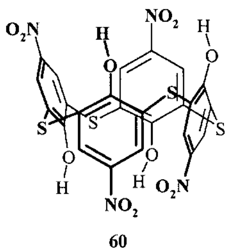
Scheme 11. Upper rim amination of thiacalix[4]arenes: (i) $NaOH/Na_2S_2O_4$, water, 90 °C (90 %); (ii) p-MeC_6H_4CHO, toluene, room temp. (56 %)



Scheme 12. Nitration of thiacalix[4]arene: (i) MeI/K_2CO_3, reflux (95 %); (ii) $H_2O_2/CF_3COOH/CHCl_3$, room temp. (87 %), (iii) 100 % HNO_3/CF_3COOH, 80 °C, 2 days to give **57** (45 %) or (iii) 100 % HNO_3/CF_3COOH, 80 °C, 4 days to give **58** (59 %)

already been oxidized could be used as starting materials (Scheme 12). Accordingly, *tert*-butylthiacalix[4]arene **2** was alkylated to provide the tetramethoxy derivative **18** in 95 % yield. Subsequent oxidation with a 35 % aqueous solution of H_2O_2 in trifluoroacetic acid/$CHCl_3$ gave the corresponding tetrasulfone **56** in high yield (87 %). Attempted nitration of **56** using 65 % or 100 % HNO_3 in glacial acetic acid did not lead to any nitration products, but the use of 100 % HNO_3 in trifluoroacetic acid was successful (Scheme 12). The best results were obtained at an elevated temperature (80 °C) with a large excess of nitrating agent (200 equiv.). Under these conditions, either one or two nitro groups could be introduced into the upper rim of the thiacalixarene derivative, depending on the reaction time.[63] A shorter reaction time (two days at 80 °C) gave the mononitro derivative **57** (45 % yield) whereas four days at the same temperature led to the diametrically substituted dinitro derivative **58** (59 %), accompanied by a small amount of the proximally substituted derivative **59** (2 %). It is noteworthy that the tetrasubstituted product could not be isolated under any of the conditions used (i.e. larger excess of nitrating agent and longer reaction time). This implies that the reactivity of the sulfone system towards *ipso* nitration is much lower in comparison with that of classical calix[4]arenes, where tetrasubstitution is common even under much milder conditions (65 % HNO_3 in CH_2Cl_2/CH_3COOH at room temperature). The electron-withdrawing effects of the two introduced nitro groups (and four sulfonic bridges) make the whole system unreactive towards subsequent nitration. Hence, under the conditions used, the dinitro derivative is the main product. The above-described reaction pathway offers us quite a rare opportunity for the regioselective mono- or di- *ipso*-functionalization of the upper rim of thiacalixarenes. ^1H NMR and X-ray crystallography of **57** and **58** revealed that both compounds prefer the *1,3-alternate* conformation.[63]

Very recently, nitration of the parent thiacalixarene **13** without concomitant oxidation of sulfur atoms was described.[54] The method uses $KNO_3/AlCl_3$ in di-, tri- or tetraglyme and gives 5,11,17,23-tetranitro-25,26,27,28-tetrahydroxythiacalix[4]arene (**60**) in good yields (67 %). The choice of solvent is crucial for the reaction — use of THF, acetonitrile, or toluene did not result in the desired nitration products. It seems that the key step of the process is in situ formation of N_2O_4, which is then stabilized as the active electrophilic species $NO^+NO_3^-$, but only in the presence of complexing ethers. The proposed mechanism was supported by an experiment in which **13** was treated with a previously prepared complex of $NO^+NO_3^-$ and 18-crown-6, which led to the same nitration product. Interestingly, the X-ray crystal structure of **60** proved that the molecule adopts a *1,2-alternate* conformation.



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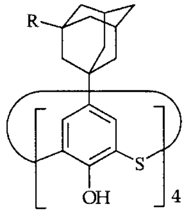
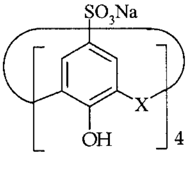


7, R = H
61, R = COOH

Friedel−Crafts alkylation of **13** was achieved[5] by refluxing for three days with 1-adamantanol in trifluoroacetic acid in the presence of a catalytic amount of $LiClO_4$, leading to *p*-(1-adamantyl)thiacalix[4]arene (**7**) in 89 % yield. 3-Carboxy-1-adamantanol reacts in the same way to give the analogous derivative **61** almost quantitatively (96 %). Very recently, the introduction of the chloromethyl group onto the upper rim of thiacalixarene **13** (in 90 % yield) using chloromethyl methyl ether and $AlCl_3$ was reported.[60]

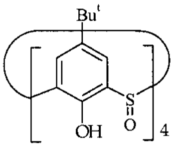


62a, X = S
62b, X = SO
62c, X = SO_2

Thiacalixarenes are essentially insoluble in water, and therefore the introduction of sulfonate functions onto the upper rim would enable the extension of their chemistry into aqueous solutions, which would be essential for potential biological applications. Although a direct sulfonation of **13** has not yet been described, *ipso*-sulfonation was successfully accomplished by the treatment of **2** with conc. H_2SO_4 at 90 °C.[64] The resulting sulfonate **62a** was isolated as the tetrasodium salt in 69 % yield. The single-crystal X-ray structures of this tetrasodium salt[65] and the corresponding dimanganese complex[66] have recently been published. It is noteworthy that the tetrasulfonate **62c**, which possesses four sulfone bridging groups (-SO_2-) was prepared by *ipso*-substitution of the corresponding tetrasulfone[67] using chlorosulfonic acid at 140 °C (compare with the above-described *ipso*-nitration of thiacalix[4]arene). The product was obtained as the pentasodium salt in 72 % yield. Attempts to prepare the appropriate sulfoxide derivative **62b** by *ipso*-substitution failed.

4.4. Reactions Involving the Bridging Groups

The presence of sulfur atoms in the thiacalixarene skeleton offers another pathway for derivatization of the molecule: reactions on the bridging moieties. Such reactions are rare in classical calixarene chemistry, but the derivatization of sulfur is much easier. Oxidation of the parent thiacalixarene **2** with aqueous H_2O_2/trifluoroacetic acid or excess $NaBO_3/CHCl_3$/acetic acid leads in high yield to the derivative **64** possessing four sulfone bridging groups. However, using a slight excess of the oxidizing agent ($NaBO_3$) gives the tetrasulfoxide **63**.[68,69] The introduction of the sulfoxide functionality induces a novel type of stereoisomerism in thiacalixarene derivatives, which originates from the relative positions of the oxygen atoms.



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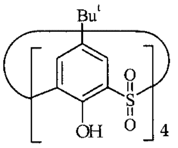

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Therefore, assuming free rotation of the phenol subunits, the derivative **63** could adopt four different configurations, as depicted in Figure 10. X-ray analysis confirmed that the thiacalixarene skeleton of **63** had the *1,3-alternate* conformation, with the sulfoxide groups in a *rtct* configuration.[70] The sulfone **64** also prefers the *1,3-alternate* conformation in the solid state,[52] which is held together by a 3D network of intermolecular hydrogen bonds between the OH and SO groups.

Because only the *rtct* and *rctt* stereoisomers are available[70] by direct oxidation of **2** (27 % and 17 % yield, respectively), the other two isomers were prepared[2a,16a] by the route shown in Scheme 13 (the *rctt* isomer is obtainable[2a,71] from the methanol-soluble part of the crude oxidation product). The synthesis employs benzyl groups for the protection of the hydroxyl functionalities and consequent immobilization of the thiacalixarene in one conformation (*cone* or *partial cone*). Subsequent oxidation and deprotection leads to the *rccc* and *rcct* stereoisomers. The synthesis of chiral compounds via oxidation of the sulfur bridges was also reported.[72]

Our attempts to carry out *ipso*-nitration of the tetraacetate **14a** using conditions described for classical calix[4]arene derivatives were completely unsuccessful. However, the results of this "nitration" were identified as partly oxidized products, containing S=O groups. These compounds represent novel building blocks that could find many potential applications in supramolecular chemistry. Consequently, we focused our interest on the development of methods leading

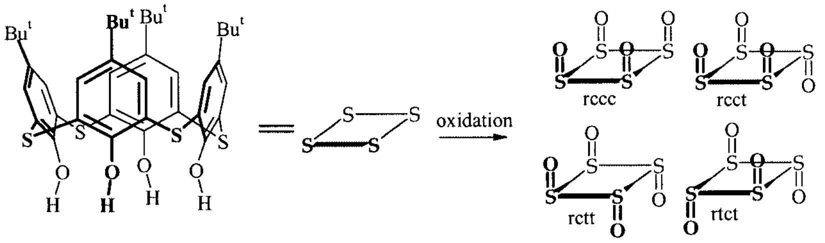
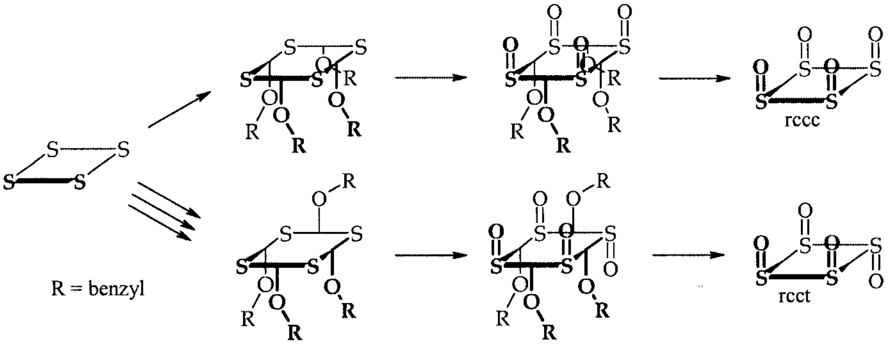


Figure 10. The four stereoisomers of **63**; *r* = reference group, *c* = *cis* to *r*, *t* = *trans* to *r*



Scheme 13. Stereocontrolled synthesis of stereoisomers of derivative **63** (schematic)

to the regioselective oxidation of **14a** in acceptable yields.[61] We found that the tetrasulfinyl derivative **65** can be obtained almost quantitatively by reaction with hydrogen peroxide in acetic acid or by 100 % HNO_3 in dichloromethane. The relative orientation of the sulfoxide oxygens and the substituents on the lower rim of the thiacalix[4]arene results in the formation of several stereoisomers. As shown in Figure 11, the *cone* conformation of the tetrasulfinylcalix[4]arene **65** could display up to six isomers **65a**−**f**.

However, during our investigations we have always isolated only one stereoisomer, which possesses C_4 symmetry, consistent with structures **65a** and **65b**. The final evidence was obtained by X-ray crystallography, which confirmed that the sulfoxide groups in **65** were in opposition to the acetate substituents (structure **65a**). We propose that the oxidizing agent preferentially attacks the thiacalix[4]arene skeleton from the "upper" surface in order to minimize the steric interaction with the substituents on the lower rim. As a consequence, oxidation of immobilized *cone* thiacalix[4]arenes proceeds stereoselectively, with the acetate and sulfoxide groups pointing down and up, respectively (compare with oxidation of the tetrabenzyl derivative[16a]).

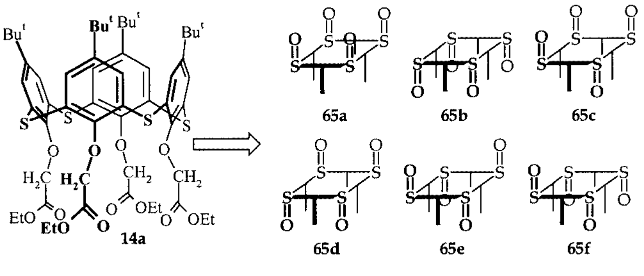


Figure 11. All possible stereoisomers of tetrasulfinyl derivative **65**

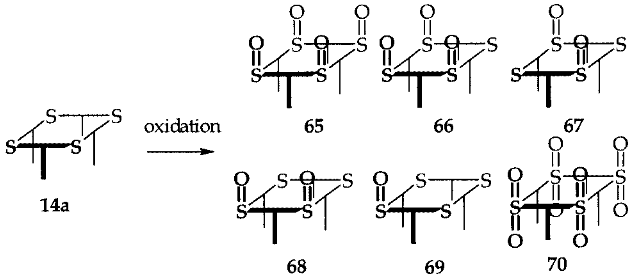


Figure 12. Oxidation of the tetraacetate derivative **14a** (schematic)

The preparation of the partly oxidized products **66**−**69** was not as easy as the synthesis of the tetrasulfoxide **65** (Figure 12). The product mixtures always contained several (chromatographically isolable) regioisomers, which we expected to have upwards-pointing sulfoxide groups, although it was not possible to confirm this because X-ray analysis was unsuccessful. Finally, the tetrasulfonyl derivative **70** was obtained in 70 % yield using an excess of *m*CPBA in boiling 1,2-dichloroethane (Figure 12).

A similar approach was recently applied to fix the tetraacetates **14b** and **14d** in the *partial cone* and *1,3-alternate* conformations, respectively. Regio- and stereoselective oxidation[73] enabled a collection of novel building blocks to be prepared. For example, the oxidation of **14b** with $NaNO_3$ as the oxidizing agent gave the tetrasulfoxide **71** (containing the *rctt* configuration of sulfoxides) in 64 % yield. Analogously, the *1,3-alternate* conformer **14d** was transformed into the sulfone **72** and to **73**, which possesses three sulfone groups and one sulfinyl group (Figure 13).[74] Such partly oxidized derivatives may find potential application for the construction of various receptors and more sophisticated

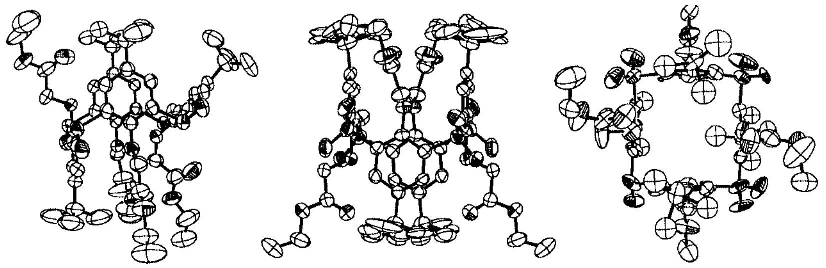

71 72 73

Figure 13. X-ray structures of oxidized products

thiacalixarene-based structures. Some of these compounds are chiral due to the asymmetric nature of the sulfoxide substituents.

5. Applications of Thiacalixarenes

The presence of sulfur atoms (which possess lone pairs and vacant 3d orbitals) in thiacalixarenes results in many novel features, especially in the field of metal complexation. In contrast to classical calix[4]arenes, the parent thiacalixarene **2** was found to extract a wide range of transition metal ions from aqueous solutions.[75] The influence of oxidized bridges (SO, SO_2) upon the complexation ability of derivatives **63**, **64** and their *tert*-octyl analogues was also systematically studied.[68,69] These results can be summarized as follows: (i) **2** prefers soft-to-intermediate metal ions (e.g. Ag^+, Zn^{2+}, Cd^{2+}, Hg^{2+}), (ii) sulfone **64** extracts hard metal ions (alkaline earth metals, lanthanoids), and (iii) sulfoxide **63** represents a somewhat intermediate situation and extracts both the above mentioned groups of metals. These results enable us to speculate about the binding modes of thiacalixarenes. The situation is depicted schematically in Figure 14.

Whereas the binding modes of **2** and **64** are imposed by their molecular structures, the sulfoxide **63** can switch between an interaction involving the sulfoxide lone pair or its oxygen, depending on the coordinating metal.[68,69] Similar binding modes have also been proposed for metal complexation by thiacalix[6]arene (**4**).[76] Recently, many X-ray structures of thiacalixarene complexes with various transition metals have appeared in the literature.[77−82] These crystallographic results confirmed the presence of the above-mentioned binding modes. Moreover, many crystallographic structures revealed a characteristic feature of thiacalixarenes; namely, formation of multinuclear metal complexes through multiple M···O and/or M···S interactions, leading ultimately to cluster assemblies.[83−87]

The interactions of thiacalix[4]arenes (bearing acetate or amide groups on the lower rim) with transition metals[88] and alkali metal cations[10,12,89] have also been studied. Although the absolute values of the complexation constants for tetraacetates **14a**,**b**,**d** and **15a**,**b**,**d** are much lower that those of the corresponding calix[4]arene derivatives, the selectivities for alkali metals were quite interesting. ^{1}H NMR titration experiments carried out in a 4:1 mixture of $CDCl_3$ and CD_3CN revealed that **14a** prefers to complex sodium over potassium cations [$K(Na^+) = 6600\ \text{M}^{-1}$, $K(K^+) = 320\ \text{M}^{-1}$]; the addition of Rb^+ or Cs^+ did not induce any changes in the NMR spectrum of **14a**. The selectivity of **15a** is shifted towards the smaller sodium cation [$K(Na^+) = 2900\ \text{M}^{-1}$]; K^+, Rb^+, and Cs^+ were not complexed at all under the conditions used.[12]

The important feature of thiacalixarenes **2** and **4** is their ability to accommodate neutral molecules (i.e. solvent molecules) within their cavities or in the crystal lattice.[90] The inclusion of guest molecules into **2** and **4** was studied using NMR spectroscopy. The thiacalixarenes were recrystallized from the appropriate solvent, the crystals formed were dried under vacuum, and then subjected to NMR analysis. The host:guest ratio was assigned by integration of the appropriate signals.[4,7] This ratio was usually 1:1 (thereby indicating an interaction with the cavity), but some exceptions were also found. Thus, the host:guest ratio for 1,2-dichloroethane was 1:2, and that for toluene was 2:1. The structure-affinity relationships for guest inclusion within solid **2** were studied for a vapour guest-solid host system using headspace gas chromatographic analysis.[91]

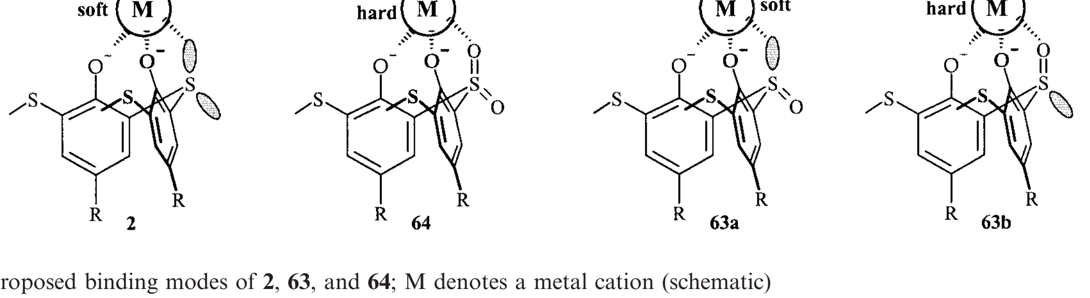
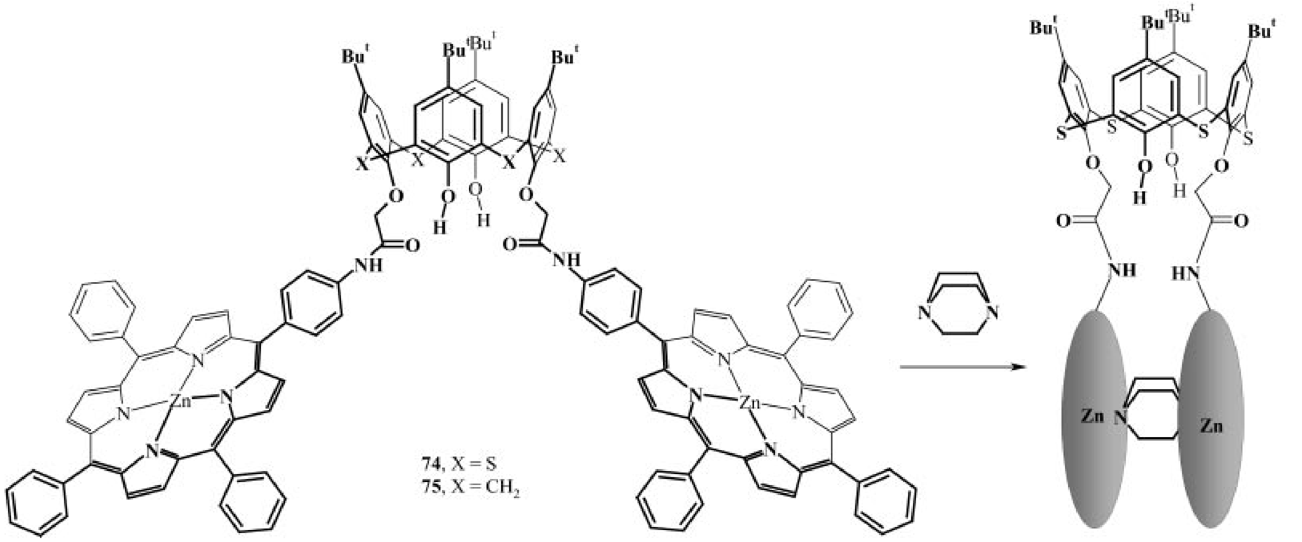


Figure 14. Proposed binding modes of **2**, **63**, and **64**; M denotes a metal cation (schematic)



74, X = S
75, X = CH$_2$

Scheme 14. The complexation of DABCO

Recently, interesting differences in the behaviour of classical- and/or thiacalixarene-based metalloporphyrin conjugates have been observed.[92] It was found that the ligand 1,4-diazabicyclo[2.2.2]octane (DABCO) can be complexed by metalloporphyrin units in two different ways, depending upon the structure of the metalloporphyrin (Scheme 14).

We found that the thiacalix[4]arene **74** prefers an intramolecularly closed cavity with a very high binding constant of (1.0 ± 0.1) × 10^7 M^{-1} in $CHCl_3$ at 294 K (host:guest 1:1), the classical calix[4]arene **75** forms an intermolecular complex by coordinating two DABCO molecules (host:guest 1:2). The differences observed can be rationalized in terms of cavity size and preorganization due to intramolecular hydrogen bonding of the calixarene lower rim.

Interesting inclusion properties were found for the case of the water-soluble sulfonate **62a**. This compound can create complexes with a range of both water-miscible organic molecules (ketones, alcohols and ethers)[93] and water-immiscible mono-substituted benzenes.[94] The dependence on the stabilities of the complexes with respect to the electronic effect of the substituent in mono-substituted benzenes indicates that $\pi-\pi$ interactions between the guest and host molecules are a predominant factor in complexation. The thiacalixarene **62a** exhibits much higher complexation abilities than the corresponding classical tetrasulfonate, which is attributed to the differences in the cavity size.[94] Moreover, **62a** can almost completely remove traces of halogenated compounds from water,[95] which is very attractive from an ecological point of view. Several other applications, such as the use as a stationary phase for gas chromatography,[96] a specific pre-column chelating agent for Ni^{II} in KD HPLC,[97] a chelating adsorbent for heavy metal ions,[98] a highly selective means for the luminescence determination of terbium,[99] and in the construction of ion-sensors[100] or self-assembled monolayers[101−104] have also been reported.

6. Concluding Remarks

The chemistry of calixarenes has been "rejuvenated" by the appearance of thiacalixarenes. The research reviewed here demonstrates some novel possibilities arising from the modification of the classical skeleton with sulfur atoms. The presence of heteroatoms results in many novel features, such as metal complexation through the sulfur atoms, easy chemical modification of the bridges, as well as different ring sizes and dynamic properties. Thiacalixarenes exhibit a broad range of interesting functions, chemical behaviour and novel conformational preferences, which make these compounds good candidates for building blocks in supramolecular chemistry. Although the field is still young, thiacalixarenes, with their unusual metal-binding properties, have already shown potential for many useful applications. It is evident that the continuing progress in the chemistry of these compounds will bring many fascinating discoveries in the future.

Acknowledgments

The author is grateful to his colleagues and students whose names appear in the list of references.

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