Heteroatom-Containing, Carbon-Bridged Calix[4]arene, Thiacalix[4]arene and Sulfonamide Bridged Calix[4]arene

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Abstract: This review provides a discussion of developments in heteroatom-containing, carbon-bridged calixarene and thiacalixarene. These compounds are described with regard to their syntheses and inclusion properties.

Keywords: Calix[4]pyrrole, calix[4]furan, calix[4]pyridine, thiacalix[4]arenas, aromatic tetrasulfonamide macrocycles.

I. INTRODUCTION

Calixarenes have a long history, stretching back to 1872 when Adolph Von Baeyer reported reactions between phenols and aldehydes [1-3]. Over the last several decades, calixarenes have developed into a class of macrocyclic receptors after crown ethers and cyclodextrins. These molecules, with their cup-shaped cavities that complex various small molecule and ion, can be used as ion carrier, chromogenic sensors, molecular carrier, construction materials, enzyme mimetic and so on. The research on calixarenes has involved organic chemistry, analytical chemistry, inorganic chemistry, electrochemistry, biochemistry and materials chemistry. Thus it is becoming increasingly important to design and synthesize various calixarenes. Most calixarenes are designed by introducing functional groups to the calixarene platform *via* etherification of the phenolic oxygens and substitution at the *p*-position. Modifying conventional calixarenes by replacing the methylene bridges with heteroatoms or the phenyl rings with other heteroatom-containing aromatic rings represents alternative resorts for constructing calixarene-type receptors. Many heteroatom-containing calixarenes have been developed. They are characterized by the size of their cavities, their complexation properties and their ease of modification. In this account we summarize reported studies on the synthesis and conformation of heteroatom-containing, carbon-bridged calixarene and thiacalixarene.

II. CALIX[4]PYRROLE

A nonconjugated macrocycle possessing pyrrole rings **1** was synthesized more than 100 years ago by Baeyer from pyrrole and acetone [4]. In recent years, calix[4]pyrroles have attracted a lot of attention because of their applications in designing receptors and molecular devices [5], and their oxidation into porphyrins [6-7]. Calix[4]pyrroles derivatives can be obtained by two methods: (1) modifying the starting pyrroles or acetone, followed by condensing the modified pyrroles with acetone in the presence of Lewis or Bronsted acid; (2) carrying out the modification on the base of simple calix[4]pyrroles.

It was reported [8] that the condensation of cyclohexanone and pyrrole catalyzed by *p*-toluenesulfonic acid in benzene could give the mixture of calix[4]pyrrole **2** and other isomers. On the other hand, **2** was reported as the only product when hydrochloric acid was used as the catalyst in ethanol. To probe the best conditions for obtaining N-fused calix[4]pyrrole **2**, the group led by Wim Dehaen reinvestigated the reaction in a systematic manner. It was found that when hydrochloric acid was used as the catalyst in ethanol, the product was not just **2**, but the mixture containing **2** and its isomer **3**. In this systematic study, it was concluded that trifluoroacetic acid (TFA)/ethanol was the best catalyst/solvent system (with a total y ield of 97%) [9]. The macrocyclization reaction of pyrrole with cyclopentanone using zeolite catalysts in liquid phase under microwave irradiation gave calix[4]pyrrole **4** in 62.7% [10]. Compounds **1**, **5**, and **6** were also obtained in high yields under similar conditions by the condensation of pyrrole with the corresponding ketone.

Macrocycle **7** was prepared from the condensation of difluropyrrole and acetone catalyzed by methane-sulfonic acid in 55-60%, along with calyx[5] and calyx[8] as the side products [11] (Scheme **1**). The introduction of the electron-withdrawing fluorine atoms to the β-pyrrolic positions of the calix[4]pyrrole results in dramatic increases in the affinity toward anionic substrates by these receptors in solution. Another similar, octabromo-substituted calix[4]pyrrole **8** was synthesized in 90% yield by the reaction of compound **1** with *N*-bromosuccinimide(NBS) in dry THF under reflux [12].

Treating the monopyrrole-TTF (tetrathiafulvalene) with an excess of TFA in a mixture of CH_2Cl_2 and Me_2CO gave the tetra-TTF calix[4]pyrrole **9** as a yellow solid in 18% yield (Scheme **2**) [13]. Compound **9** can act as an effective receptor for neutral electron acceptors, such as 1, 3, 5-trinitrobenzene, tetrafluoro-*p*-benzoquinone, tetrachloro-*p*-benzoquinone, and *p*-benzo-quinone, in CH_2Cl_2. In the case of 1, 3, 5-trinitrobenzene, tetrafluoro-*p*-benzoquinone and Me_2CO, complexes also formed in the solid state.

It was reported that calix[4]pyrrole **10** could be prepared from the condensation of *p*-hydroxyacetophenone with pyrrole in methanol using methanesulfonic acid as the catalyst [14].

In the presence of potassium carbonate, **10** reacted with iodomethane in acetonitrile to give 4-methoxyphenyl congeners **11** [14]. Compound **12** could be synthesized by treating compound **9** with acetyl chloride in dry THF in the presence of triethylamine for 5 days [15]. Compounds **10-12** belong to the calix[4]pyrroles that contain deep cavities and fixed walls.

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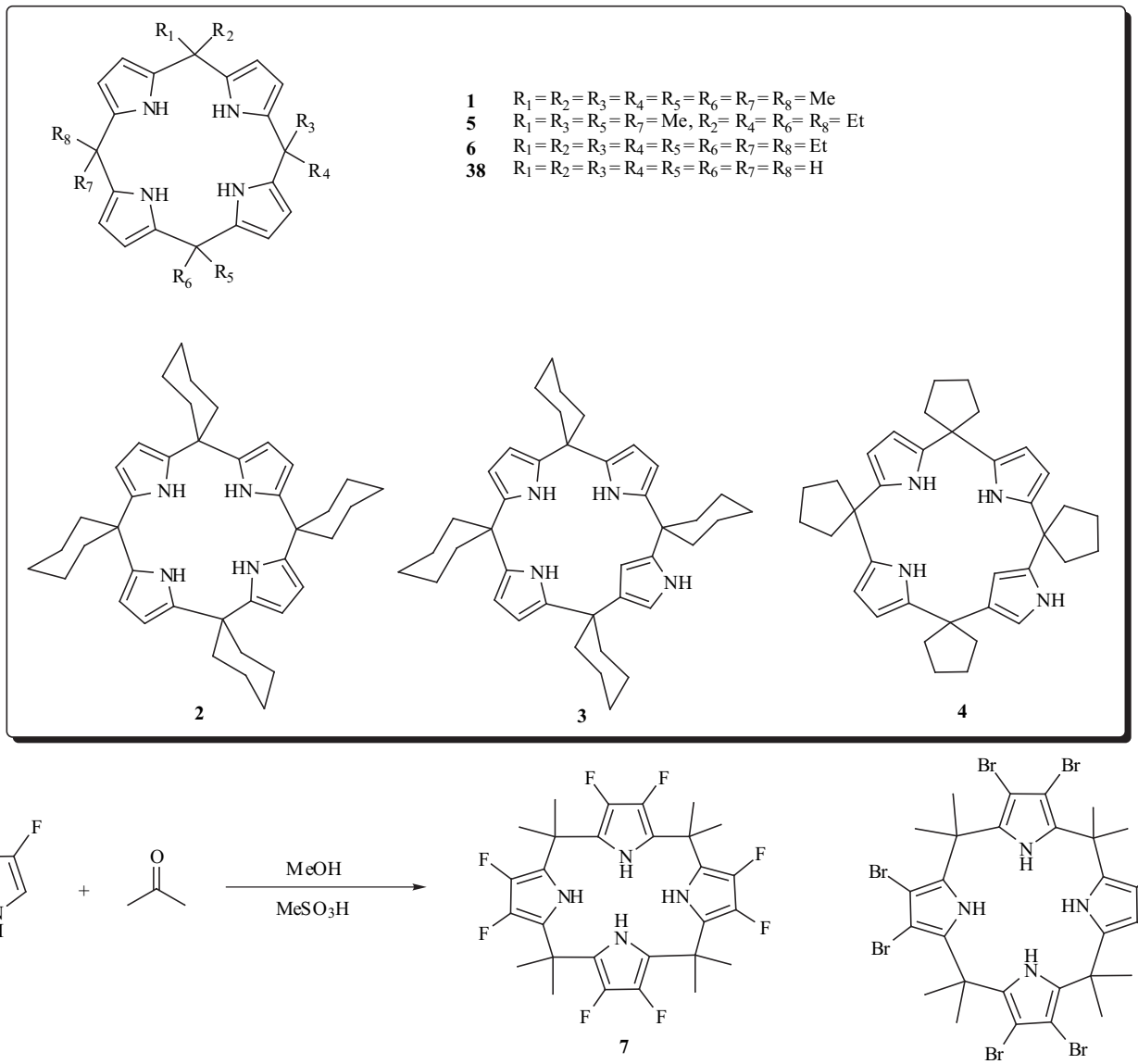
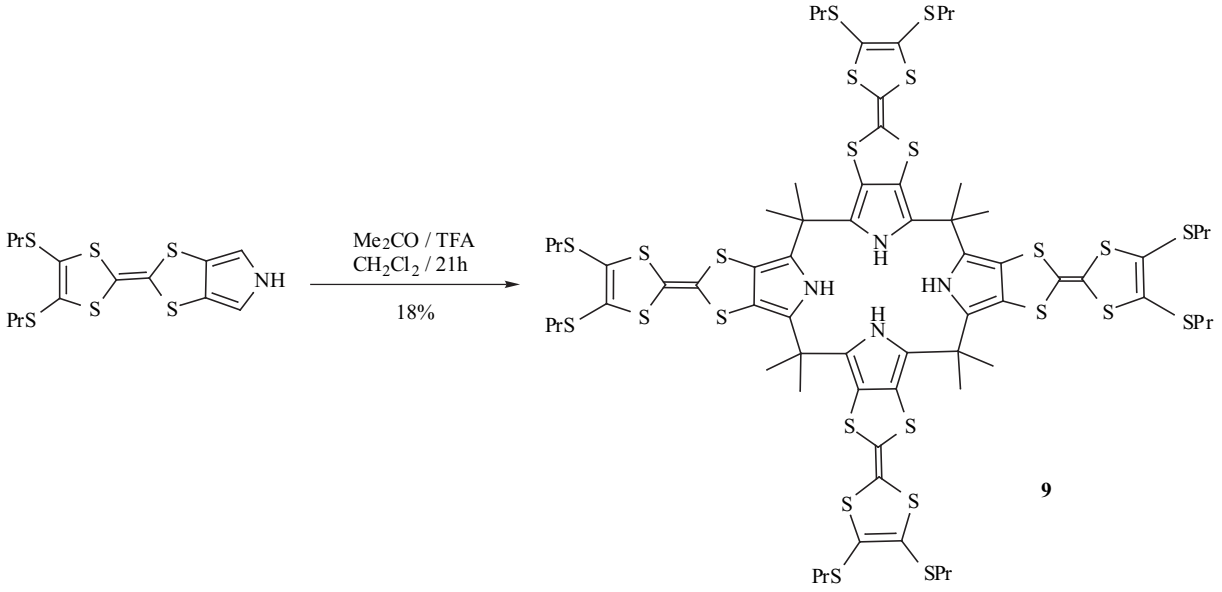
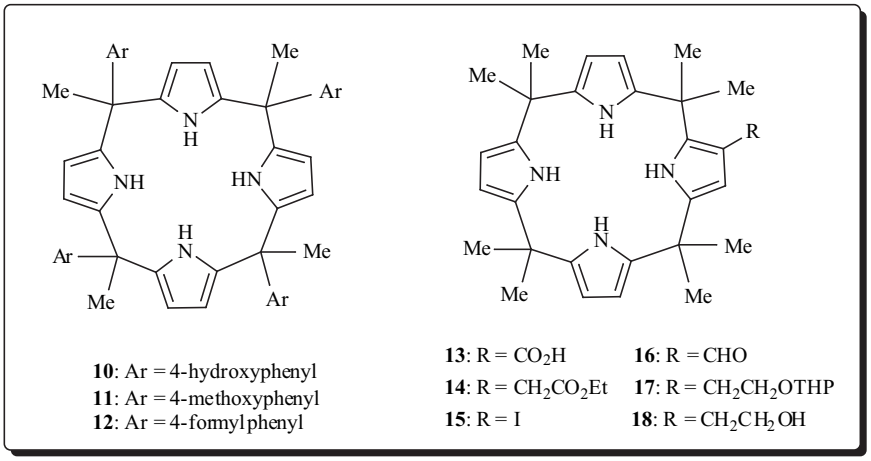


Scheme 1.



Scheme 2.



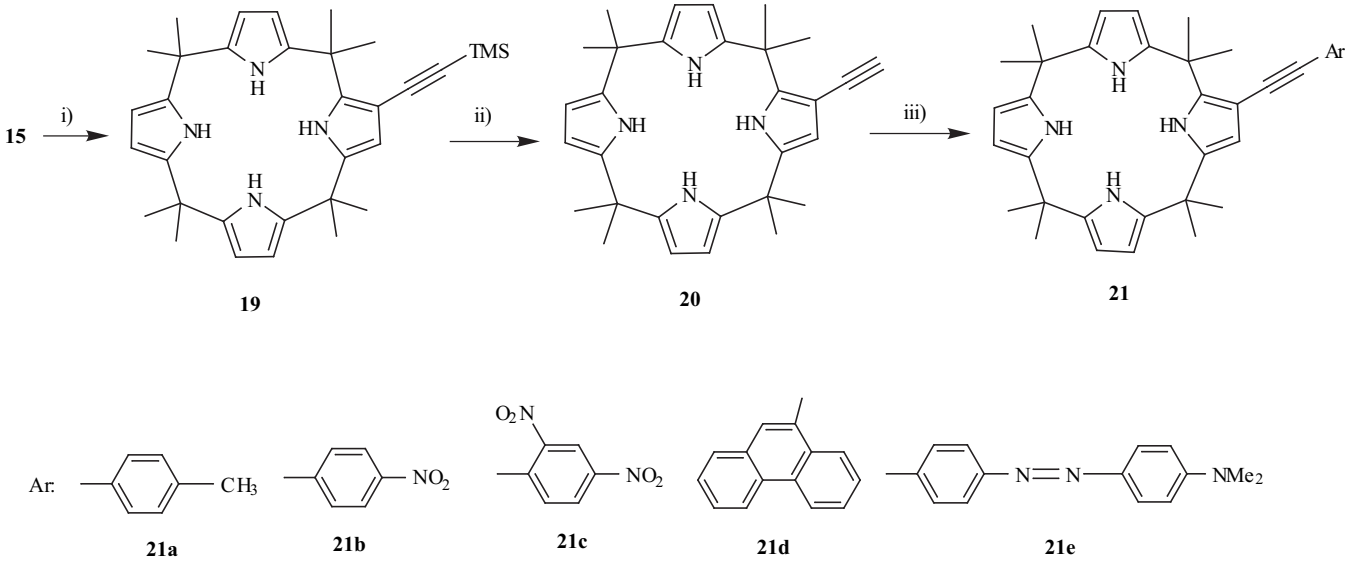
10: Ar = 4-hydroxyphenyl
11: Ar = 4-methoxyphenyl
12: Ar = 4-formylphenyl

13: R = CO_2H **16**: R = CHO
14: R = CH_2CO_2Et **17**: R = CH_2CH_2OTHP
15: R = I **18**: R = CH_2CH_2OH

Lithiation and subsequent addition of an electrophile to *meso*-octamethylcalix[4]prrole represents a straightforward synthetic route to C-rim monosubstituted calix[4]pyrroles, as reported by the group of Philip A. Gale [16]. Six calix[4]pyrrole derivatives **13-18** were prepared based on this method. Using indocalix[4]pyrrole **15** as starting material, Hidekazu Miyaji *et al.* prepared a system of arylalkynyl-substituted calix[4]pyrrole derivatives **21a-e** which may be applied as anion sensors (Scheme **3**) [17]. The same authors subsequently reported the design and preparation of calix[4]pyrrole dimers **22-24** by similar method [18].

Recently the research group led by Sessler J. L. described a new class of fluorescent anion sensors **25-30** by using octamethyl calixpyrrole as anion recognition element [19-20]. The synthesis of **25** is shown in Scheme **4**. Compound **26** was obtained in 63% by coupling calixpyrrole monoacid **32** [21-22] with 1 equiv. of 1-aminoanthrancene using the amide coupling reagent, benzotriazol-1-yloxytris (dimethylamino) phos-phonium hexafluorophosphate (BOP) (1.1 equiv.), in DMF in the presence of excess Et_3N. Compound **27** was prepared in an analogous manner by coupling compound **32** with 9-aminomethylanthracene in a yield of 51%.

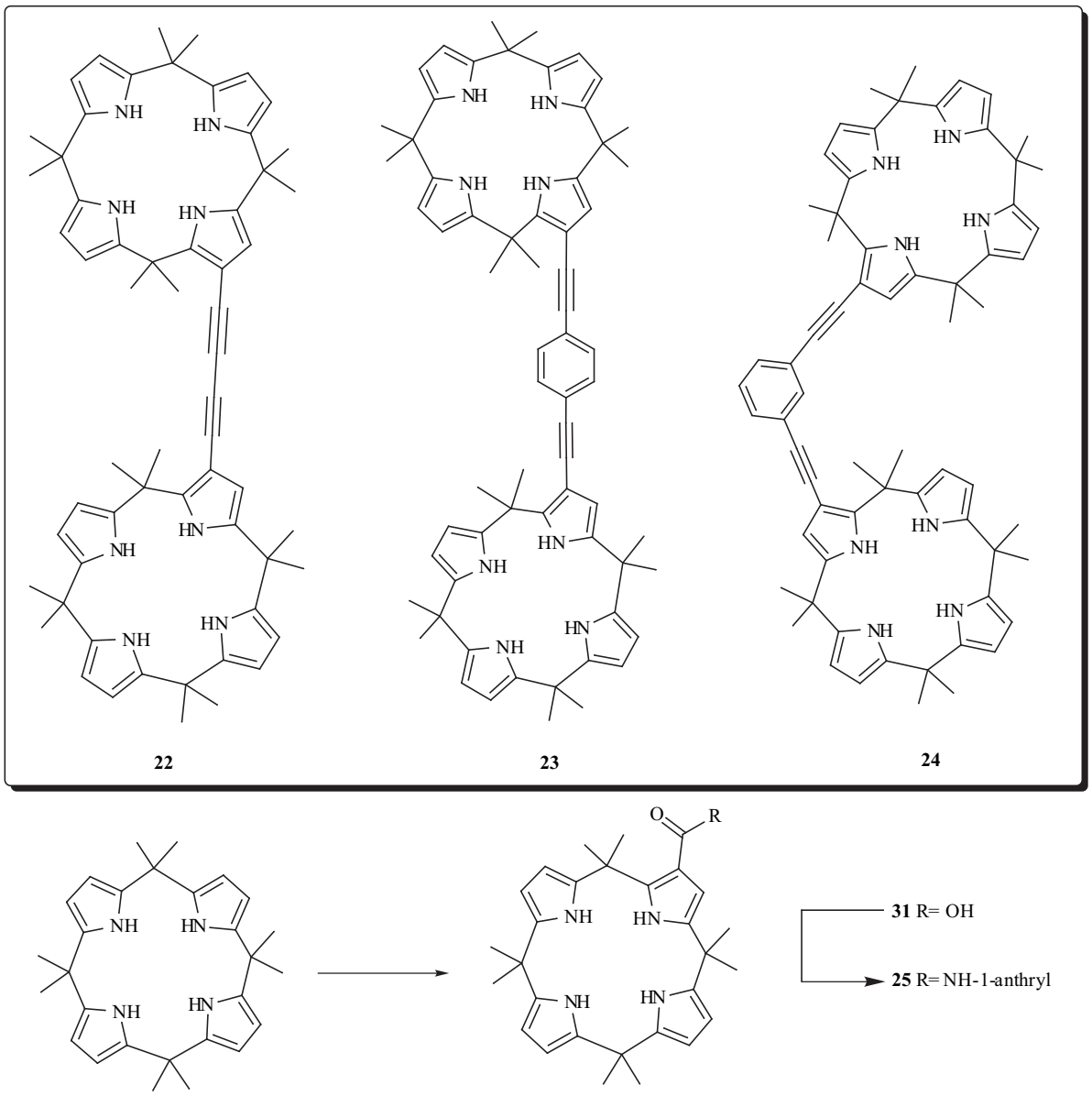
Compound **25-27**, as the first-generation sensors, had low selectivity ratios toward phosphate chloride and less-than-ideal general affinities for anions, hence the second-generation sensors **28-30** were prepared. The key intermediate for preparing **34** could be prepared in two steps from Cbz-protected 3-aminoacetophenone, 3-pentone and pyrrole in the presence of $BF_3 \bullet Et_2O$ (Scheme **5**). Deprotecting the initial product **33** led to **34** in an overall yield of 21%. Sensors **27-29** were then prepared using standard labeling methodologies [23] and were isolated in 92%, 68%, and 93% yields, respectively. These three sensors displayed high binding affinities for anions and high phosphate/chloride selectivities. Pavel Anzenbacher, Jr *et al.* later reported a series of octamethylcalix[4]pyrrole **1** based chromogenic sensors **35-37** [24]. Sensor **35** was synthesized by an electrophilic aromatic substitution reaction of **1** with tetracyanoethylene. Compounds **36** and **37** were obtained by condensing **15** with 1-indanylidenemalononitrile and anthrone, respectively. These three compounds sense preferentially carboxylate and pyrophosphate anions with high affinity and selectivity, while showing dramatic change in color, even at high ionic strength.



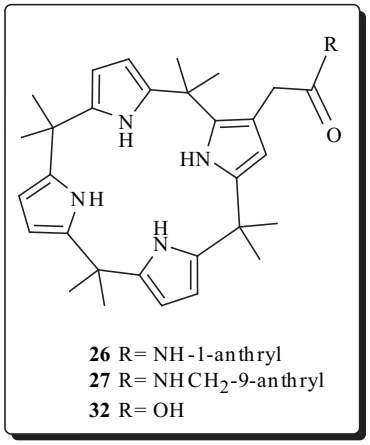
19 **20** **21**

21a **21b** **21c** **21d** **21e**

Scheme 3. i) TMS acetylene, $Pd(PPh_3)_4$(73 %), CuI; ii) tetrabutylammonium fluoride, then $NaHCO_3$ (89 %); iii) Ari, $Pd(PPh_3)_4$, CuI (**a**, 87 %; **b**, 82%; **c**, 67 %; **d**, 81 %; **e**, 79 %).



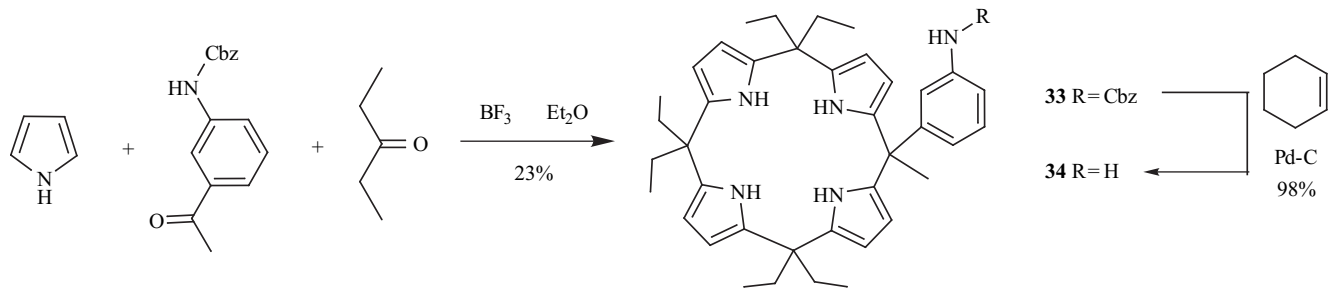
Scheme 4. i) BuLi (4 equiv.), THF; ii) CO_2; iii) aminoanthrancene, DCC, HOBt, DMF.



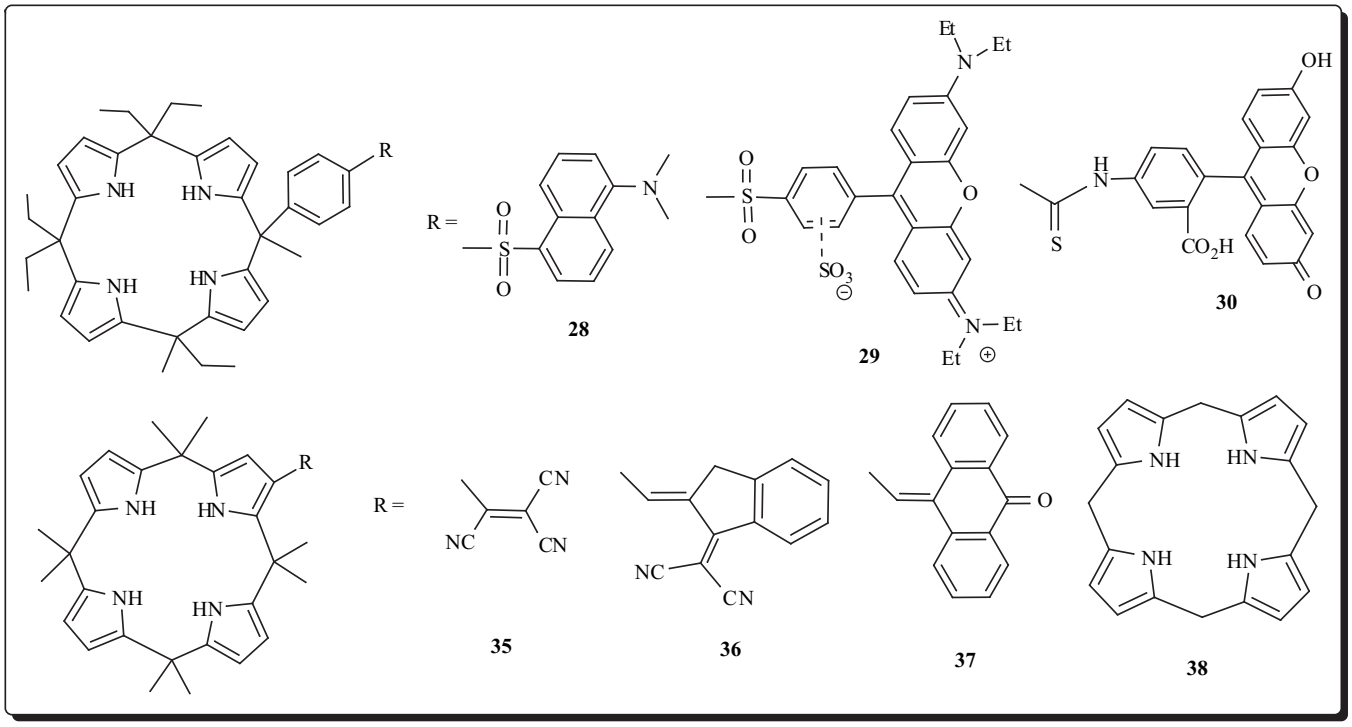
Although the chemistry of *meso*-substituted and β-substituted calix[4]pyrroles have been studied extensively, as shown above, the unsubstituted calix[4]pyrrole **38** remained unexplored until 2001, when **38** was isolated for the first time by a '3+1' approach from 2,5-*bis*(hydroxymethyl)pyrrole in a yield of 14% [25]. Attempts to collect X-ray diffraction data on **38** was unsuccessful, but ^{1}H NMR spectroscopic studies suggested that **38** underwent rapid conformational inversion in chloroform at room temperature.

III. CALIX[4]FURAN

The first calixfuran was discovered in 1906 by Hale, McNally, and Pater. In an attempt to dehydrate 3-furyl-3-pentanol to prepare 3-furyl-2-pentene, the cyclic tetramer, 2, 2, 7, 7, 12, 12, 17, 17-octaethyl-21, 22, 23, 24-tetraoxaquaterene **39**, was obtained [26]. Although calixfuran was clearly obtained, it had received little attention due in part to the problem of limited accessibility of such materials. Comparing to calixpyrrole, the number of methods for preparing calixfuran and their classes are more limited. A number of known calixfurans are listed in Scheme **6**. The synthesis of

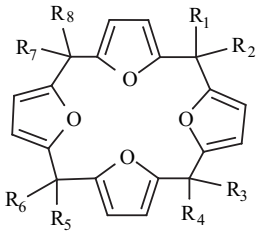


Scheme 5.

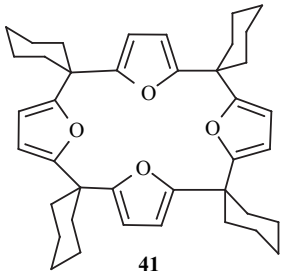


calix[4]furan can be divided into two routes: (1) direct methods involving the condensation of furan with carbonyl compounds at a mole ratio of more than 1:2; (2) indirect methods based on the cyclization of linear oligomers, which in turn are produced by the condensation of furan and carbonyl compounds where the mole ratio is less than 1:2 [27].

Ackman, Brown and Wright reported the synthesis of calix[4]furan from furan and ketones in 1955. Methyl ketones



39 $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = Et$
40 $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = Me$
47 $R_2 = R_3 = R_4 = R_6 = R_7 = R_8 = H$, $R_1 = R_5 = Me$
48 $R_3 = R_4 = R_7 = R_8 = H$, $R_1 = R_2 = R_5 = R_6 = Me$
49 $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_8 = H$
46 $R_1 = R_3 = R_5 = R_7 = H$, $R_2 = R_4 = R_6 = R_8 = Me$



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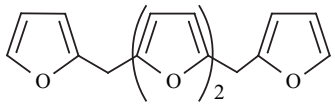

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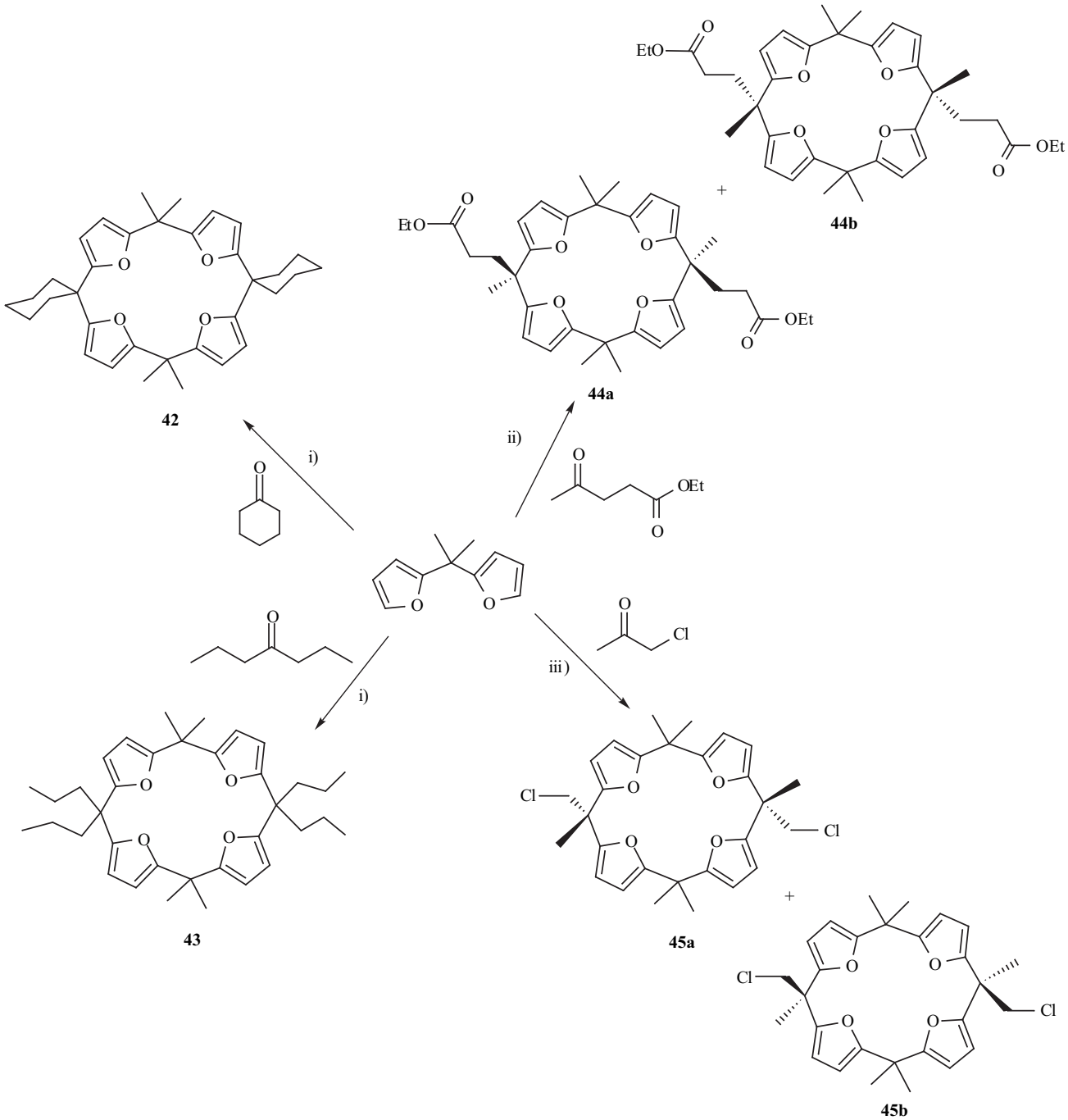
Scheme 6.

condensed with furan in the presence of hydrochloric acid to form the corresponding difurylalkenes. Subsequent reaction of two molecules of the difurylalkene with two molecules of parent methyl ketone lead to the formation of a calix[4]furan, i.e., based on the indirect method [28].

When acetone and furan were condensed in acidic solution, a yield of 18-20% of calixfuran **40** was obtained. The addition of $LiClO_4$ could increase the yield up to 25%, which was attributed to the acidity effects (pH) [29]. When acetone was replaced with cyclohexanone, compound **41** was obtained in yields ranging from 9 to 16% [30]. The presence of metal salts enabled the furan-cyclohexanone macrocycle to be prepared by direct method for the first time. Prior to the direct condensation, the same product was only obtained from the condensation of oligomers [31]. Thus it is obvious that some compounds that can not be prepared by the direct method can be synthesized in an indirect way, and pH values significantly affect the yield of the condensation reaction. As a result, some research groups tried to change the acid catalysts in an attempt to improve the synthetic methods.

In a study reported by the group of Janusz Jurczak [32], the one-pot reaction of furan with acetone in the presence of hydrochloric acid and lithium was modified. The use of highly concentrated (88-91%) sulfuric acid afforded the desired products **40** and **41** in a yield of 71 and 49%, respectively. This method, when applied to chloroacetone, using various methyl



Scheme 7. i) aq H_2SO_4 (90.5%), dioxane; ii) aq H_2SO_4 (90.5%), EtOH; iii) aq H_2SO_4(90.5%), dioxane, $NaClO_4$, 45°C.

alkyl ketones, acetonphenone, and higher symmetric ketones, was unsuccessful. The synthesis was then performed in a two-step manner, i.e., based on the indirect method. In the first step, 2, 2-difurylpropane was obtained in a yield of 21%, and four non-symmetric calix[4]furan **42-45** were prepared efficiently (Scheme **7**). The yields of **42** and **43** were 20% and 11% respectively. Compound **44** was synthesized as a mixture of diastereomeric calixfuran (*cis*- and *trans*-) in 46% overall yield. Similarly, compound **45** was prepared as a mixture of diasteromeric calixfuran in an overall yield of 54%.

It is difficult to prepare calixfuran by condensing furan with aldehyde in one step. Kobuke and coworkers [33] reported that the condensation of furan and acetaldehyde gave compound **46** in an 18% yield. However, the study reported by Sanae Tanaka [27] found that **46** could only be obtained by the indirect method. Thus, 1, 1-difurylethane was treated with acetaldehyde in the presence of lithium perchlorate, which led to **46** in 18% yield.

Mixed dimethyl- and tetramethyl-substituted calix[4]furan **47** and **48** were prepared in poor yields by treating 2, 2'-difurylmethane with acetaldehyde or acetone respectively in the presence of hydrochloric acid. Both are compounds that can only be prepared by the indirect method [27].

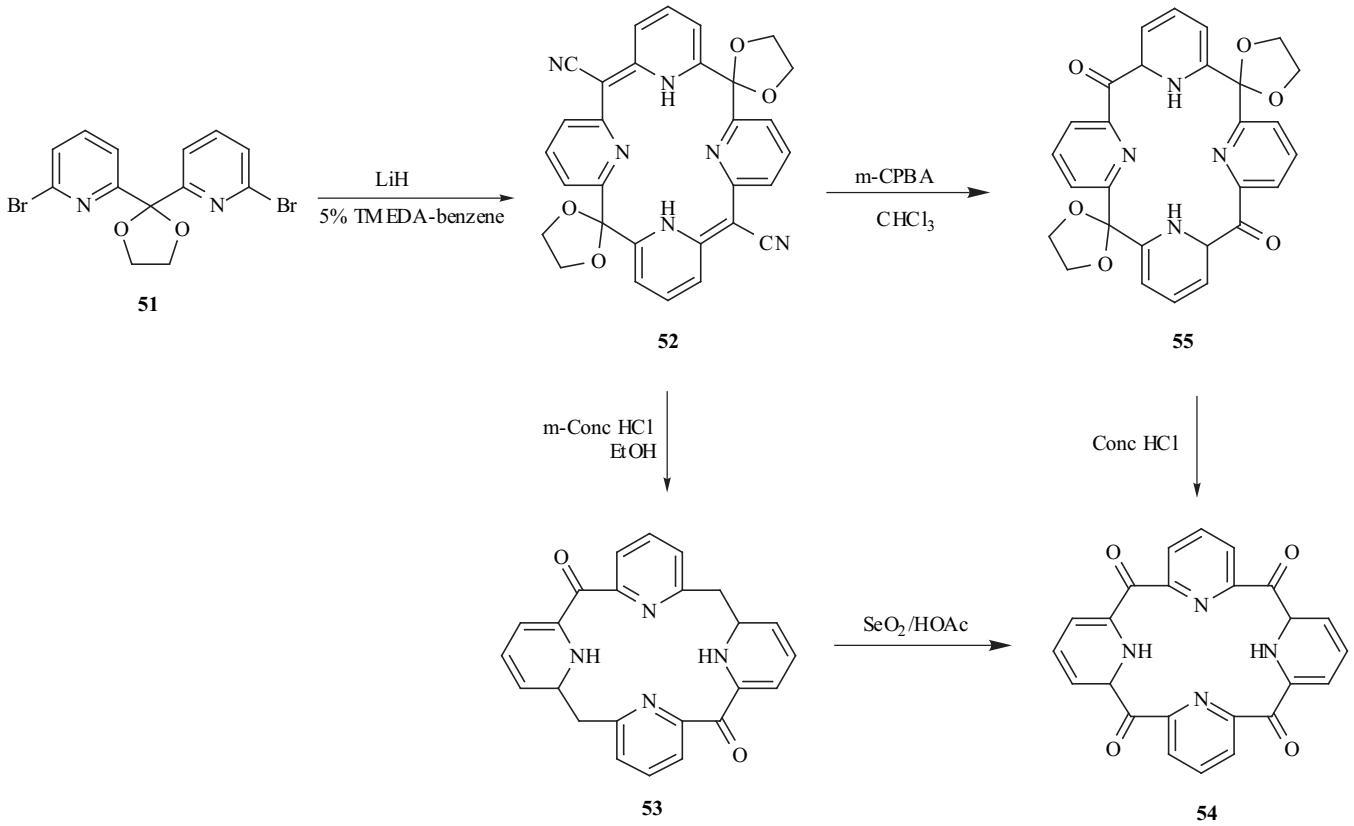
The simplest of all tetraoxaquaterene derivative **49** has been made by several groups, with yields varying from 0.5 to 1% [27-34]. Andrew Whiting *et al.* reported their endeavors to synthesize **49**. The linear tetramer **50** was converted into the cyclic tetramer **49** by using dimethoxymethane for alkylation and $BF_3 \cdot Et_2O$ as the catalyst in CH_2Cl_2 from 0°C to room temperature. The reaction was nearly quantitative. However, decomposition of the product took place when purification was performed using column chromatography on silica gel, leading to a final yield of only 34% [35]. Compound **49** could be converted to calix[4]thiophene in 66% yield. To the best of our knowledge, this is the only report about calix[4]thiophene [36].

IV. CALIX[4]PYRIDINE

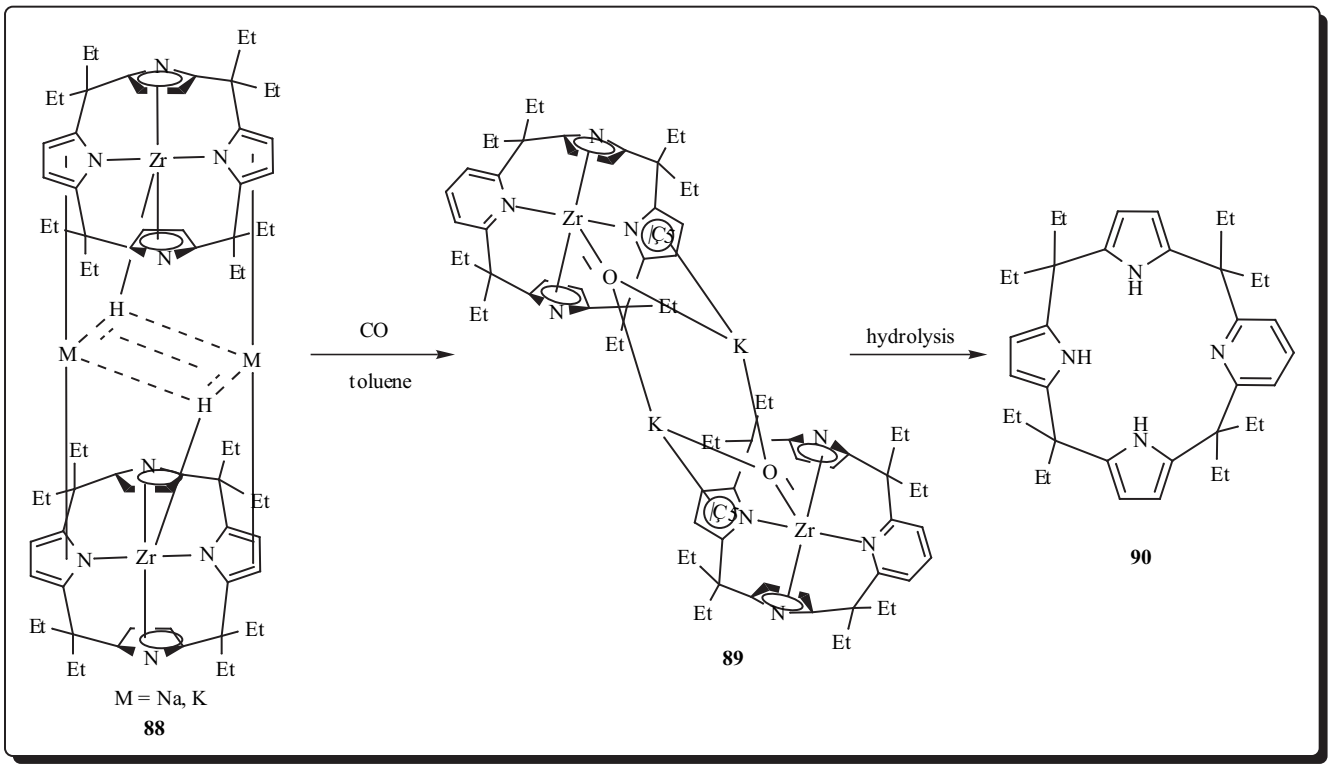
As discussed above, the major synthetic routes to carbon-bridged calixarenes are condensation reactions of arenes or heterarenes and carbonyl compounds, but this method is not suitable for the synthesis of calix[4]pyridine.

The first calix[4]pyridine was reported in 1987 by George R. Newkome *et al.* [37]. MeCN was treated with LiH in 5% tetramethylethylenediamine (TMEDA)-benzene to generate lithioacetonitrile, which upon reaction with **51** afforded macrocycle **52** in 22% yield. Compound **52** was hydrolyzed with alcoholic HCl to give dione **53**, which was oxidized with SeO_2 to afford the desired tetraketone **54**. Alternatively, **54** was prepared by the oxidation of **52** with *m*-chloroperbenzoic acid (*m*-CPBA) to give diacetal **55**, which was deprotected with conc. HCl to afford tetraketone **54** (Scheme **8**). Compound **54** is severely distorted from a planar conformation into a saddle shape, with N-lone pairs pointing alternately above and below the best plane of the four nitrogen atoms.

Corrado Rizzoli reported the use of metal-assisted transformations of porphyrinogen skeleton in macrocyclic modification. An organometallic carrier was added to form the alkali metal hydrido derivatives **88**. Then, the derivatives were treated with CO in toluene. After hydrolysis, the *meso*-octaethylmonopyridine-trispyrrole macrocycle **90** was obtained [75].

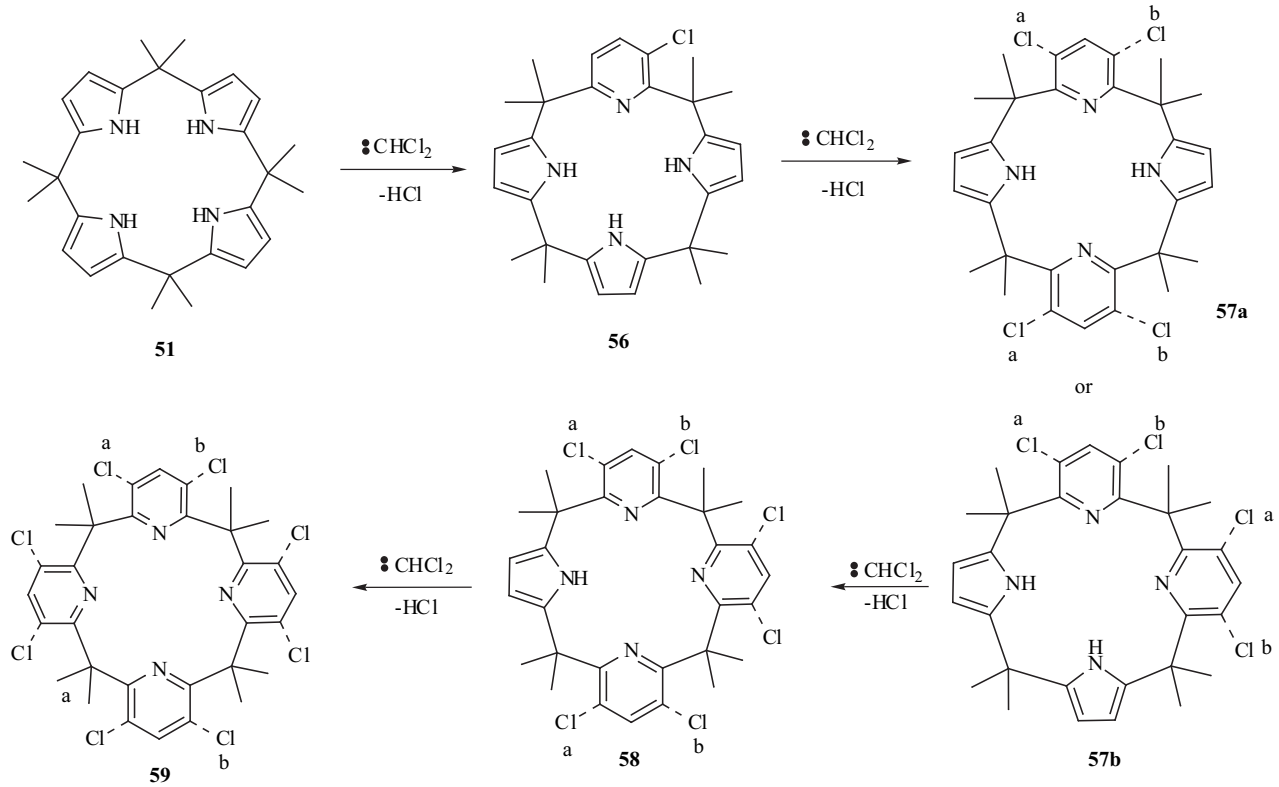


Scheme 8.

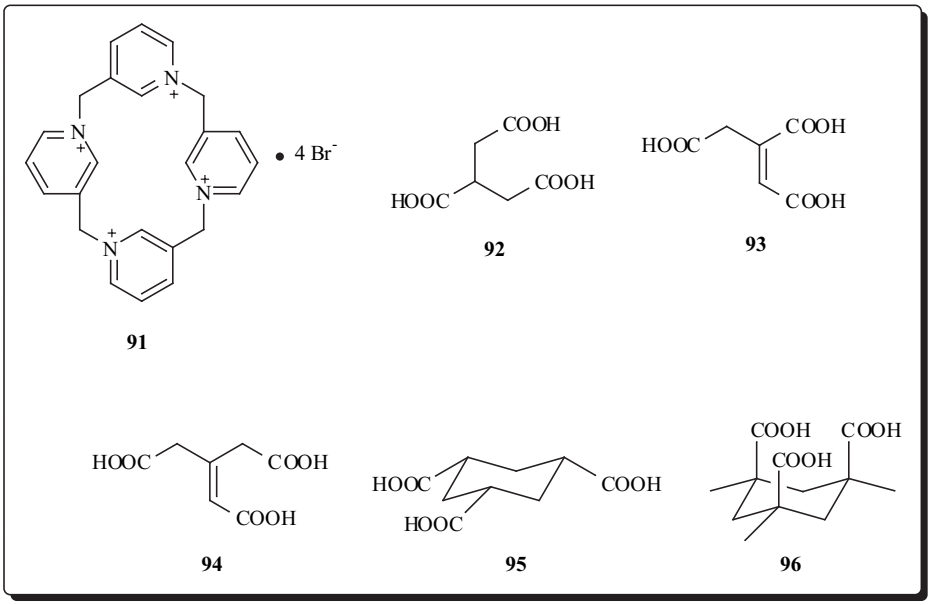


The group of J. L. Sessler reported the first sp^3 hybridized carbon bridged calix[4]pyridine [38]. *meso*-octamethylcalix [4]pyrrole could be converted to macrocycles containing one, two, three and four pyridine rings. Using dioxane as solvent and 15 equiv. of sodium trichloroacetate, a 2.4:1 mixture of the mono- and di-pyridine macrocycles **56** and **57** were formed. When the same reactions were employed using 1,2-dimethoxyethane as solvent, a mixture of di-, tri- and tetra-pyridine species **57**, **58** and **55** was obtained in a 1:1:1 ratio (Scheme **9**).

Satoshi Shinoda *et al.* reported a new specific macrocyclic receptor **91** *via* a one-step synthesis. The



Scheme 9. The chlorine atoms indicated may be present in position 'a' or 'b', but not both. This results in isomers.



tricarboxylic acid **92-96** was deprotoned, and the anion could be used as guests [78].

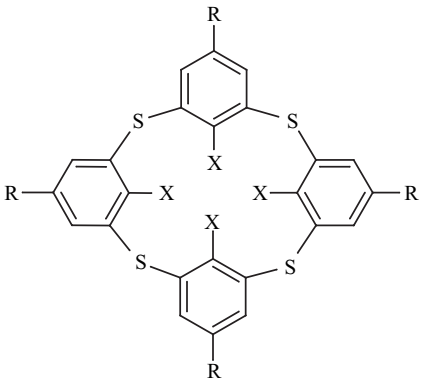
V. THIACALIX[4]ARENES

Similar to conventional calix[4]arene, *p-tert*-butylthiacalix [4]arene has four conformations, i.e., cone, partial cone, 1, 3-alternate, and 1, 2-alternate [39]. Thiacalix[4]arenes have three advantages over conventional calixarenes: (1) Thiacalix [4]arenes enlarge the calix skeleton to provide larger cavity; (2) ready oxidizability of the sulfur bridges to sulfoxide and sulfone provides new members of S bridged calixarenes; (3) coordination to specific metal ions could be controlled by the oxidation state of S [40]. As a result, thiacalixarenes developed rapidly in recent years.

Sone *et al.* reported the synthesis of *p-tert*-butylthiacalix[4]arene **60** [41], with a very low yield. Kumagai later reported a simpler method for synthesizing *p-tert*-butylthiacalix[4]arene, which led to the development on the study of thiacalix[4]arene and its derivatives. The method involved heating *p-tert*-butyl phenol and sulfur to 230 °C for 4h in the presence of base, which gave thiacalix[4]arene in a yield of 54% together with small amounts of *p-tert*-butylcalix[5]arene and *p-tert*-butylcalix[6]arene. Several other thiacalix[4]arenes could also be prepared directly using this method. Pavel Lhoták reported the synthesis of a deep-cavity thiacalix[4]arene derivative **61** from the condensation of biphenyl-4-ol with element sulfur at 230 °C for 6 h [42]. In addition, the synthesis of thiacalix[4]arene analogs in which the bridge CH_2 was substituted by one, two, and three sulfur atoms was achieved [43].

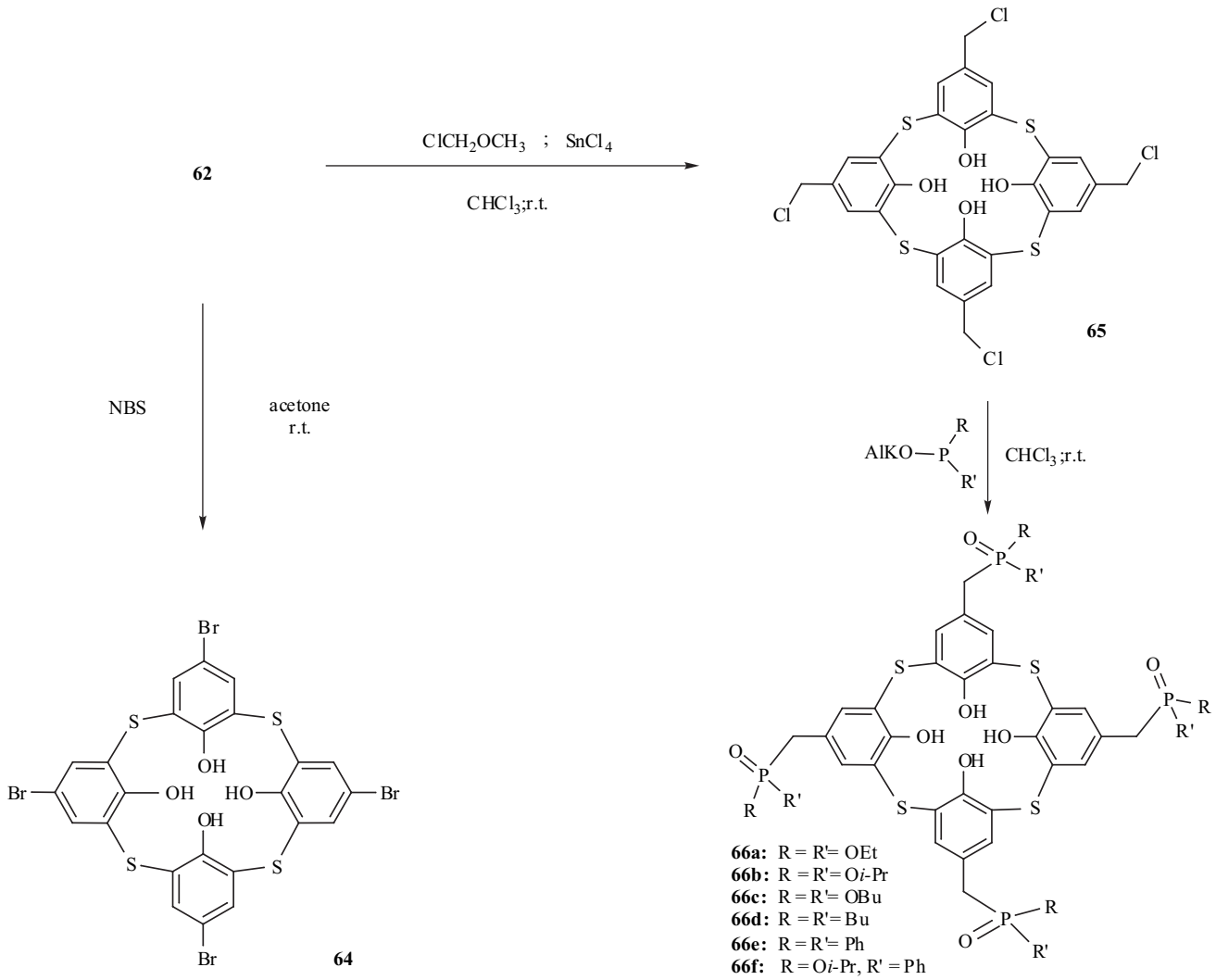
Various thiacalix[4]arene derivatives can be obtained by modifying thiacalix[4]arene. There are three major classes of modification methods: (1) modifying the wide rim chemically; (2) oxidizing the sulfur to sulfoxide and sulfone to enable the molecules to recognize different metal ions; (3) introducing functional group to the phenol hydroxyl at the narrow rim, which leads to the adjustment of the size of the cavity [44].

Treating *p*-tert-butylthiacalix[4]arene with 10.5 equiv of $AlCl_3$ at 80 °C led to compound **62** with the removal of the *tert*-butyl groups [45]. If the amount of $AlCl_3$ was decreased, thiacalix[4]arene derivatives with different numbers of *tert*-butyl groups were obtained. For example, with 7.4 equiv. $AlCl_3$, thiacalix[4]arenes with three, two, and one *tert*-butyl group were obtained, and the yields were 6.5%, 20%, and 21%, respectively [46-47]. By treating *p-tert*-butylthiacalix[4]arene with concentrated H_2SO_4 at 80 °C, a hydrophilic thiacalix[4]arene **63** with sulfonic group at the wide rim was obtained [48]. Compound **63** was isolated in the form of its sodium salt. The synthesis of



Several derivatives of calix[4]arene

Thiacalix[4]arene	X	R
60	OH	But
61	OH	phenyl
62	OH	H
63	OH	SO_3Na
69	NH_2	But
72	SH	But
73	OCH_2COOEt	But
74	OCH_2COOH	But
75	$OC_2H_4OCH_3$	H



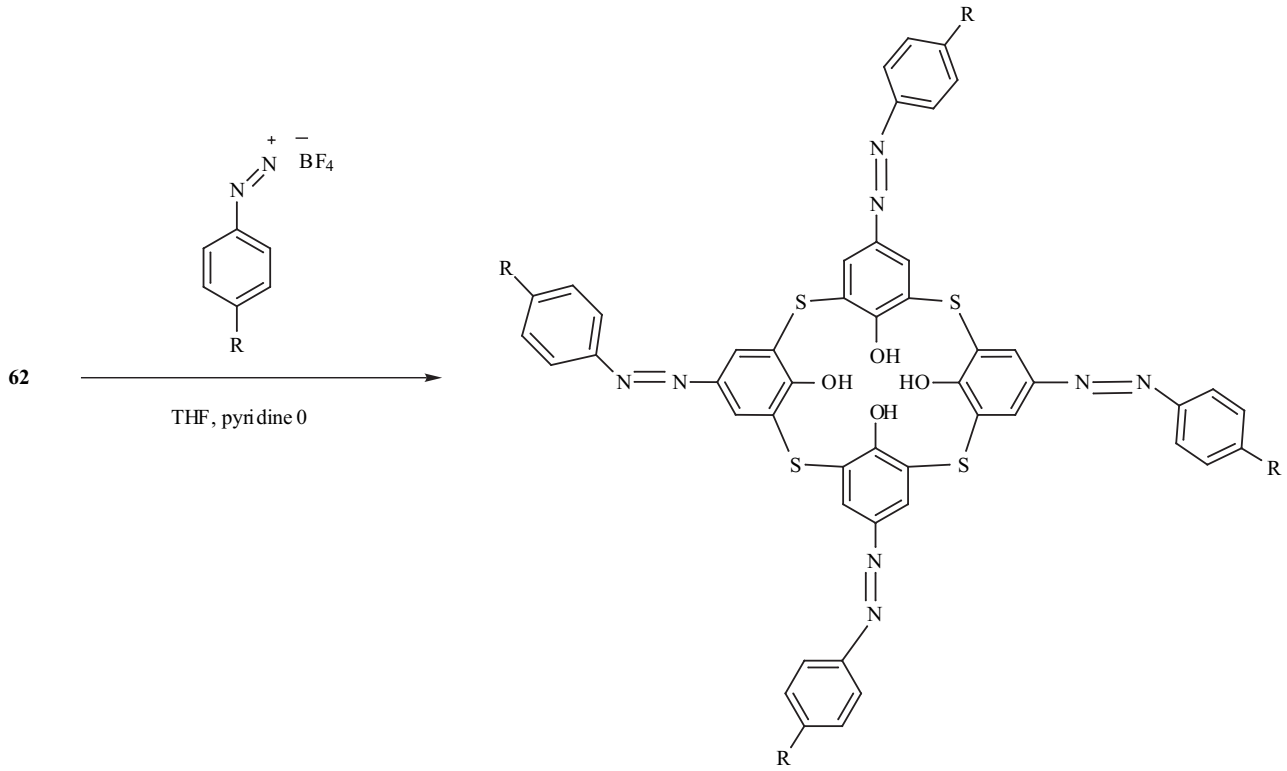
Scheme 10.

thiacalix[4]aren derivatives **64, 65,** and **66a-f** possessing reactive bromide, chloromethyl and diorganophos-phoryl groups on the upper rim of macrocycle was reported by Vitaly Kalchenko [49] (Scheme **10**).

Conventional Gross reaction for the formylation of tetraproxythiacalix[4]arene using $TiCl_4$ afforded 18-(chloromethyl)-28-hydroxyl-25, 26, 27-tripropoxythiacalix[4] arene substituted in the *meta*-position of the macrocycle. *p*-Tetraformyl-tetrapropoxythiacalix[4]arene, which was an interesting intermediate to the upper-rims functionalization of thiacalixarenes, was prepared in a very good yield using BuLi and *N*-formylpiperidine [50]. Compounds **67** and **68** were prepared by reacting the respective benzenediazonium tetrafluoroborate salts with **62** in THF, in the presence of pyridine, in yields of 71% and 64%, respectively (Scheme **11**) [51]. Compound **67** could be reduced by Sn/HCl, leading to **69** as the major product [52].

The mixture of H_2O_2, acetic acid, and *m*-chloroperbenzoic acid could oxidize thiacalix[4]arene to the corresponding tetrasulfone derivative **70** and tetrasulfone derivative without *tert*-butyl, with yields of 28% and 20% respectively. The later product formed a three–dimensional network attributed to the packing interaction of phenyl ring [53]. Sulphonylcalix[4]arene **71** could be received through oxidizing thiacalix[4]arene using the mixture of H_2O_2 and $NaBO_3$ in acetic acid [54]. Oxidizing the *p-tert*-butylthiacalix[4]arene in which the hydroxyl groups were protected by methyl groups led to sulphinylcalix[4]arene and sulphonylcalix[4]arene with methoxy groups substituted at the narrow rim [55-56]. A series of alkyl substituted thiacalix [4]arene derivatives could be oxidized with $NaNO_3/CF_3COOH$ and led to the corresponding tetrasulfoxides where alkyl and sulfoxide groups were oriented in the opposite directions in a stereoselective manner [57].

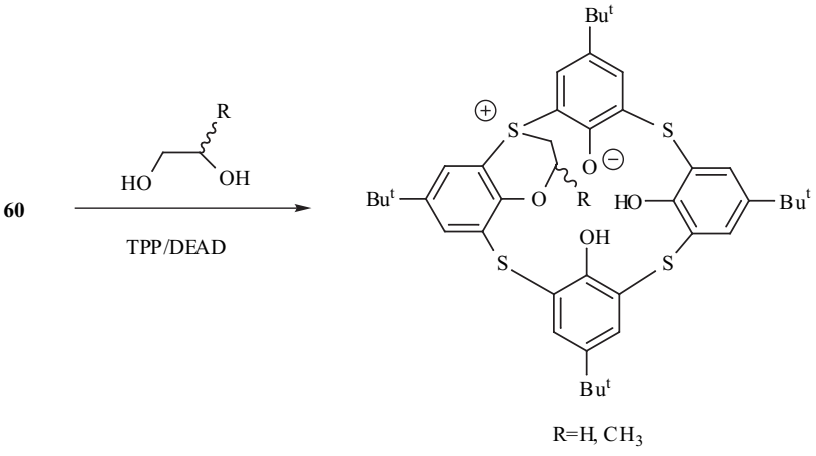
Rao *et al.* attempted, without success, the synthesis of hydroxyl substituted thiacalix[4]arene at the narrow rim using *p-tert*-butyl benzenethiol and sulfur as starting material through the method of preparing *p-tert*-butylcalix[4]arene. *p-tert*-Butylthiacalix[4]arene used as the starting material was refluxed with $ClC(S)NMe_2$ and K_2CO_3 in acetone. The product was obtained by carrying out Newman-Kwart rearrangement at 300°C in vacuum. After using anhydrous hydrazine at 100°C for deprotection, p-*tert*-butylthiacalix[4]arene derivative **72**, with the four original hydroxyl groups replaced by sulfhydral groups, was obtained with yields up to 80% [58]. Refluxing thiacalix[4]arene with alkylation agents (RI, RBr) and K_2CO_3 or Cs_2CO_3 in acetone or acetonitrile, thiacaix[4]arene derivatives that were alkylated at the four site at the narrow rim were



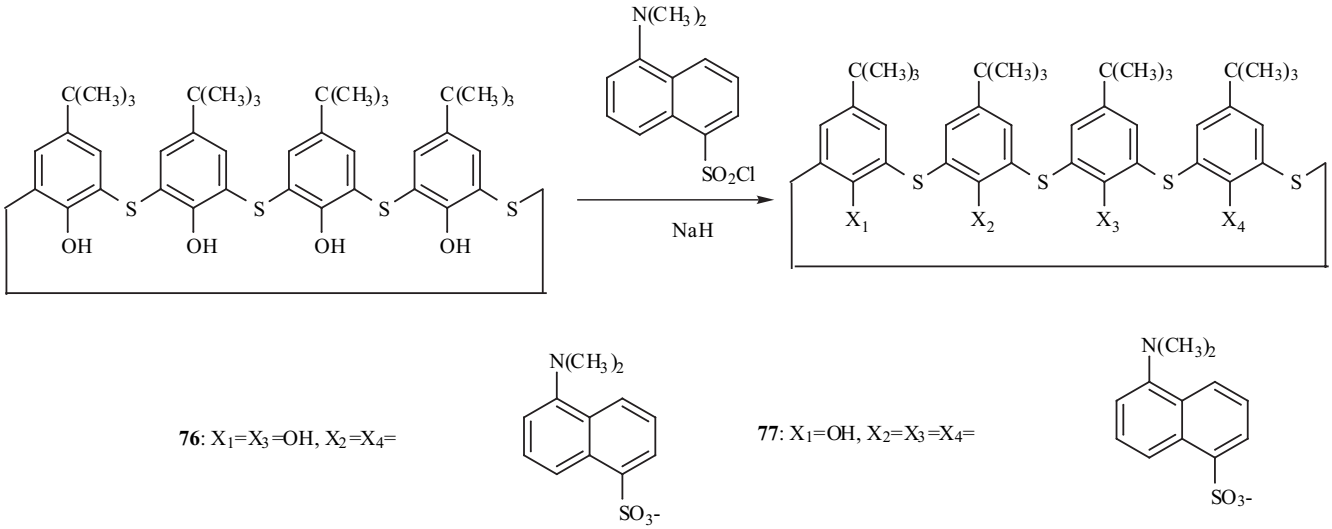
Scheme 11.

obtained, with yields between 45-92% [59-60]. By reacting *p-tert*-butylthiacalix[4]arene with a large excess of $BrCH_2COOCH_2CH_3$ in acetone catalyzed by Na_2CO_3, K_2CO_3 and Cs_2CO_3 respectively, thiacalix[4]arene derivative **73** was obtained [61-63]. If only two equivalents of $BrCH_2COOCH_2CH_3$ were used, thiacaix[4]arene diacetate was obtained from the reaction catalyzed with Na_2CO_3. Compound **74** was obtained upon hydrolysis of thiacalix[4]arene tetraacetates using LiOH in THF/H_2O solution [64]. Based on this reactive intermediate a series of derivatives were obtained [65-67]. O,O''- and O,O'-*Bis*(2-aminoethyl)-*p-tert*-butylthiacalix[4]arene were prepared by reduction of the corresponding O,O''- and O,O'-bis(cyanomethyl) ethers. Their syn-O,O''- and O,O'-counterparts had been prepared by alternative routes *via* the Mitsunobu reaction of the thiacalix[4]arnene with *N*-(2-hydroxyethyl) phthalimide and the reduction of a *O,O'*-disiloxanediyl-bridged O'',O'''-*bis*(cyanomethyl) ether with a 1,2-alternate conformation, respectively. These products were expected to serve as useful precursors of highly elaborated synthetic receptors, including biscalixarenes [68]. In addition, derivative **75** with four ether groups at the narrow rim could be obtained by reacting thiacalix[4]arene with 1-methoxy-2-(toluene-4-sulfonyloxy)ethane and Cs_2CO_3 in DMF [64]. Cycloalkylations of **60** with various alphatic glycols were performed by the group of István Bitter using the Mitsunobu protocol involving the triphenylphosphine (TPP)/diethyl azodicarboxylate (DEAD) system [69]. The reaction of *p-tert*-butylthiacalix[4]arene with diols afforded sulfonium phenoxide betaines *via* O,S-cyclization, which was the first example of the alkylation of the sulfide bridge (Scheme **12**).

In the presence of Cs_2CO_3, treating thiacalix[4]arene with chloromethylpyridine led to a derivative that was substituted



Scheme 12.

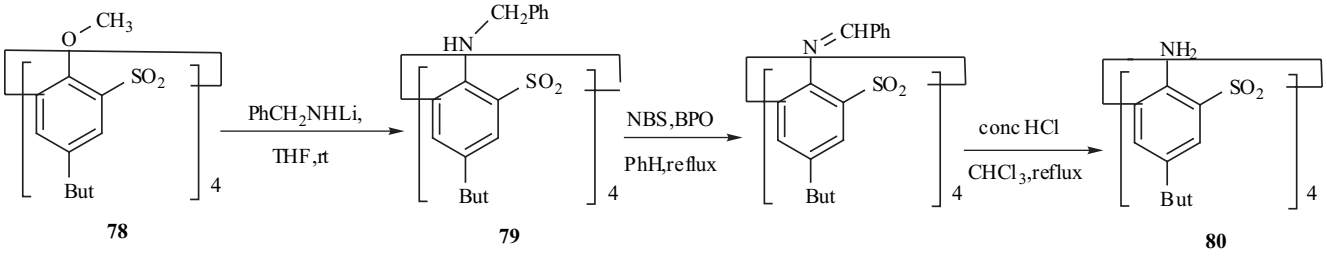


Scheme 13.

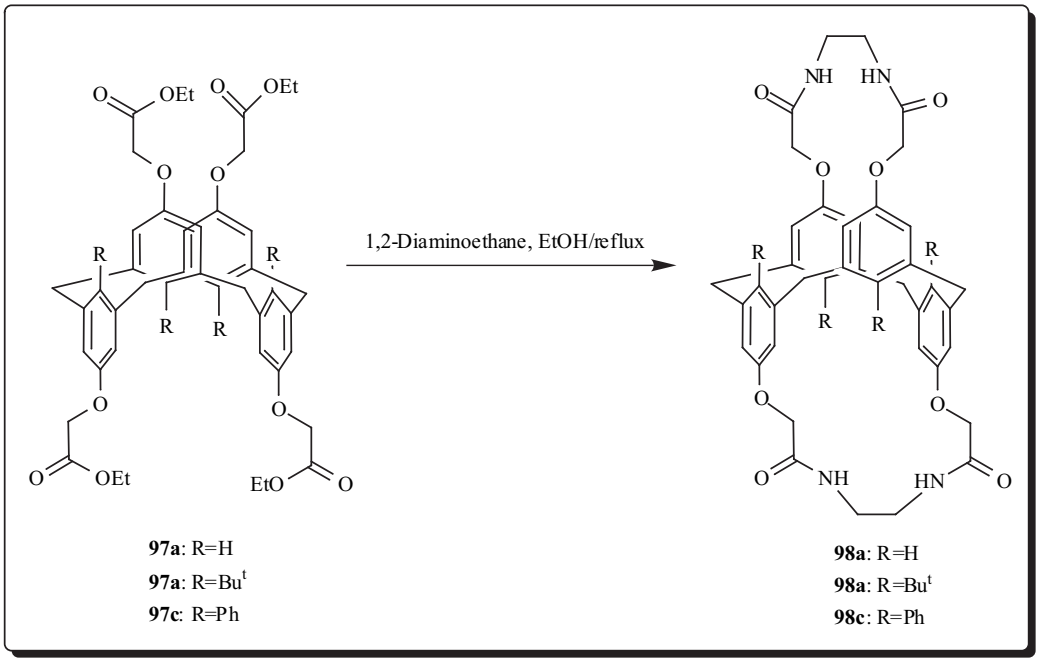
by four methylpyridinyl group at the narrow rim [69]. Narita *et al.* prepared **76** and **77** using *p-tert*-butylthiacalix[4]arene as the stating material (Scheme **13**), **76** and **77** were both found to be water-solubility.

Higuchi subsequently prepared 11 products containing different numbers of dansyl and *tert*-butyl groups by changing the amount of dansyl chloride used [46].

Katagiri *et al.* reported the preparation of thiacalix[4]arene derivative **80** [70]. Reacting **78** with $PhCH_2Li$ in THF, compound **79** could be obtained. Dehydrogenation of **79** followed by hydrolysis resulted in compound **80**. The introduction of the amino group allowed simple modification of thiacalix[4]arene. Sulfinylcalix[4]arene derivative could be prepared using a similar method (Scheme **14**).



Scheme 14.



Pavel Lhoták *et al.* [79] reported that the cagelike thiacalix[4]arene derivatives in a 1, 3-alternate conformation was prepared. The products **98a-c** were obtained by using thiacalix[4]arene tetraethyl esters **97a-c** and 1, 2-ethanediamine.

VI. AROMATIC TETRASULFONAMIDE MACROCYCLES

In recent years, a class of backbone-rigidified aromatic oligoamides with a localized, three-center H-bond was reported [71-74]. We tried to extend the backbone-rigidification strategy to the design of folded aromatic oligosulfonamides, as shown by general structure **81**. Using benzenedisulfonyl chloride **82** and diamine **83** as the starting materials, in the presence of Et_3N, and CH_2Cl_2 as solvent, the initial expectation was to obtain backbone-rigidified aromatic polysulfonamides. Surprisingly, compound **84a-d** that adopt a cone conformation similar to that observed for calix[4]arene, were obtained in yields ranging from 38% to 51%.

Before our discovery, calix[4]arenes bridged by the sulfonamide group were not known. Compound **84a** was crystallized from DMF. The crystal structure of **84a** revealed a cone conformation with a *C*2 axis. Such a cone conformation contains a cavity surrounded by four aromatic residues, in which the two diamine residues are parallel to the *C*2 axis and thus to each other. The alkoxy side chains of the four residues are attached to the wider rim of the molecule and the four sulfonamide groups define the narrower rim. All four N-H groups point away from the center of the cavity, thus there are no intramolecular H-bonds between the alkoxy oxygens and the sulfonamide protons.

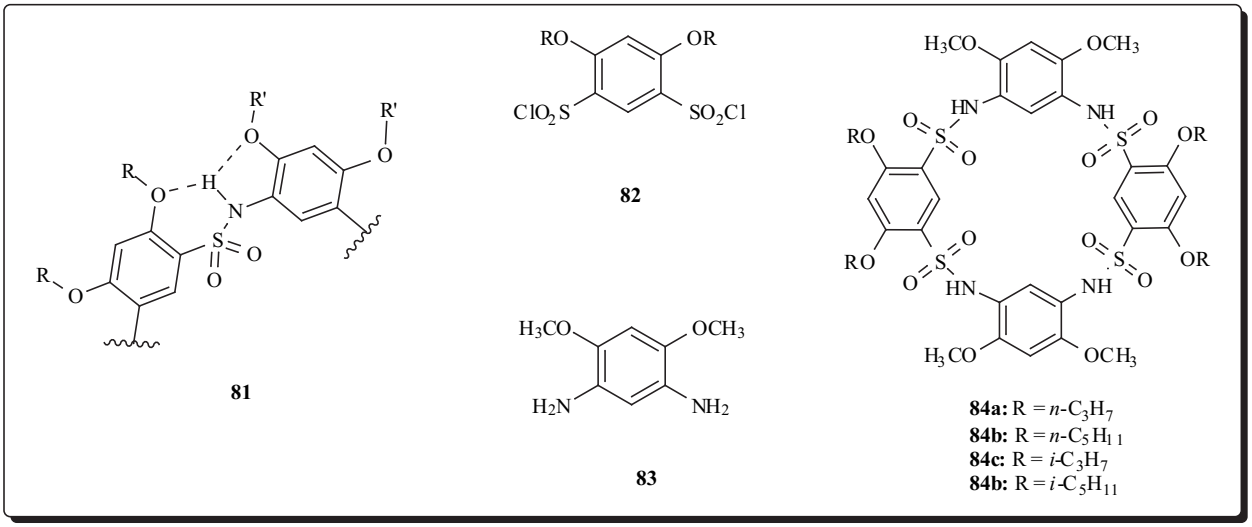
While the cone conformation clearly exists in the solid state, it was not clear whether it prevails in solution. Variable-temperature ^{1}H NMR experiments were performed with the more soluble **84b** in DMF-d_7. It was found that there was a very small downfield shift (~0.06 ppm) for all aromatic and alkyl protons as temperature was varied, which indicated that any change of **84b** from one conformation to another through the annulus of the molecule was unlikely. These results suggest that this class of molecules have a very stable cone conformation in both solid state and in solution, a feature that is not associated with many other calix[4]arenes. In the crystal structure of **84a**, a DMF molecule was also found to be sandwiched between the diamine residues. This observation suggests that other guest molecules may also be complexed in the cavity of **84a-d**.

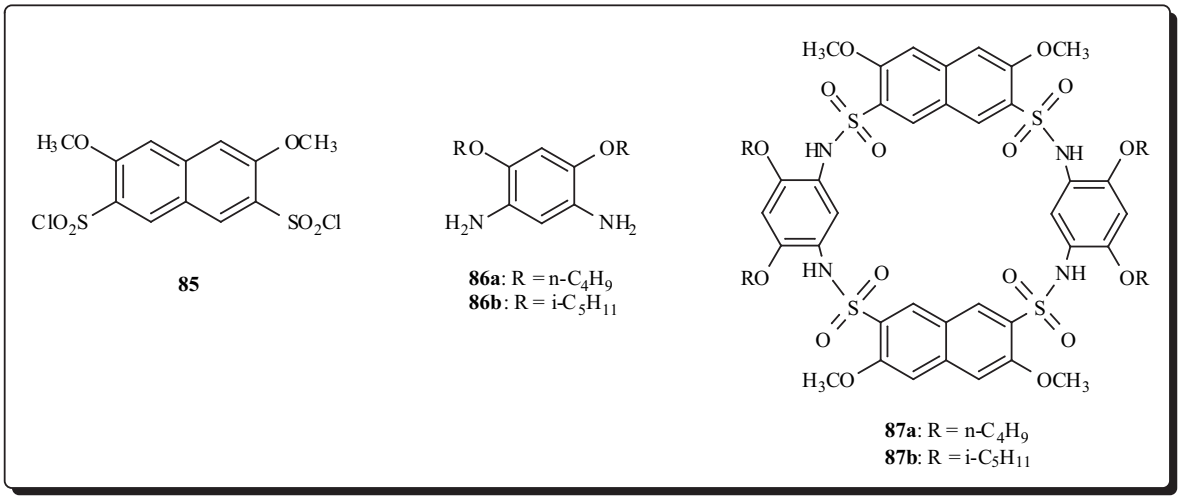
If the diarysulfonamide moiety is indeed a generalized structural motif, aromatic oligosulfonamide macrocycles with similar conformations, but larger cavities than those of **84a-d**, should be available by including larger aromatic rings into the design. Thus, naphthalenedisulfonyl chloride **85** was reacted with diamines **86a-b** in methylene chloride in the presence of triethylamine at room temperature, followed by heating the solution under reflux for 12 hrs. Indeed, sulfonamide bridged calix[4]arenes **87a-b** were obtained as the major products. In the solid state, macrocycle **87a** adopts a cone conformation that is very similar to that of compound **84a**. NOEs between the protons of methoxy and butyl groups were revealed by NOESY, which suggests that in solution, **87a** adopts a conformation that is similar to the one in the solid state. As expected, the naphthalene residue of **87a** leads to a cavity (8.47Å x 8.89 Å, measured by distances between the centers of non-adjacent aromatic rings) that is larger than that of **84a** (6.98 Å x 7.97 Å).

Single crystals of **87a** were grown by cooling from DMF. A DMF molecule was found to sit deep in the cavity of **87a**. In order to probe whether molecules larger than DMF can be accommodated by such an enlarged cavity, macrocycle **87b**, which differs from **84a** only in is side chains, was washed with THF and then crystallized by cooling from pyridine. The crystal structure of **87b** reveals a conformation that is essentially the same as that of **87a**. A pyridine molecule is found to be sandwitched between the two benzene rings of the diamine residues, which suggested that this class of macrocycles have a sufficiently large, well-defined cavity with the potential ability to undergo conformational fine-tuning for binding organic molecules of a variety of sizes. Even more interesting is the presence of a THF molecule that is "holding up" by four isopentyl side chains. This result suggests that it is possible to design sophisticated hosts by incorporating different side chains into the macrocycles [75-77].

CONCLUSIONS

The introduction of various aromatic rings and heteroatoms as bridging atoms into calixarene-type macrocycles offers numerous opportunities for tuning the affinity and selectivity





of these hosts toward ions or small molecules. Compared with conventional calixarene, the number of heterocalixarenes, and the corresponding studies on the conformations and applications of these molecules is still rather limited. This area remains largely unexplored.

ACKNOWLEDGEMENTS

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