SYNTHESIS III - ADVANCED FUNCTIONALIZATION OF THIACALIXARENES

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Thiacalixarenes have been synthesized by using calixarenes as templates for pre-organization of phenol units in a conformation suitable for subsequent cyclization (Chapter 3). The same strategy was applied successfully to synthesize calixpyrrole and related structures using thiacalixarenes as templates, in anticipation of developing a diverse variety of cation and anion sensors. In the present approach, we appended/pre-organized bridges (to the lower rim of thiacalix framework) first and then added arene units (pyrrole in this case) later. Thus, apart from creating thiacalix-calixpyrrole nanotubes in analogy with the templated thiacalixarene synthesis, we had an option of adding pyrrole units when the thiacalix framework is locked in 1,3-alternate conformation. This would give a flexible claw like bipyromethane pairs on both above and below the molecular plane (arene framework). These claws in turn can be used for ionic recognition by way of NH-anion hydrogen bonding, as bipyromethanes are very good functions for anion recognition, especially in the case of inorganic anions.
**1 | INTRODUCTION**

Calixpyrroles 1 (also known as porphyrinogens) are among the oldest of the synthetic cyclooligomers, having first been obtained by Baeyer in 1886 by condensation of acetone with pyrrole.\(^1\) Later, the synthesis was refined by many research groups\(^2-15\) as putative anion binders and metal complexing agents. A variety of ketones, like alkanones, cycloalkanones, and acetophenones have been used\(^16\) in place of acetone (Scheme 4.1). The products in most cases are the calix[4]pyrroles 1, except when diaryl-di-(2-pyrrolyl)methanes are condensed with acetone, calix[6]pyrroles 3 can be synthesized in as high as 25% yields using appropriate catalysts\(^16,17\) (Scheme 4.2).

Although the condensation of pyrrole generally proceeds via the 2,5-positions leading to structure 1, isomeric structures have also been found in which one or more of the pyrrole rings are incorporated via the 2,4-positions.\(^19\) The distribution of isomers is strongly dependent on solvent, catalyst and temperature. With cyclohexanone, for example, in ethanol (reflux, 4h) gives up to 22% of calix[4]pyrrole 4 with one inverted pyrrole ring, while p-toluenesulfonic acid in CHCl\(_3\) (reflux, 60h) gives 57% of calix[4]pyrrole 5 with two adjacent inverted pyrrole rings (Figure 4.1).\(^18\) Condensations of pyrrole with hydroxy acetophenones lead to mixtures of all possible configurational isomers, which can be separated by column chromatography.\(^16,14\) The hydroxy groups at the aryl moieties can be used to introduce additional functionalities.\(^15\) Condensation of pyrrole with ketone
mixtures occurs randomly, leading to products with two different bridges,\textsuperscript{[19,20]} for example, 6 & 7 (Scheme 4.3).

A novel series of macrocycles 8-10, called \textit{calixphyrins}, intermediate between porphyrins and calixpyrroles, have been prepared by acid-catalysed condensation of mesityldipyrromethane with acetone followed by DDQ oxidation. Calix[4]- and -[8]phyrin 8 & 10 were characterised by X-ray crystallography (Scheme 4.3).\textsuperscript{[21,22]} Particularly interesting examples are - (a) the cylindrical compound 11 obtained in 32\% yield from the condensation of pyrrole with the \( p \)-t-butylicalix[4]arene 2-ketopropyl ether\textsuperscript{[23]} In like fashion, using the calix[5]arene counterpart, a cylindrical compound 12 containing calix[5]arene and calix[5]pyrrole rings is obtained in 10\% yield,\textsuperscript{[24]} (Scheme 4.4) - (b) the "strapped calixpyrrole" 13 was obtained using a "pre-strapped" diketone (Figure 4.2).\textsuperscript{[16]} Several partially but usefully functionalized calix[4]-pyrroles 14 & 15 have been synthesized via lithiation of one or two \( \beta \)-positions followed by quenching with electrophiles like ethylbromoacetate\textsuperscript{[7]} or \( \text{CO}_2 \),\textsuperscript{[25]} or \textit{via} iodination\textsuperscript{[26]} of one \( \beta \)-position.\textsuperscript{[27]} The latter one was used in a synthesis of the mono-ethynyl calix[4]pyrrole 15 which then was converted into bis-calix[4]pyrroles.\textsuperscript{[28]} Various applications of calixpyrroles have been based on their capacity to form NH hydrogen bonds to anions.\textsuperscript{[29-35]}
As noted in preceding description, brief as it may be, calixpyrroles offer diverse opportunities as far as their synthesis and applications go. This rich potential of calixpyrroles led us towards exploration of novel calixpyrrole assemblies built upon thiacalix framework, in anticipation of manifesting some sophisticated supramolecular hosts for ionic recognition and, hopefully, neutral host-guest assemblies.

2 Objectives and Investigation

Thiacalixarenes have been synthesized by using calixarenes as templates for pre-organization of phenol units in a conformation suitable for subsequent cyclization (Chapter 3). The same strategy can be applied successfully to synthesize other supramolecular structures using thiacalixarenes as templates. In fact, Sessler et al.\cite{23,24} has already synthesized calixarene capped calixpyrrole, which was our inspiration for using calixarenes as templates for thiacalixarene synthesis in the first place. Thus, we channeled our efforts towards synthesis of thiacalixarene capped calixpyrroles and related compounds with an intention of developing a host molecules for ionic recognition.

In templated thiacalixarene synthesis - we preorganized aromatic units and added sulfur bridges subsequently for cyclization, the approach here was, however, different from the one illustrated in Chapter 3 in that, in present approach, we appended/pre-organized bridges (to the lower rim of thiacalix framework) first and added arene units (pyrrole in this case) later. This means, apart from creating thiacalix-calixpyrrole nanotubes in analogy with the templated thiacalixarene synthesis, we had an option of adding pyrrole units when the thiacalix framework is locked in 1,3-alternate conformation. This would give us a flexible claw like bipyrromethane pairs on both above and below the molecular plane (arene framework). These claws in turn can be used for anionic recognition by way of NH-anion hydrogen bonding. As has already been discussed later (in Chapter 6), bipyrromethanes are very good functions for anion recognitions, especially in the case of inorganic anions.
As illustrated in Scheme 4.5 two pyrrolyl assemblies can be constructed upon thiacalixarene framework, using cone and 1,3-alternate tetraacetonyl thiacalixarenes 17 & 18 respectively. Compounds 17 & 18 were synthesized by alkylation of thiacalix hydroxyl groups with chloroacetone in presence of alkali carbonates as templates to lock the alkylation products in cone (Na₂CO₃) or 1,3-alternate (K₂CO₃) conformations. Subsequent reactions with pyrrole in presence of a lewis acid catalyst (methanesulfonic acid) resulted in products 19 (in case of cone conformer) and 20 (for 1,3-alternate) conformer. Complexation studies of 20 for anion recognition have been covered in chapter 6.

2.1 STRUCTURE OF PYRROLYL-THIACALIX[4]ARENES

The ¹HNMR of 19 in CDCl₃ shows that the pyrrole NH protons, which were observed at unusually high δ 11.22 ppm in calix[4]arene-calix[4]pyrrole tube prepared by Sessler et. al. (23), resonate at δ 9.13 ppm. This upfield shift of NH protons can be attributed to the weakening of hydrogen bonding between the pyrrole NH groups and the thiacalixarene lower rim oxygen atoms due to migration on an enlarged framework (C-S bond in TCA bridge is ca. 15% longer than C-C bond in CA). Step wise addition (0.5×10⁻² M in CDCl₃, 0.1mL×6) of CD₃OD to the NMR solution of 19 (0.5×10⁻³M, 1.2mL) in an attempt to disturb this hydrogen bonding interaction, shifted the NH proton resonance downfield to δ 9.92 ppm, a significant change (Figure 4.3). Similarly, addition of fluoride ions (as tetrabutylammonium fluoride), which has been known to bind strongly to other calix[4]pyrroles,
caused 0.37 ppm downfield changes in the NMR spectrum. However, calix[4]arene-calix[4] pyrrole tube prepared by Sessler et. al. remained unaffected by aforementioned attempts to disrupt the intramolecular hydrogen bonding between NH protons and lower rim O functions of calix[4]arene. Moreover, the calix[5]arene-calix[5]pyrrole tube, also prepared by Sessler et. al. showed a weaker hydrogen bonding as compared to corresponding [4]homolog, and the NMR characteristics of 19 are more comparable to the [5]homolog. Based on these findings, we can safely conclude that compound 19 is adopting a cylindrical conformation in solution due to these clearly favorable NH-O hydrogen bonds, yet the said hydrogen bonding is not strong enough to withstand external approaches.

3 EXPERIMENTAL

All the reagents used were of AR grade, procured from Sigma-Aldrich. The reagents were used without further purification. The solvents were dried appropriately wherever required. Melting points were taken in a single capillary tube using a Toshniwal melting point apparatus and are uncorrected. Elemental analysis was carried out on Heraeus CarloEbra 1108 elemental analyzer. FT-IR spectra were recorded on Bruker tensor 27 Infrared Spectrophotometer as KBr pellets and expressed in cm⁻¹. UV absorption studies were carried out on a JASCO 570 UV/VIS/NIR Spectrophotometer. NMR spectra were recorded on Bruker DPX-400 AVANCE in CDCl₃ with tetramethylsilane as internal standard. Mass measurements were done on Thermo Finnigan TQS Quantum Discovery Mass Spectrometer using electrospray ionization. Thermal studies were carried out on Mettler Toledo DSC 822e. Powder XRD analysis was performed on Panalytical X’Pert PRO X-Ray Diffractometer. Purity of the synthesized compounds was ascertained on Perkin Elmer 200 Series Liquid Chromatograph with Thermo Electron Betasil C₁₈ reversed phase column (100mm long and 3.0mm internal diameter, 3μm particle size) maintained at 45°C, mobile phase composition was methanol:0.01% acetic acid (90:10, v/v).

3.1 SYNTHESIS AND ISOLATION

3.1.1 SYNTHESIS OF THIACALIXARENES TETRA-KETONES

1 and Na₂CO₃ (for cone) or K₂CO₃/Cs₂CO₃ (for 1,3-alt) were added to chloroacetone in dry acetone. The reaction mixture was heated to reflux and stirred under inert (N₂) atmosphere for 6-12h, after completion of reaction as dictated by TLC (complete consumption of 1). After cooling, the mixture was filtered through a bed of celite, which was washed thoroughly with fresh acetone. Evaporation of the solvent furnished an
orange-red solid, which was then suspended in water at 60°C and stirred. The product was extracted into dichloromethane and washed with 0.1 N solution of sodium thiosulfate. Removal of the solvent left a yellow solid. Chromatography of the solid on silica gel (acetone/petroleum ether 1:5) afforded the product 1 (Na+) or 3 (Cs⁺/K⁺)(Scheme 4.6).

17: MP 180°C (d), MS m/z 944 (M+1), 1H NMR (300MHz, CDCl₃) δ 1.10 (36H, s, Bu′), 4.96 (8H, s, -CH₂O-), 7.25 (TC₄A-Ar), 1.49 (12H, s, CH₃), 13C NMR (75MHz, CDCl₃) δ 24.6, 31.4, 34.4 (Bu′) 126.1, 130.2, 147.3, 153.7, 210.4 (Ar), 80.6 (-OCH₂). EA: Calc. for C₃₄H₆₄O₈S₄ (C:66.07, H:6.82, S:13.54), Found (C:66.18, H:6.78, S:13.51).

1H NMR Spectrum of 17
13CNMR Spectrum of 17

1H NMR Spectrum of 18
3.1.2 SYNTHESIS OF THIACALIX-CALIXPYRROLE NANOTUBE

cone-p-tert-Butylthiacalix[4]arene tetraketone 2 (5g, 5.7mmol) was stirred at ambient temperature with pyrrole (1.53g, 23mmol) in a dichloromethane/ethanol mixture under inert atmosphere (N₂), in the presence of methanesulfonic acid for 2 days, closely monitored by TLC. The reaction mixture was then quenched with acetone. The solid residue was filtered and redissolved in chloroform followed by column chromatography on silica gel (CH₂Cl₂, eluant) affording the calixpyrrole-thiacalixarene pseudo dimmer 4 (nanotube) in 17% yield (Scheme 4.7). Compound 4 gave spectroscopic and analytical data in accord with the assigned structure.
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19: MP >300°C (d), MS m/z 1142 (M+1), ¹H NMR (300MHz, CDCl₃) δ 1.22 (36H, s, Bu₃), 3.89 (8H, s, CH₂O-), 7.25 (Tc4A-Ar), 5.79 (8H, s, pyrrolic-Ar), 1.51 (12H, s, CH₃), 9.13 (4H, s, pyrrolic-NH). ¹³C NMR (75MHz, CDCl₃) δ 18.9, 31.4, 34.2 (Bu₃), 114.9, 126.1, 143.3, 157.7, (Ar), 75.1 (-OCH₂). EA: Calc. for C₇₃H₆₇N₄O₄S₄ (C:71.54, H: 6.71, N:4.91, S:11.23), Found (C:71.44, H:6.76, N:4.89, S:11.12).

¹H NMR Spectrum of 19

¹³C NMR Spectrum of 19
3.1.3 **SYNTHESIS OF THIACALIXARENE BIPYROMETHANE ASSEMBLIES**

1,3-alt-p-tert-Butylthiacalix[4]arene tetraketone 3 (5g, 5.7mmol) was stirred at ambient temperature with pyrrole (3.06g, 46mmol) in dichloromethane solvent under inert atmosphere (N2), in the presence of methanesulfonic acid, for 3d. The reaction mixture was quenched in acetone or methanol and solid residue was redissolved in chloroform. Slow diffusion of acetone in the chloroform solution afforded needle shaped crystalline mass, which was filtered and washed with acetone. The mass was recrystallized from dichloromethane solution giving 5 in 41% yield (Scheme 4.8).


**20:MP >300°C (d), MS m/z 1410 (M+1), ¹H NMR (300MHz, CDCl₃) δ 1.32 (36H, s, Bu¹), 4.76 (8H, s, -CH₂O-), 7.75 (TC₄A-Ar), 6.09-6.75 (24H, m, pyrrolic-Ar), 1.59 (12H, s, CH₃), 8.93 (8H, s, pyrrolic-NH), ¹³CNMR (75MHz, CDCl₃) δ 23.2, 31.4, 35.2, 39.5 (Bu¹) 109.4, 114.4, 122.9, 126.1, 130.2, 135.0, 147.3, 153.7, (Ar), 77.6 (-OCH₂).


**¹H NMR Spectrum of 20**

![¹H NMR Spectrum of 20](image)
4 CONCLUSIONS

The templated synthesis was applied successfully to synthesize calixpyrrole and related structures using thiacalixarenes as templates. The approach yielded, in addition to anticipated thiacalix-calixpyrrole nanotubes in analogy with the templated thiacalixarene synthesis, a novel bipyrromethane cluster assembled upon thiacalix motif. The bipyrromethane cluster consists of a flexible claw like bipyrromethane pairs on both above and below the molecular plane (arene framework). These claws in turn can be used for ionic recognition by way of NH-anion hydrogen bonding (as demonstrated in chapter 6), as bipyrromethanes are very good functions for anion recognition, especially in the case of inorganic anions.
REFERENCES