Chapter II

CHAPTER II


2.1. Introduction

Anions play essential roles in biological systems and are important environmental pollution such as nuclear waste produced during the reprocessing of nuclear fuel. Anions participate 70% of all enzymatic binding events, serving as either enzyme substrates or cofactors. Further, excess phosphate and nitrate as the result of agricultural run-off and urban use are responsible for eutrophication in water-ways.

Simmons and Park reported the first synthetic polyammonium-based anion receptors in 1968.\(^1\) Since then especially over the course of the last two decades numerous anion receptors have been synthesized and studied. Over the past several decades a large number of acyclic and macrocyclic compounds have been synthesized as cation receptors and evaluated for their abilities to recognize cations.\(^2\) In recent years as the importance of anions in biological and environmental systems has become increasingly recognized and attention has been directed towards the design and construction of anion receptors. As a consequence both cation and anion recognition are now well-established branches of supramolecular chemistry.\(^3,4\) To effect anion recognition most ion pair receptors take advantage of hydrogen bonding donors (urea, amide, imidazolium, pyrrole, and hydroxyl group), Lewis acidic sites (boron, aluminum and uranyl) and positively charged polyammonium groups.

![Figure 2.1: Ion-pair interaction to receptor mediated ion-recognition](image)

---

1. Simmons, L. R.; Park, J. J. Am. Chem. Soc. 1968, 90, 5418.
2.2. *Calix[4]pyrrole as a anion receptor based on pyrroles*

The tetapyrrolic macrocycle *calix[4]pyrrole* was found in 1996 by Sessler *et al.* to be able to bind certain anions in organic solvents. In 2005 Moyer, Sessler and Gale et al reported that *calix[4]pyrroles* can act as an ion pair receptor for various cesium salts and certain organic halide salts in the solid state. X-ray crystal structures of several cesium and organic cation-containing anion complexes of *calix[4]pyrroles* were solved, Taken in concert they revealed that the anions are bound to the pyrrolic NH protons *via* hydrogen bonding. These interactions which were expected on the basis of prior studies serve to fix the *calix[4]pyrrole* in the cone conformation. This conformational locking in turn, provides an electron-rich bowl-shaped cavity into which, *e.g.*, cesium cation is bound *via* a combination of π-metal and dipole interactions. Further evidence that *calix[4]pyrrole* is effective for ion pair recognition came from liquid-liquid extraction studies carried out by Wintergerst *et al.* This study demonstrated that compound can extract CsCl and CsBr, but not CsNO₃, from an aqueous phase into nitrobenzene, a relatively polar organic phase. The solvent extraction process was modeled in terms of three thermochemical steps. The first of these steps involves a partitioning of the cesium cations and the halide anions into the nitrobenzene phase from the water phase. The second step involves a conformational change of the *calix[4]pyrrole* such that it adopts the cone conformation, a geometry it maintain as the results of halide anions binding. The third step involves the cesium cation binding within the bowl-shaped calix cavity created as the result of the conformational change takes place in 2nd step. While thermodynamically equivalent in terms of the final state it was appreciated that these steps could be taking place concurrently. The key point is that under conditions of this extraction *calix[4]pyrrole* binds both the cesium cation and a halide anions (Cl⁻ or Br⁻).

2.3. *History and structure of calix[4]pyrroles*

The white crystalline material first synthesized by Baeyer in 1886, by the cyclocondensation of pyrrole with acetone in the presence of hydrochloric acid. Later Chelintzev and Tronov repeated the reaction and proposed the structure of the compound which was named as α,β,γ,δ-octamethylporphinogen by Fischer. In 1955,
Rothemund and Gage improved this synthesis by using methanesulfonic acid as the catalyst. Other than these important findings this class of compounds (e.g., octamethylcalix[4]pyrrole) were only studied sporadically in the 100 years following their discovery, most of which merely focused on the refined synthesis of these macrocycles and their meso-substituted derivatives but not their applications. This situation changed in the early 1990s when Floriani and coworkers began exploring their metal coordination chemistry extensively, thus reviving interest in these venerable macrocycles after a long dormant period.

Calix[4]pyrroles, originally named “pyrrole-acetone” and formally known as meso-octaalkylporphyrinogens are macrocycles composed of four pyrrole units linked via four di-substituted meso-carbons at the α positions. Figure 2.2 describe the basic skeleton of calix[4]pyrrole where bracket number indicates the repeating pyrrolic units linked to each other by sp³ hybridized carbon atoms. calix[4]pyrroles are not readily oxidized to form porphyrin-like structures. As a consequence the four pyrrole units are all in their neutral NH-bearing forms in calix[4]pyrroles and no electron delocalization exists within the macrocyclic system as a whole.

![Figure 2.2: Structure of calix[4]pyrrole](image-url)

Calix[4]pyrrole can adopt four different confirmations: 1,3-alternate, 1,2-alternate, partial cone and cone, similar to calix[4]arene which has been observed experimentally and noted theoretically.

Calix[4]pyrroles or meso-substituted porphyrinogens are an important class of neutral macrocycles receptor capable of binding anions, transition metals and neutral molecules in both solution and solid states. The synthesis of calix[4]pyrroles bears analogy to that of porphyrin in that they obtained from the electrophilic α-substitution of pyrrole with ketones in the presence of acid catalyst.

There are three general method for the synthesis of calix[4]pyrroles:

(a) one-pot [1+1+1+1+1] condensation;
(b) [2+2] condensation and
(c) [3+1] condensation.

Scheme 2.1: Mechanistic presentation of the synthesis of calix[4]pyrrole
Although calix[4]pyrroles have been synthesized 100 years ago by the acid catalyzed condensation of ketones and pyrrole, after that a number of strategies have been employed to synthesized and characterized various functionalized calix[4]pyrroles by using a wide varieties of catalyst including HCl, Lewis acids, chlorzinc, p-toluenesulfonic acid or zeolites to improve the yield of specific calix[4]pyrroles. Among which an alternate synthetic protocol using acidic zeolites catalyst gave a facile and efficient method for the synthesis of variety of calix[4]pyrroles. The graphite oxide and reduced graphene oxide has been used as solid acid catalysts in organic and aqueous solutions for the preparation of 5,5-dimethyl-dipyrromethane and octamethylcalix[4]pyrrole at room temperature.

Interestingly, meso-octamethylcalix[4]pyrrole (OMCP) or acetonpyrrole was first reported by Baeyer, and its structure is shown in Figure 2.2 and N-confused calix[4]pyrrole (Figure 2.3) both macrocycles are position isomers. While in the regular calix[4]pyrrole the meso-carbons are always connected to C2 and C5 position of the pyrrole moieties, the N-confused isomer comprises at least one pyrrole moiety connected to the rest of the macrocycle via C2, C4-connection.

Scheme 2.2: Selective synthesis of calix[4]pyrrole and dipyrromethane using different catalyst
In the early 1990s, first reports emerged describing the identification of porphyrin isomers, in which one or more of the four pyrrole moieties are inverted.\textsuperscript{25,26} The inverted pyrrole in these N-confused porphyrins is connected to the rest of the macrocycle via one α-carbon (C2-position) and one β-carbon (C4-position) as opposed to α,α’-carbons (C2, C5-positions) in regular porphyrins.

Similarly to the formation of N-confused porphyrins, the condensation of ketones and pyrrole also produces a certain number of C2, C4-pyrrole connections giving rise to N-confused calix[4]pyrroles. The first N-confused calixpyrrole synthesis was reported in 1975 although the structural assignment may not have been correct, as the NMR spectra were not recorded at the time.\textsuperscript{27} Inspired by the earlier report and by further reports on N-confused porphyrins, Dehaen and co-workers mounted the first systematic effort aimed at the preparation of N-confused calix[4]pyrroles which provided the first rational synthesis of this calix[4]pyrrole isomer.\textsuperscript{28}

### 2.5. Conformations of calix[4]pyrrole and their relative energies

Calix[4]pyrrole shows geometrical resemblance to calix[4]arene and that it would be expected to adopt four major conformations like calix[4]arene. Energies optimization by BLYP/6-31G, and BLYP/6-31+G** methods reveals that the predicted orders of stabilities for the gas phase and CH$_2$Cl$_2$ solution are namely 1,3-alternate > partial cone > 1,2-alternate > cone. Molecular mechanics calculations indicate that the 1,3-alternate conformation is most stable conformation in case of calix[4]pyrrole having torsional interaction of about 1-2 kcal/mol smaller than that of the other conformations. Each set of adjacent pyrrole rings in calix[4]pyrrole has an inherent propensity to exist in an anti rather than syn orientation. In the 1,3-alternate conformation each adjacent pyrrole pair
is anti as a result this particular conformation benefits the most from this electrostatic effect. On the other hand, the pyrroles in the cone conformation are point to the same direction and as a result this conformation suffers the most from electrostatic repulsion.


Experimental results indicate that meso-alkyl substituted calix[4]pyrrole form 1:1 complexes with fluoride and chloride anions. In these anion complexes the calix[4]pyrrole macrocycles are observed to adopt the cone conformation with the anion sitting above the cone and forming four hydrogen bonds with the four pyrrole N-Hs.\(^{29}\) On the other hand neutral molecules such as alcohols and amides form 2:1 complexes with calix[4]pyrroles. Optimization of all the putative anion-binding structures for all the four limiting conformations of calix[4]pyrrole showed that 1,3-alternate structure is unstable and is converted into the cone structure upon geometry optimization.\(^ {30}\)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{conversion.png}
\caption{Conversion of 1,3-alternate conformation into cone in the presence of anion}
\end{figure}

In the case of cone structure it has four equivalent NH---F bonds of about 1.68 Å. Due to the short NH---F hydrogen bonds, the calix[4]pyrrole become flattened. This is indicated by the decrease of N1-C2-C3-C4 dihedral angles from -76° in F-free cone structure 6 to -64.8° in cone-F\(^ - \) complex. In contrast to the cone complex, the partial cone complex forms three NH- - -F hydrogen bonds.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Calculated structure of calix[4]pyrrole-F and their relative energies at BLYP/6-31-G* level}
\end{figure}
Table 2.1: Binding energy (kcal/mol) of 1:1 fluoride anion binding modes of calix[4]pyrrole calculated at the blyp/6-31+g** level

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,2-alternate $\Delta E_{binding}$</th>
<th>Partial cone $\Delta E_{binding}$</th>
<th>Cone $\Delta E_{binding}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas phase</td>
<td>-44.6</td>
<td>-56.0</td>
<td>-66.6</td>
</tr>
<tr>
<td>Solution</td>
<td>-7.0</td>
<td>-17.5</td>
<td>-27.6</td>
</tr>
</tbody>
</table>

There is a considerable change in geometry observed upon fluoride anion binding, the flat pyrrole in partial cone tilts upward while the other three pyrroles become relatively flattened. The cone complex is calculated to be most stable whereas the partial cone complex is predicted to be the second most stable. In the gas phase partial cone anion complex is higher in energy by 10.6 kcal/mol than that of cone complex. When the solvent effect by dichloromethane is accounted for the destabilization of partial cone as compared to cone is decreased to 9.3 kcal/mol. The 1,2-alternate complex is predicted to be less stable than the cone structure by 25.4 and 20.4 kcal/mol in the gas phase and in CH$_2$Cl$_2$ solution respectively. The relative stabilities reflect the number of hydrogen bonds in these complexes indicating that the ionic hydrogen bonds in these complexes are very strong.

2.7. β-Substituent effects on anion-binding abilities of calix[4]pyrrole

One simple way to strengthen the anion-binding is to increase the binding force i.e. hydrogen bond strength between the host and anion. Modification of the hydrogen bond acceptor (host part) is apparently a possible approach to tune the binding ability of calix[4]pyrroles. In the anion-free pyrroles the bond length of N-H is about 1.01-1.02 Å at the BLYP/6-31+G** level. When fluoro anion is involved, the N-H bond is elongated to 1.24-1.46 Å varying in different substituted structures. The stronger electron-withdrawing group normally elongates the N-H bond more while the H-F bond is significantly shortened. This implies that the basicity of F$^-$ is stronger than those of the pyrrole anions in the gas phase.
It appears that both σ and π effects of the substituents affect the anion binding energy. Methoxy group is a strong π donor and a weak σ acceptor. While the π-donating factor decreases the binding energy, the σ-accepting factor increases the binding energy. As a result, the methoxy group has little effect on the binding energy. Fluoro, chloro, and bromo groups are stronger σ-acceptors and behave as electron-acceptors. Therefore they all increase the binding energy to similar extents. Cyano group is a strong electron-acceptor and it can significantly increase the binding energy.\(^\text{31}\)

### Table 2.2: Calculated anion-binding energies in kcal/mol of different β-disubstituted calix[4]pyrrole with fluoride ion

<table>
<thead>
<tr>
<th>β-substituted CP-X</th>
<th>BLYP 6-31+G**</th>
<th>BLYP6-31+G**(sol.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R^1=R^2=\text{OCH}_3)</td>
<td>-40.4</td>
<td>-13.3</td>
</tr>
<tr>
<td>(R^1=R^2=\text{CH}_3)</td>
<td>-38.9</td>
<td>-13.1</td>
</tr>
<tr>
<td>(R^1=R^2=\text{H})</td>
<td>-38.6</td>
<td>-13.4</td>
</tr>
<tr>
<td>(R^1=R^2=\text{F})</td>
<td>-48.4</td>
<td>-18.7</td>
</tr>
<tr>
<td>(R^1=R^2=\text{Cl})</td>
<td>-51.6</td>
<td>-19.0</td>
</tr>
<tr>
<td>(R^1=R^2=\text{Br})</td>
<td>-52.9</td>
<td>-19.2</td>
</tr>
<tr>
<td>(R^1=R^2=\text{CN})</td>
<td>-68.3</td>
<td>-27.5</td>
</tr>
</tbody>
</table>


Introduction of aryl or other rigid groups into the meso-like positions of calix[4]pyrroles could serve not only to change the intrinsic anion selectivity of the calix[4]pyrrole skeleton but also in appropriate cases to introduce secondary binding sites that might
allow for selective recognition of cationic, anionic or neutral guests. The aryl ketone, pyrrole and acid were dissolved in methanol and stirred at room temperature in inert atmosphere to give four conformational isomers namely \( \text{aaaa}, \text{aaab}, \text{aab\beta}, \text{a\beta\beta} \) and \( \text{a\beta\beta} \). In the specific case of the \( \text{aaaa} \) isomer of a deep cavity structure was observed in the solid state, wherein the calixpyrrole core is in a so-called cone conformation. Structures of lower symmetry are seen in the case of the other isomers with conformations other than pure cone (e.g., 1,3-alternate, partial cone) being observed in certain instances (e.g., the \( \text{aaab} \) isomer). Proton NMR spectroscopy was used to confirm the configurational assignments and to analyze conformational effects in solution. As a general rule it was found that free rotation around the pyrrole-bridging meso-like carbons and ipso-aryl bonds pertains at room temperature in acetonitrile-\( d_3 \)-\( D_2O \) (99.5:0.5; v/v) in the absence of an added anionic substrate. Thus the symmetries of the various isomers were reflected directly in their \(^1\text{H} \) NMR spectra particularly in the number of pyrrole CH resonances. The \( \text{aaaa} \) isomers have one type of CH group represented by an “a” in Scheme 2.4, while the \( \text{a\beta\beta} \) isomer has two types of pyrrolic CH group (represented by “a” and “b”), and the \( \text{aaab} \) isomer possesses four different CH groups (“a”, “b”, “c” and “d”) and in all cases the requisite number of signals were observed.

Scheme 2.4: Synthesis of conformational isomer of calix[4]pyrrole
2.9. Results and discussion

The discovery of octamethyl calix[4]pyrrole as an anion receptor has prompted the synthesis of a variety of calix[4]pyrrole derivatives, expanded calixpyrroles, strapped calixpyrroles and N-confused calixpyrroles to understand the binding of different anions with specific calix[4]pyrrole. From chemical viewpoint calix[4]pyrroles are being explored as catalyst in organic synthesis as well as precursor of important organic molecules such as calixpyridines and calixpyridinopyrrole. Beside these, they have been found applications as fluorescent, colorimetric, electrochemical signaling device and new solid supports capable of separating anion mixtures. This macrocycles are also used as anion transporter across lipid bilayer membrane.

Moreover, in contrast to the well-studied templating properties of cationic and neutral species anion templates have been very little exploited in synthetic chemistry. This relative lack of anion-templated processes is partially attributed to some of the intrinsic properties of anions such as their diffuse nature, pH sensitivity, and their relative high solvation free energies. However, as the increasing number of anion-directed assemblies reported in the last few years, these limitations are not as critical as initially thought. They act as template in the coordination, supramolecular and inorganic hybrid structures. The use of anions templates to prepare cyclic structures is not exclusive confined to metal-containing assemblies, but it is also found in organic systems. For example Alcalde et al., have reported the halide-directed synthesis of a series of [14]imidazoliophanes, trihalogenated-templates in the synthesis of calix[6]pyrroles and solution phase anion directed self-assembly of meso-functionalized calix[4]pyrroles. Owing to their tremendous applications in the area of supramolecular chemistry they have gained significant importance. The synthesis of calix[4]pyrroles and N-confused calix[4]pyrroles in higher yields have been discussed in the following subsection:


The reaction of equimolar quantity of pyrrole (1) with acetone (2a) in the presence of tetrabutylammonium fluoride in dichloromethane at 25°C afforded a isomeric mixture
of octamethylcalix[4]pyrrole (OMCP) (3a) and N-confused octamethylcalix[4]pyrrole (NC-OMCP) (4a) in 81% and 18% yield respectively. (Scheme 2.5)

\[
\begin{array}{c}
\text{1} \quad \text{2} \\
\text{2a. } R_1=R_2 = \text{CH}_3 \\
\text{2b. } R_1=R_2 = \text{C}_2\text{H}_5 \\
\text{2c. } R_1 = \text{CH}_3, R_2 = \text{C}_2\text{H}_5 \\
\text{2d. } R_1=R_2 = (\text{CH}_2)_4 \\
\text{2e. } R_1=R_2 = (\text{CH}_2)_5 \\
\text{2f. } R_1=R_2 = (\text{CH}_2)_6 \\
\end{array}
\]

\[
\begin{array}{c}
\text{3a. } R_1=R_2 = \text{CH}_3 \\
\text{3b. } R_1=R_2 = \text{C}_2\text{H}_5 \\
\text{3c. } R_1 = \text{CH}_3, R_2 = \text{C}_2\text{H}_5 \\
\text{3d. } R_1=R_2 = (\text{CH}_2)_4 \\
\text{3e. } R_1=R_2 = (\text{CH}_2)_5 \\
\text{3f. } R_1=R_2 = (\text{CH}_2)_6 \\
\end{array}
\]

\[
\begin{array}{c}
\text{5a. } R_1=R_2 = \text{CH}_3 \\
\text{5b. } R_1=R_2 = \text{C}_2\text{H}_5 \\
\text{5c. } R_1 = \text{CH}_3, R_2 = \text{C}_2\text{H}_5 \\
\text{5d. } R_1=R_2 = (\text{CH}_2)_4 \\
\text{5e. } R_1=R_2 = (\text{CH}_2)_5 \\
\text{5f. } R_1=R_2 = (\text{CH}_2)_6 \\
\end{array}
\]


Using the catalytic amount of anion along with .01 equivalent of methanesulfonic acid fasten the reaction as well as improved the yield of the products. To analyze the role of anions in the reaction the cyclocondensation reaction of the pyrrole and acetone was performed using different solvent and acid catalyst with and without the use of anion and the results obtained were summarized in Table 2.2. It was observed that when the reaction of equimolar quantity of pyrrole (1) and acetone (2) was performed using ethanol as a solvent and methanesulfonic acid catalyst the reaction was completed in four hours at refluxing temperature giving 65% of OMCP (3a) and 15% of NC-OMCP (5a) along with some polymeric product. Whereas using ytterbium triflate in ionic liquid for the cyclocondensation of pyrrole and acetone gave octamethylcalix[4]pyrrole as the only product in excellent yield.\(^{53}\) Cyclocondensation reaction of pyrrole with acetone without using anions gave acceptable results taking Amberlyst\textsuperscript{TM}-15 as a catalyst in 8 hours at ambient temperature.\(^{54}\)
Table 2.2: Synthesis of *meso*-octamethylcalix[4]pyrrole (3a) and N-confused octamethylcalix[4]pyrrole (5a) using different catalyst and solvent

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Anions</th>
<th>Reaction time (mins)</th>
<th>Conversion of pyrrole</th>
<th>% yield of 3a</th>
<th>% yield of 5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethanol</td>
<td>Conc. HCl</td>
<td>-</td>
<td>300</td>
<td>62&lt;sup&gt;a&lt;/sup&gt;</td>
<td>56</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>CH₃SO₃H</td>
<td>-</td>
<td>120</td>
<td>90&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Ethanol</td>
<td>BF₃OEt₂</td>
<td>-</td>
<td>200</td>
<td>85&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Ethanol</td>
<td>CF₃COOH</td>
<td>-</td>
<td>140</td>
<td>87&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>CH₃SO₃H</td>
<td>-</td>
<td>140</td>
<td>85&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>BF₃OEt₂</td>
<td>-</td>
<td>260</td>
<td>80&lt;sup&gt;a&lt;/sup&gt;</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>CF₃COOH</td>
<td>-</td>
<td>150</td>
<td>94&lt;sup&gt;a&lt;/sup&gt;</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>[bmim][BF₄]</td>
<td>Yb(OTf)₃</td>
<td>-</td>
<td>90</td>
<td>95&lt;sup&gt;b&lt;/sup&gt;</td>
<td>92</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>CH₂Cl₂</td>
<td>Amberlyst&lt;sup&gt;TM&lt;/sup&gt;-15</td>
<td>-</td>
<td>480</td>
<td>99&lt;sup&gt;b&lt;/sup&gt;</td>
<td>83</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>CH₂Cl₂</td>
<td>CH₃SO₃H</td>
<td>F⁻</td>
<td>5</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
<td>81</td>
<td>17</td>
</tr>
<tr>
<td>11</td>
<td>Toluene</td>
<td>CH₃SO₃H</td>
<td>F⁻</td>
<td>10</td>
<td>87&lt;sup&gt;b&lt;/sup&gt;</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>CHCl₃</td>
<td>CH₃SO₃H</td>
<td>F⁻</td>
<td>7</td>
<td>98&lt;sup&gt;b&lt;/sup&gt;</td>
<td>80</td>
<td>15</td>
</tr>
</tbody>
</table>

(a) at refluxing temperature; (b) at 25°C

The structure of 3a and 5a were confirmed by IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and ESI-MS spectroscopic data. In fact <sup>1</sup>H NMR-spectroscopy is particularly useful for the differentiation of the OMCP (3a) and NC-OMCP (5a). The <sup>1</sup>NMR-spectrum of compound 3a, showed a sharp singlet at δ 1.52 ppm were assigned for the twenty four methyl group protons at *meso* position, a doublet at δ 5.90 ppm for the eight β-pyrrolic protons and a broad resonance at δ 7.08 ppm for the four pyrrolic N-H protons (Figure 2.7). The integration ratio of the three peaks areas were 6:2:1, in agreement with the empirical formula and D₄ symmetry of the compound 3a.

![Figure 2.7: <sup>1</sup>H NMR spectrum of 5,5,10,10,15,15,20,20-octamethylcalix[4]pyrrole](image)
On the contrary, in the $^1$NMR-spectrum of 5a, multiplet appeared at $\delta$ 1.53-1.56 ppm for the 24 methyl protons. Signals for the $\alpha$-pyrrole hydrogen (1H) and $\beta$-pyrrole hydrogen (1H) of the 2,4-disubstituted pyrrole appear at $\delta$ 6.51(doublet) and 5.09, respectively, which was well apart from those of the $\beta$-hydrogens atoms (6H) of the 2,5-disubstituted pyrrole ($\delta$. 5.82-5.97). The coupling constant between the band $\alpha$-hydrogen atoms of the confused pyrrole in 5a has a typical value of 2.0 Hz. Four distinct broad resonances at $\delta$ 7.00 (1H), 7.15 (1H), 7.54 (1H) and 7.78 (1H) ppm is due to four pyrrolic N-H protons indicates the reduction of symmetry in case of N-confused-octamethylcalix[4]pyrrole (5a) as compared to octamethylcalix[4]pyrrole. The higher polarity and non-zero dipole moment of the compound 4a have been attributed to their lower symmetry. The highly unsymmetrical nature of the compound 5a is also seen in its carbon spectrum which gives total of twenty four peaks. The four peaks at $\delta$ 28.94, 29.34, 29.67 and 30.30 ppm is due to CH$_3$ carbons, at $\delta$ 31.40, 31.90, 34.59 and 35.32 ppm for four meso carbons, at $\delta$ 101.55, 101.77, 102.13, 102.75, 103.33, 103.89 and 104.21 ppm for $\beta$-pyrrolic carbon, at $\delta$ 111.61 ppm for the $\alpha$-carbon of inverted pyrrole ring and at $\delta$ 133.19, 137.59, 137.82, 138.28, 138.45, 138.77, 138.89, 139.48 and 141.13 ppm for $\alpha$-pyrrolic carbon atoms.

![Figure 2.8: $^1$H NMR spectrum of N-confused 5,5,10,10,15,15,20,20-octamethyl calix[4]pyrrole in CDCl$_3$](image)
The reaction of equimolar quantity of pyrroles (1) with acetone (2a) in the presence of tetrabutylammonium fluoride in dichloromethane was also monitored by the high pressure liquid chromatography (HPLC). The reaction was monitored at different intervals and the chromatograms obtained were identified by comparison with authentic samples prepared. After the completion of the reaction two peaks were obtained having retention time of 3.45 and 3.96 respectively (Figure 2.10), which was assigned for the N-confused octamethyl calix[4]pyrrole and octamethyl calix[4]pyrrole respectively by comparing with authentic samples. Whereas the examination of reaction mixture after two minutes of the shows three peaks having the retention time of 3.02, 3.39 and 3.97 were assigned for dipyrromethane, calixpyrrole and N-confused calixpyrrole respectively. The peak at 3.02 was appeared due to the dipyrromethane formation in the reaction, which was confirmed by comparison with authentic samples.
Figure 2.10: High pressure liquid chromatogram of (A) dipyrrmethane, (B) 5,5,10,10,15,15,20,20-octamethyl calix[4]pyrrole

Figure 2.11: High pressure liquid chromatogram of reaction mixture

Figure 2.12: High pressure liquid chromatogram of N-confused 5,5,10,10,15,15,20,20-octamethyl calix[4]pyrrole
Owing to our curiosity and high yields of compound 3a and 5a in the presence of anions prompted us to examine the role of anions in the cyclization of other ketones 2b-2h with pyrrole (Table 2.5). The reaction of cyclohexanone with pyrrole in the presence of tetrabutylammonium fluoride in dichloromethane gave solid precipitate within minutes indicates formation of two products on TLC with Rf values 0.85 and 0.42 respectively. Crystal of the compound was grown by the slow evaporation of the CHCl3 solution of the crude mixture without any further purification. Examination of the crystalline product shows the association of the fluoride ion with the NH proton of the calix[4]pyrrole (3e). The crystal structure of the complex between calix[4]pyrrole and tetrabutylammonium fluoride reveals the role of tetrabutylammonium fluoride as the template. The fluoride atom of the guest is anchored to the cavity of the calix[4]pyrrole through the hydrogen bonds between the fluoride atom of the guest and hydrogen atom of the NH of four pyrrole rings. The crystal of N-confused-cyclohexyl calix[4]pyrrole with anion cloud not be obtained from the mixture this could be attributed to the lower percentage of N-confused-cyclohexyl calix[4]pyrrole in the reaction mixture as compared to the percentage of cyclohexyl calix[4]pyrrole. In 1H NMR spectrum of 5,5,10,10,15,15,20,20-tetraspiro-cyclohexylcalix [4]pyrrole (3e) two multiplets at 1.46 and 1.89 ppm were assigned for the cyclohexyl methylene group protons, and a doublet at 5.88 ppm with coupling constant J = 2.7 Hz was assigned for the eight β-pyrrolic protons and a broad singlet at 7.04 ppm was assigned for four pyrrolic NH protons. 13C NMR spectrum confirmed the symmetry of the molecule in 13C NMR spectrum of compound 3e showed three peaks at 22.69, 25.96, and 37.13 ppm for cyclohexyl carbon, peak at 39.55 ppm for the meso-carbon, and two peaks appeared at 103.41 and 136.39 ppm for β-pyrrolic carbon and α-pyrrolic carbon respectively, confirmed the formation of compound 3e. A band appeared at 3445 cm⁻¹ in IR spectrum of compound 3e which indicates the presence of NH group in the molecule.

In a given templated reaction the size and shape of the directing anions are the main factors that determine the reaction. It was seen that when the reaction was performed in the presence of anions other than fluoride the yield of the reaction decreases as
compared to that in the presence of fluoride ion as well as reaction time also increases table 2.3. This could be attributed to the stronger binding affinity of fluoride ion towards the compound 3a and 5a. Apart from its strong affinity towards calix[4]pyrrole and N-confused calix[4]pyrrole, fluoride ion also favors the reaction as a template due to its smaller size.

![Figure 2.13: ESI-MS spectrum of crude reaction mixture of 1 and 2 after completion of reaction](image)

**Table 2.3: Anion catalyzed condensation of pyrroles and acetone in dichloromethane**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Anions</th>
<th>% Yield of 3a</th>
<th>% Yield of 5a</th>
<th>Reaction time (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F^-</td>
<td>81</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Cl^-</td>
<td>80</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>I^-</td>
<td>71</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>AcO^-</td>
<td>70</td>
<td>9</td>
<td>30</td>
</tr>
</tbody>
</table>

Further the reaction of pyrrole and acetone was also examined in different solvent. A subsequent solvent screening revealed that low-polarity solvents led to higher yield, with CH₂Cl₂ providing the best results (Table 2.4). Reaction carried out in toluene and benzene gave comparatively low yield with prolonged reaction time.
Table 2.4: Anion templated synthesis of octamethylcalix[4]pyrrole and N-confused octamethylcalix[4]pyrrole in the presence of fluoride ion in different solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvents</th>
<th>% Yield of 3a</th>
<th>% Yield of 5a</th>
<th>Anions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH (EtOH)</td>
<td>65</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₃</td>
<td>80</td>
<td>15</td>
<td>F⁻</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>81</td>
<td>17</td>
<td>F⁻</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN</td>
<td>78</td>
<td>14</td>
<td>F⁻</td>
</tr>
</tbody>
</table>

The reactions of different ketones with pyrrole were performed in the presence of fluoride ion and the results were summarized in Table 2.5. The reaction of cycloheptanone with pyrrole in the presence of fluoride ion gave the corresponding calix[4]pyrrole and N-confused calix[4]pyrrole in thirty minutes at room temperature and the isolated yields were 70% and 10% respectively, but the time required for the conversion was relatively long. This could be attributed to the bulkiness of corresponding ketone. The ¹H NMR-spectrum of compound 5f shows two multiplets appeared at δ 1.46-1.63 ppm and 2.00-2.08 ppm for the methylene protons. Signals for the α-pyrrole hydrogen (1H) and β-pyrrole hydrogen (1H) of the 2,4-disubstituted pyrrole appear at δ 6.41(doublet, J=2 Hz) and 5.74, respectively. Whereas multiplet appears for β-hydrogens atoms (6H) of the 2,5-disubstituted pyrroles at δ 5.82-5.97). Four distinct broad resonances at δ 6.82 (1H), 6.97 (1H), 7.43 (1H) and 7.65 (1H) ppm is due to four pyrrolic N-H protons.

Table 2.5: Anion templated synthesis of different calix[4]pyrroles and N-confused calix[4]pyrroles in the presence of fluoride ion

<table>
<thead>
<tr>
<th>Entry</th>
<th>3, 5</th>
<th>% Yields</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a, 5a</td>
<td>81, 17</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>61</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>3c, 5c</td>
<td>78, 13</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>3d, 5d</td>
<td>86, 12</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>3e, 5e</td>
<td>79, 20</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>3f, 5f</td>
<td>70, 10</td>
<td>30</td>
</tr>
</tbody>
</table>
2.9.2. Synthesis of meso-unsubstituted porphyrinogens and N-confused porphyrinogens in the presence of anions

One equivalent of sodium borohydride was added portion wise to the solution of pyrrole-2-carboxaldehyde in 20 ml of THF under nitrogen atmosphere. The mixture was stirred for 2-3 hours under nitrogen atmosphere. After completion of the reaction, reaction mixture was treated with water for complete dissolution of the suspension of NaBH₄ and the mixture was extracted with dichloromethane. The combined organic phase was further washed with water and dried over anhydrous sodium sulfate. Triethylamine (2-3 drops) was added and solvent was evaporated under reduced pressure to give yellow oil. Further 1-2 drop of triethylamine was added and the pure compound was distilled off under reduced pressure as colorless liquid. The pure compound was stored in the refrigerator to avoid polymerization. The structure of compound was confirmed by IR and ¹H-NMR spectroscopic data.
Further acidic cyclocondensation reaction of the 2-hydroxymethylpyrrole (19a) was performed in the presence of tetrabutylammonium fluoride (TBAF) in deuterated chloroform under nitrogen atmosphere and completion of the reaction was monitored by TLC. After the completion of reaction the mixture was examined by $^1$H NMR spectroscopy. In $^1$H NMR spectrum of the reaction mixture showed four broad resonances at δ 8.60, 8.76, 8.96 and 9.22 which can be assigned for the N-confused porphyrinogen and porphyrinogen respectively. Downfield shift in the peak of NH proton can be attributed to the fluoride ion binding to the NH-proton of the porphyrinogen. Appearance of the three broad peaks in the reaction mixture can be assigned as the presence of N-confused porphyrinogen in the mixture. The peak appeared at 4.45 ppm was assigned for the meso-methylene protons of porphyrinogen.
2.10. Conclusion

Acid catalyzed condensation of different aliphatic ketones and pyrrole using tetrabutylammonium anions (F\(^-\), Cl\(^-\), I\(^-\), AcO\(^-\)) as a template in dichloromethane at room temperature gave octamethylcalix[4]pyrroles and N-confused octamethylcalix[4]pyrroles in different reaction conditions. Anions templated synthesis of calixpyrroles and N-confused calixpyrroles were less time consuming with high yields of desired products. The reaction of pyrrole with different ketones were performed in presence of methane
sulfonic acid in dichloromethane using different anions as template and best results were obtained when F anion was used as a template due to the smaller size and greater affinity to bind with calixpyrrole and N-confused calixpyrrole. The reaction of bulky alkyl and cycloalkyl ketones with pyrrole gave the calix[4]pyrroles in good yields whereas N-confused calix[4]pyrroles in low yields but in case of cyclohexanone the yield of calixpyrrole and N-confused calixpyrrole is equal to like acetone this is due to the greater reactivity of cyclohexanone than other cyclic ketones.

The meso-unsubstituted porphyrinogen or calixpyrrole and N-confused calixpyrroles are highly unstable and readily oxidized to corresponding stable porphyrins due to this effect

The meso-unsubstituted porphyrinogen or calixpyrrole and N-confused calixpyrrole were also formed in situ by the acid catalyzed tetramerization of 2-hydroxymethyl pyrrole which was synthesized by the reaction of pyrrole-2-carboxylddehyde with sodium borohydride, in presence of F anion in deuterated chloroform at room temperature and formation of the products were confirmed by $^1$H NMR spectroscopy.

2.11. Experimental

All melting points are uncorrected and expressed in degree centigrade and were recorded on Thomas Hoover Unimelt capillary melting point apparatus. The infrared spectra were recorded on Perkin-Elmer FT-2000 spectrometer and $\nu_{\text{max}}$ are expressed in cm$^{-1}$. $^1$H NMR was recorded on Jeol-delta-400 spectrometer using tetramethylsilane (TMS) as an internal standard and chemical shifts ($\delta$) are expressed in ppm. ESI-MS were recorded by LC-TOF (KC-455) mass spectrometer of Waters. The starting materials such as pyrrole, acetone, diethyl ketone, ethylmethyl ketone, cyclopentanone, cyclohexanone and methane sulphonic acid were purchased from Spectrochem Chemicals India. The quaternary ammonium salts; normal tetrabutylammonium halides (n-Bu$_4$NF, n-Bu$_4$NCl, n-Bu$_4$NBr, n-Bu$_4$NI), and normal tetrabutylammonium acetate (n-Bu$_4$NACO) were purchased from Aldrich. The pyrrole was distilled prior to use and the solvents used were of analytical reagent grade. The compounds synthesized were separated by column chromatography using neutral alumina and characterized by melting points, $^1$H NMR, $^{13}$C NMR, IR and ESI-MS techniques.
2.11.1. 5,5,10,10,15,15,20,20-Octamethyl calix[4]pyrrole (3a)

Equimolar amount of pyrrole (1 ml, 14 mmol) and acetone (1.04 ml, 14 mmol) were taken up in dry dichloromethane (10 mL). Tetrabutylammonium fluoride (0.95 mg, 0.003mmol) was added to the reaction mixture, which was stirred at 25˚C for a minute and then methanesulfonic acid (0.1 mmol) was added. The progress of reaction was monitored by thin layer chromatography (TLC). After the completion of reaction, the reaction mixture was extracted by dichloromethane and washed several time with water. Organic phase was separated and dried over sodium sulfate. The filtrate was concentrated at vacuum to gave the crude product, which was subjected to column chromatography over neutral alumina eluting with petroleum ether-chloroform (9:1, v/v) to afford pure meso octamethylcalix[4]pyrrole (3a).

5,10,15,20-Octamethyl-calix[4]pyrrole (3a)

**Physical state:** White solid

**Yield:** 2.05 g (81%)

**mp:** 295 ˚C (Lit. mp. 296 ˚C)

**Rf** = 0.8 (SiO₂, 1:1 petroleum ether/chloroform)

**IR (KBr pellet, cm⁻¹):** 3444(br, pyrrole NH), 2973, 2932, 2870, 1578, 1448, 1414, 1279, 1233, 1044, 759

**¹H NMR (400 MHz, CDCl₃):** δ = 1.52 (s, 24H, CH₃), 5.90 (d, J = 2.92 Hz, 8H, β-pyrrole CH), 7.08 (brs, 4H, Pyrrole NH)

**¹³C NMR (100 MHz, CDCl₃) δ =** 29.08 (CH₃), 35.15 (meso C), 102.67 (β-pyrrole CH), 138.55 (α-pyrrole C)

**HRMS (ESI-MS) for C₂₈H₃₆N₄ [M+H]⁺:** calcd, 429.2862; found, 429.2860.

2.11.2. 5,5,10,10,15,15,20,20-Octamethyl-N-confused calix[4]pyrrole (5a)

Further elution of the column with petroleum ether-chloroform (3:2, v/v) gave the N-confused isomer of octamethylcalix[4]pyrrole (5a).

**Physical state:** white solid

**Yield:** 250 mg (17%)
mp 184 °C  
\( R_f = 0.45 \) (SiO\(_2\), 1:1 petroleum ether/chloroform);  

IR (KBr pellet, cm\(^{-1}\)): 3430, 2910, 2845, 1521, 1616, 1179, 749.  

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 1.48-1.54 \) (m, 24H, CH\(_3\)), 5.07 (brs, 1H, \( \beta \)-pyrrole CH), 5.87 (m, 2H, \( \beta \)-pyrrole CH), 5.89 (brs, 2H, \( \beta \)-pyrrole CH), 5.90 (brs, 2H, \( \beta \)-pyrrole CH), 6.51 (s, 1H, \( \alpha \)-pyrrole CH), 6.97 (brs, 1H, pyrrole NH), 7.13 (brs, 1H, pyrroles, NH), 7.48 (brs, 1H, pyrrole NH), 7.76 (brs, 1H, pyrrole NH);  

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 29.0, 29.4, 29.6, 30.3 \) (4x CH\(_3\)), 34.6, 35.3, 35.8, 35.9 (4x meso C), 101.6, 101.8, 102.1, 102.8, 103.3, 103.9, 104.2 (7x \( \beta \)-pyrrole CH), 111.6 (\( \alpha \)-pyrrole CH), 133.2 (\( \beta \)-pyrrole C), 137.5, 137.8, 138.2, 138.7, 138.8, 139.4, 141.1 (7x \( \alpha \)-pyrrole C)  

ESI-MS for C\(_{28}\)H\(_{36}\)N\(_4\) [M+H]: calcd, 429.2862; found, 429.2860.  


Similar procedure was used for the synthesis of the compound as used above for the 3a  

Physical state: white solid  

Yield: 1.97 g (61%)  

Mp: 224 °C  

\( R_f = 0.76 \) SiO\(_2\), 1:1 petroleum ether/chloroform)  

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 0.64-0.68 \) (t, 24 H, CH\(_3\)-), 1.79-1.57 (q, 16H, -CH\(_2\)-), 5.89 (d, \( J=2.80 \) Hz, 8H, \( \beta \)-pyrrole CH), 7.09 (brs, 4H, NH)  

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 8.04 \) (CH\(_3\)), 29.18 (-CH\(_2\)-), 42.63 (meso-C), 104.98 \( \beta \)-pyrrolic C), 135.78 (\( \alpha \)-pyrrolic C)  

ESI-MS for C\(_{36}\)H\(_{52}\)N\(_4\) [M+H]: calcd, 539.4113; found, 539.4120.  


Similar procedure was used for the synthesis of the compound as used above for the 3a  

Physical state: white solid  

Yield: 1.86 g (78%)
mp 144 °C

$R_f = 0.76$ SiO$_2$, 1:1 petroleum ether/chloroform)

IR (KBr pellet, cm$^{-1}$): 3435 (br, pyrrole NH), 2968, 2931, 2876, 1413, 1297, 1211, 1040, 761, 706

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 0.68$-0.71 (t, 12H, CH$_3$-), 1.36-1.40 (q, 8H, -CH$_2$-), 1.85 (brs, 12H, CH$_3$), 5.88 (d, $J = 1.44$ Hz, 8H, $\beta$-pyrrole), 7.08 (brs, 4H, NH)

$^{13}$C NMR (100 MHz, CDCl$_3$, TMS): $\delta = 8.6$ (-CH$_3$), 29.9 (CH$_3$-), 33.1(-CH$_2$), 39.1($meso$-C), 103.7($\beta$-pyrrole CH), 137.2($\alpha$-pyrrole C)

ESI-MS for C$_{32}$H$_{44}$N$_4$ [M+H]: calcd, 484.1162; found, 483.2840.

2.11.5. 5,10,15,20-tetraethyl-5,10,15,20-tetramethyl N-confused-calix[4]pyrrole (5c)

Physical state: yellow solid

Yield: 180 mg (13%)

mp 120 °C

$R_f = 0.4$ SiO$_2$, 1:1 petroleum ether/chloroform)

IR (KBr pellet, cm$^{-1}$): 3435 (br, pyrrole NH), 2968, 2931, 2876, 1413, 1297, 1211, 1040, 761, 706

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 1.83$-1.12 (m, 29H, -CH$_2$CH$_3$), 1.92 (3H, s, CH$_3$), 5.53 (1H, br), 5.78 (m, 2H), 5.88 (brs, 2H), 6.03 (br, 2H, $\beta$-pyrrole), 6.40 (d, $J = 2$ Hz, 1H, $\alpha$-pyrrole CH), NH: 7.35 (br, 2H), 7.53 (br, 1H), 7.63 (br, 1H)

ESI-MS for C$_{32}$H$_{44}$N$_4$ [M+H]: calcd, 484.1162; found, 483.3482.

2.11.6. 5,5,10,10,15,15,20,20-Tetrakis spirocyclopentyl calix[4]pyrrole (3d)

Physical state:

Yield: 2.26 g (76%)

mp 235 °C;

$R_f = 0.63$ (SiO$_2$, 1:1 petroleum ether/chloroform);

IR (KBr pellet, cm$^{-1}$): 3496 (brs, pyrrole NH), 2959, 2870, 1630, 1580, 1414, 1254, 1042, 765;
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 1.71-1.69 (m, 16H, CH$_2$), 2.03-2.00 (m, 16H, CH$_2$), 5.86 (d, $J = 2.8$ Hz, 8H, $\beta$-pyrrole), 7.10 (brs, 4H, NH);

$^{13}$C NMR (100 MHz, CDCl$_3$, TMS): $\delta$ = 23.76, 38.89 (cyclopentyl C), 46.79 (meso C), 102.89 (pyrrole $\beta$-CH), 137.14 (pyrroles $\alpha$-CH);

ESI-MS for C$_{32}$H$_{44}$N$_4$ [M+H]: calcd: 531.3488; found: 531.3486.

2.11.7. 5,5,10,10,15,15,20,20-Tetrakis spirocyclopentyl N-confused calix[4]pyrrole (5d)

Physical state: white solid

Yield: 350 mg (12%)

mp 199 °C

$R_f$ = 0.42 SiO$_2$, 1:1 petroleum ether/chloroform

IR (KBr pellet, cm$^{-1}$): 3496 (br, pyrrole NH), 2959, 2870, 1630, 1580, 1414, 1254, 1042, 765

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 1.50-1.20 (m, 16H, CH$_2$), 2.25-1.98 (m, 16H, CH$_2$), 5.58 (br, 1H, $\beta$-pyrrole -CH), 5.88 (m, 2H, $\beta$-pyrrole -CH), 5.90 (br, 2H, $\beta$-pyrrole -CH), 6.00 (br, 2H, $\beta$-pyrrole -CH), 6.42 (d, $J = 1.97$ Hz, 1H, $\alpha$-pyrrole), 7.00 (brs, 2H, NH), 7.29 (brs, 1H, NH), 7.48 (brs, 1H, NH).

2.11.8. 5,5,10,10,15,15,20,20-Tetrakis spirocyclohexyl calix[4]pyrrole (3e)

Physical state: white solid

Yield: 2.79 g (80%)

mp 273 °C (lit$^{28}$-271-272 °C)

$R_f$ = 0.85 SiO$_2$, 1:1 petroleum ether/chloroform

IR (KBr pellet, cm$^{-1}$): 3445 (br, pyrrole NH), 2924, 2849, 1577, 1413, 1184, 752

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 1.40-1.47 (m, 24H, CH$_2$), 1.89-1.92 (m, 16H, CH$_2$), 5.88 (d, $J = 2.7$ Hz, 8H, $\beta$-pyrrole), 7.04 (brs, 4H, NH)

$^{13}$C NMR (100 MHz, CDCl$_3$, TMS): $\delta$ = 22.69, 25.96, 37.13, 39.55 (hexyl C), 103.41 (pyrrole $\beta$-CH), 136.39 (pyrroles $\alpha$-CH)

(ESI-MS) for C$_{40}$H$_{52}$N$_4$ [M+H]$: $-$ : calcd, 587.4114; found, 587.3860.
2.11.9. 5,5,10,15,15,20,20-Tetrakis spirocyclohexyl N-confused calix[4]pyrrole (5e)

Physical state: white solid

Yield: 600 mg (20%)

mp 223 °C (lit28-223.2-223.6 °C)

Rf = 0.42 SiO₂, 1:1 petroleum ether/chloroform

IR (KBr pellet, cm⁻¹): 3468 (br, pyrrole NH), 1423, 1280

¹H NMR (400 MHz, CDCl₃) δ=1.20-1.60 (m, 24H, cyclohexyl, CH), 1.70-2.10 (m, 16H, cyclohexyl, CH), 5.50 (br, 1H; pyrrole β-H), 5.82 (m, 2H; pyrrole β-H), 5.97 (br, 2H; pyrrole β-H), 6.03 (br, 2H; pyrrole β-H), 6.42 (d, J =1.97 Hz, 1H; pyrrole α-H), 7.10 (br, 2H; pyrrole NH), 7.44 (brs, 1H; pyrrole NH), 7.63 (brs, 1H, pyrrole NH)

¹³C NMR (100 MHz, CDCl₃, TMS): δ = 22.77, 25.91, 25.99, 26.36, 36.51, 37.0, 37.4, 37.67, 38.36, 39.31, 39.70, 39.72, (hexyl C), 101.3, 102.2, 103.9 (pyrrole β-CH), 112.8 (pyrrole α-CH), 130.1 (pyrrole β-C), 133.7, 134.6, 136.5, 137.8, 139.1, 140.3 (pyrrole α-C)

(ESI-MS) for C₄₀H₅₂N₄ [M+H]- : calcd, 587.4114; found, 587.3860.


Physical state: white solid

Yield: 2.5 g (76%)

Mp: 163 °C

Rf: .67 (SiO₂, 1:1 petroleum ether/chloroform)

¹H NMR (400 MHz, CDCl₃, TMS): δ 1.52-167 (m, 32H, cyclo-heptyl, CH); 1.92-2.02 (m, 16H, cyclo-heptyl, CH), 5.84 (d, 8H, β-pyrrolic), 6.87 (brs, 4H, NH);

¹³C NMR (100 MHz, CDCl₃, TMS): δ 23.12, 29.77, 39.33 (cycloheptyl); 42.69 (meso C); 102.88 (β-pyrrolic CH); 138.35 (α-pyrrolic CH)

(ESI-MS) for C₄₄H₆₀N₄ [M+H]− = calcd, 644.4818; found, 645.4824.

**Physical state:** white solid

**Yield:** 382 mg 10%

$R_f$: 0.49 (SiO$_2$, 1:1 petroleum ether/chloroform))

$^1$H NMR (400 MHz, CDCl$_3$, TMS): δ 1.46-1.67 (m, 32H, cyclo-heptyl, CH); 2.00-2.07 (m, 24H, cyclo-heptyl, CH); 5.18 (brs, 1H; pyrrole β-H), 5.74-5.95 (m, 6H; pyrrole β-H), 6.41 (d, $J$ =1.97 Hz, 1H; pyrrole α-H), 6.82 (br, 1H; pyrrole NH), 6.96 (brs, 1H; pyrrole NH), 7.52 (brs, 1H, pyrrole NH); 7.65 (brs, 1H, pyrrole NH)

$^{13}$C NMR (100 MHz, CDCl$_3$, TMS): δ = 23.04, 23.30, 29.68, 29.87, 30.01, 38.64, 40.78, 42.19, 42.46, (heptyl C), 100.11, 101.69, 102.27, 104.48 (pyrrole β-CH), 114.63 (pyrrole α-CH), 137.09 (pyrrole β-C), 138.43, 139.29, 139.60, 141.06, 143.05 (pyrrole α-C)

(ESI-MS) for C$_{44}$H$_{60}$N$_4$ [M+H]$^+$ = calcd, 644.4819; found, 645.4820.

2.11.12. Synthesis of 2-hydroxymethylpyrrole

A three-necked flask equipped with magnetic stirrer pyrrole-2-carbaldehyde (500mg, 5.25mmol) was dissolved in THF (15mL) under nitrogen atmosphere. Sodium borohydride (208mg, 5.5 mmol) was added to the solution in 2-3 fractions resulting in warming of the reaction flask and gas evolution. The mixture was stirred for 4h until the reaction was complete. Completion of the reaction was monitored by TLC (n-hexane/ethyl acetate 1:1) and after completion of the reaction the mixture was treated with water (25 mL). After the NaBH$_4$ in suspension was completely dissolved, the mixture was extracted with dichloromethane (4×50 mL). The combined organic extracts were washed with water and dried over Na$_2$SO$_4$. Triethylamine (2 drops) was added and the solution was concentrated with a rotary evaporator to yield light-yellow oil. The yellow oil was further purified by vacuum distillation (90 °C) to give a final product as a colorless liquid and requires storage in the refrigerator to avoid polymerization.

**Yield:** 80 (400µl).

$R_f$ = 0.32 (SiO$_2$, 1:1 n-Hexane: ethylacetate);

$^1$H NMR (400 MHz, CDCl$_3$) δ= 7.98 (brs, 1H, NH), 7.68 (m, 2H, α-pyrrole), 7.25 (m, 2H, β-pyrrole), 6.95 (d, 2H, β-pyrrole), 6.93 (s, 2H, -CH$_2$OH), 2.43 (s, 1H, OH).
2.11.13. Synthesis of *meso*-unsubstituted porphyrinogen and N-confused porphyrinogen

Tetrabutylammonium fluoride (0.03 mmol) was dissolved in the solution of 2-hydroxymethylpyrrole (195 mg, 2 mmol) in deuterated chloroform 2 ml. Reaction mixture was stirred for 2 minutes under nitrogen atmosphere and then methanesulfonic acid (10 µl, 0.1 mmol) was added to the mixture. Reaction was stirred at room temperature for further 2 minutes and completion of reaction was monitored by TLC (1:1, n-hexane:chloroform). After completion of the reaction the mixture was directly given for the $^1$H NMR analysis.

$^1$H NMR (400 MHz, CDCl$_3$) δ = 9.22 (brs, 4H, NH), 8.96 (brs, 1H, NH), 8.77 (brs, 1H, NH), 8.60 (brs, 1H, NH), 6.64 (d, 2H, $J= 1.64$ Hz, β-pyrrole), 6.03 (m, β-pyrrole), 5.22 (s, 1H, α-pyrrolic) 4.45 (s, meso-CH$_2$).
2.13. References


