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Hetero-calix[4]pyrroles: incorporation of furans, thiophenes, thiazoles or fluorenes as a part of the macrocycle ☆

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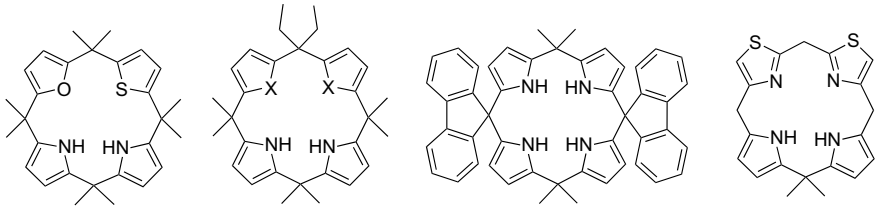
Abstract—Furans, thiazoles, fluorene or thiophene incorporated calix[4]pyrrole analogues were synthesized and characterized. The synthesis was achieved by utilization of various building blocks such as **7**, **13**, **14**, **18** and **21**. Acid catalyzed condensation of those building blocks with acetone or *meso*-disubstituted dipyrromethanes afforded desired macrocycles.

Anion binding chemistry using neutral molecules has been one of the important areas in the field of molecular recognition due to their potential biological applications.[1–3] A number of newer and specifically functionalized receptors binding selectively with anionic substrates have been developed as a result of these efforts. The anion binding mainly occurs through weak hydrogen bonding or electrostatic interactions and thus is usually weaker than cation binding. Among the anionic receptors, calix[4]pyrroles have been verified as one of the selective anion binding molecules for halide anions. Sessler et al. have synthesized variety of modified calix[4]pyrroles[4] and their anion binding properties have been studied. Recently, we have demonstrated that the strapping approach is the most useful among the various modifications[5] such as β-pyrrolic substitution, *meso*-alterations[6] or attachment of fluorescent chromophores at the periphery of calix[4]pyrrole.[7]

The systems depicted by structures **1**–**4** are designed and synthesized. The relation between structure, number of H-binding donors and binding affinity may be systematically studied with these model systems.

The most common structural variation of calix[4]pyrroles are attachment of the same substituents at *meso* positions. In this case, the synthesis can be easily achieved by condensing appropriate ketones with pyrrole in the presence of acid catalyst. On the other hand, the systems **1**–**4** are difficult to obtain by simple pyrrole–ketone condensation approach. These systems differ from other functionalized systems in the sense that the



1 **2 (X=O, S)** **3** **4**

Keywords: Calix[4]pyrrole; Hetero-calix[4]pyrroles; Anion binding; H-Bonding; Modified calixpyrrole; Dithiazolyl methane; Fluorenone.
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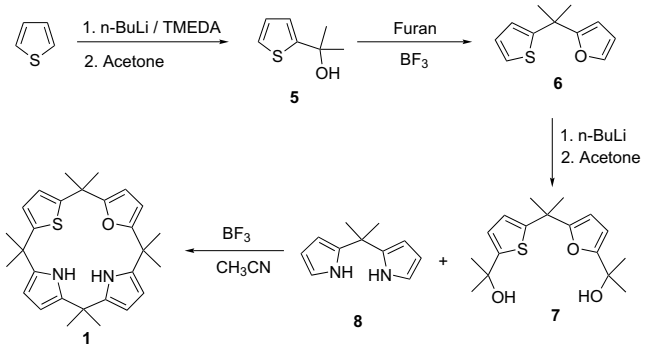
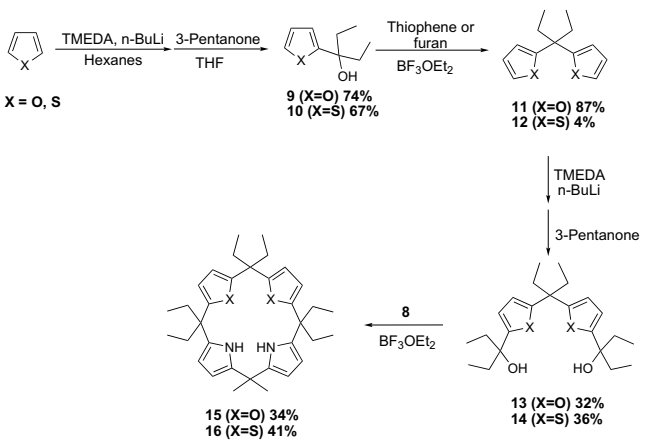


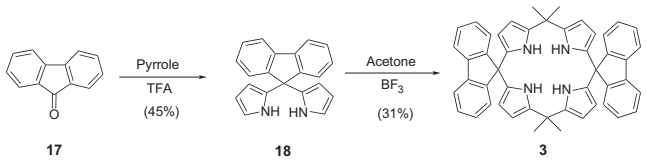
Scheme 1.

fluorophores are not only the integral part of the calix[4]pyrrole system but incorporated heterocycles such as furan or thiophene other than pyrrole can act as cationic recognition site. The cation binding characteristic of calixfuran has been documented.[8] Furan or thiophene incorporated calixpyrrole **1** was synthesized as shown in Scheme 1. Lithiated thiophene was treated with acetone in THF to afford alcohol **5**, which was converted to furylthienylmethane **6** in 70% yield. Dilithiation of **6** followed by reaction with acetone gave 33% yield of diol **7**.[9] Acid catalyzed condensation of **7** with 5,5-dimethyldipyrromethane **8** then afforded the desired host **1** in 39% yield. The proton NMR spectrum shows two pyrrolic N–H signal at 7.28 and 7.25 ppm as usual.

The first report for the synthesis of modified calixpyrroles appeared in 1955 by W.H. Brown et al.[10,12] Although the synthesis of the cyclic oligomers of furan (or thiophene) and acetone have been reported, to the best of our knowledge, the mixed oligomers of furan–thiophene have not been reported. The preparation of difurylmethane (or dithienylmethane) containing calix[4]pyrrole analogues **15** and **16** involves four-step synthesis starting from furan (or thiophene) as shown in Scheme 2. Lithiation of furan (or thiophene) followed by treatment with 3-pentanone afforded alcohols **9** and **10** in 74% and 67%, respectively.[11] Acid-catalyzed con-



Scheme 2.

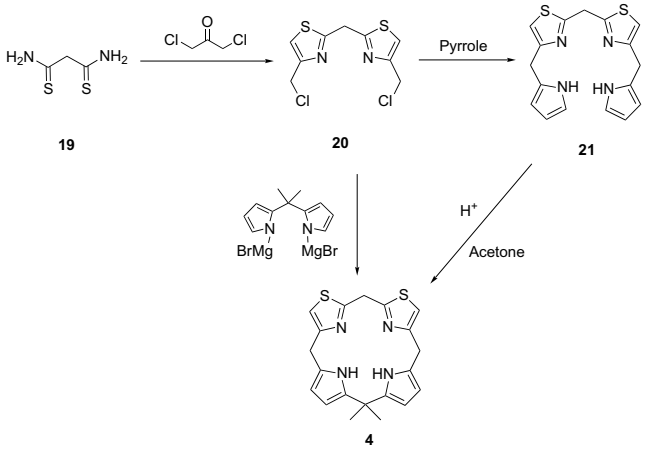


Scheme 3.

densation of **9** or **10** with furan (or thiophene) gave corresponding products **11** and **12** in 87% and 4%, respectively.[11] Bis-lithiation of **11** and **12** followed by treatment with 3-pentanone resulted in the formation of diol **13** and **14** in 32% and 36%, respectively. The choice of the 3-pentanone is purely arbitrary. Then, acid catalyzed condensation of corresponding diol with 5,5-dimethyldipyrromethane[12] **8** afforded the desired products **15** and **16** in 34% and 41%, respectively.

The fluorene-attached compound **3** was synthesized as shown in Scheme 3. 9-Fluorenone **17** and pyrrole were condensed as usual method and resulting dipyrromethane **18** was condensed with acetone in the presence of $BF_3(Et_2O)$ to afford desired product in low yield. Compound **3** was rather unstable and slow decomposition was observed in methylene chloride within 24 h of time frame. Incorporation of fluorescence probe inside or a part the rim of the calix[4]pyrrole would dramatically alter the conformation of the host compound and the anion binding behaviour would be influenced correspondingly.

The thiazole incorporated compound **4** was synthesized by condensation of **21** with acetone. As shown in Scheme 4, the bisthiazolylmethane **20** was reacted with pyrrole in the presence of acid to afford **21** in low yield. Direct replacement of benzyl-type chloride with α-carbon of pyrrole is quite unusual and the nucleophilicity of pyrrole must be exceptionally larger under the condition attempted. This reaction is only possible when pyrrole is used as the reaction solvent. **4** is the first thiazole incorporated calix[4]pyrrole analogues to be constructed. Attempted condensation of **21** with aldehydes followed by DDQ oxidation did not give corresponding



Scheme 4.

porphyrinoid macro cycle. All the intermediate compounds were isolated by column chromatography and identified with mass spectrometry and NMR spectroscopy.

The ability of the synthesized hosts as possible anion receptors was tested by following the changes in NMR or fluorescence spectra that were induced by addition of tetrabutylammonium salts of chloride and fluoride anions. Unfortunately, the hosts **1**, **2**, **4**, **15** and **16** did not show any spectral changes upon addition of anions. On the other hand, in the case of host **3**, the fluorescence titration analysis with chloride anion (as tetrabutyl ammonium salt) indicates that the binding stoichiometry is 1/1. The incremental quenching of the fluorescence was observed and the association constant was calculated. But, the calculated binding constants were far less than normal calix[4]pyrrole indicating that the geometric constraint imposed in the molecule make the receptor less flexible and is believed to be responsible for this reduced anion affinity.

In summary, we have demonstrated that the incorporation of various heterocycles as a part of the mother calix[4]pyrrole is possible. The anion affinity of the modified calix[4]pyrroles is far less than mother macro cycles. The cation binding studies of the reported new hosts are under progress.

Supplementary material

Spectroscopic data for all the reported compounds can be found in the online version of this article.

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