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# Calix[4]pyrrole-Capped Metalloporphyrins as Ditopic Receptor Models for Anions

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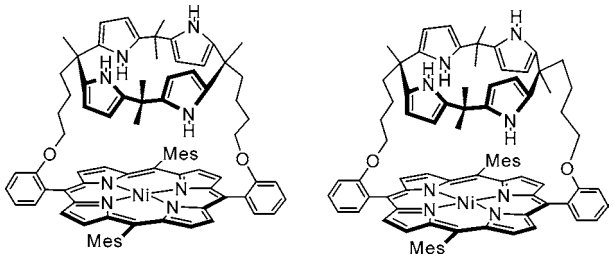
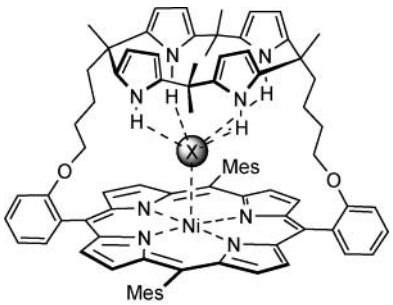
## ABSTRACT




**Strapped calix[4]pyrrole–metalloporphyrin conjugates, potential hosts for anionic guests, have been synthesized and characterized. The condensation unexpectedly resulted in the formation of the two conformational isomers of calix[4]pyrrole-capped porphyrins 6 and 7. The anion binding studies revealed that only isomer 6 showed strong binding with fluoride anion in organic solvent, and neither isomer showed any appreciable binding with $Cl^-$, $Br^-$, and $I^-$.**

The design and synthesis of synthetic anion receptors possessing high affinity and adequate selectivity for various targeted substrates represents a considerable challenge for those working in the area of supramolecular chemistry. However, this challenge continues to attract considerable attention due to the important role anions play in many biological processes.[1−3] Although considerable progress has been made, the problem appears far from solved, and it is likely that systems more elaborate than those currently available will be required if truly selective and effective anion receptors are to emerge. Among the various neutral anion receptors reported to date, calix[4]pyrroles appear particularly attractive as a starting point for the design of yet-improved anion selective receptors. They are easy to make, being readily obtained in one step from the acid-catalyzed condensation of pyrrole and acetone, and have been shown to bind various anions in organic media.[4−10]

Since their anion recognition characteristics were first described by Sessler et al. in 1996,[4] various modifications of the calix[4]pyrrole skeleton have been made in an effort to tune the binding characteristics of the parent system.[10,11]




**1 (Mes = mesityl)**

Here, some of the best enhancements, in terms of both increasing the anion binding affinities and modulating the inherent anion selectivities, came as a result of generating so-called strapped systems, wherein a covalently tethered bridge is used to link two of the "trans" *meso*-carbon atoms

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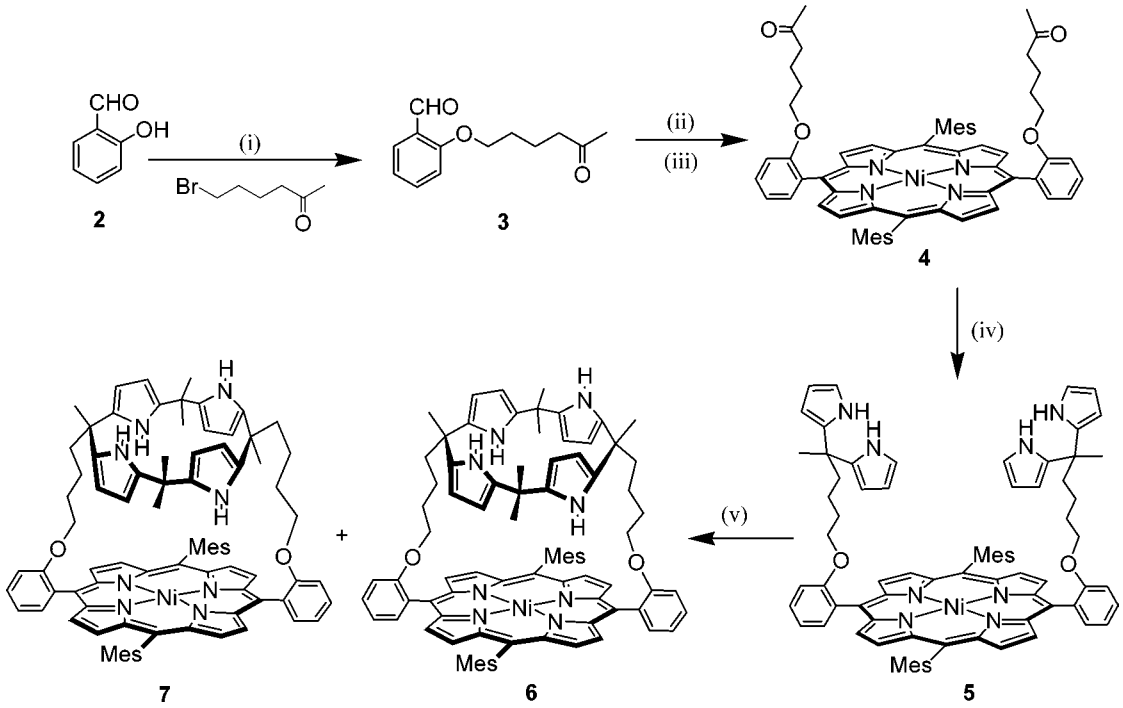
**Scheme 1** [a]




[a] (i) DMF, $K_2CO_3$, 60 °C, 24 h; (ii) (a) 5-mesityldipyrromethane, acetonitrile, $NH_4Cl$, $BF_3{\cdot}(OEt)_2$, 0 °C, 30 min, (b) DDQ, rt, 30 min; (iii) $Ni(CH_3COO)_2{\cdot}4H_2O$, DMF, reflux, 2 h; (iv) pyrrole, TFA, 50 °C, 24 h; (v) acetone, $BF_3{\cdot}(OEt)_2$, 30 min.

(specifically, atoms 5 and 15 in the porphyrin numbering system).[12,13] This bridging serves to protect one face of the calix[4]pyrrole while forcing the system as a whole to adopt a twisted, 1,3-alternating conformation.[12]

This somewhat destabilized conformation may provide additional enhancement in binding with guest molecules. However, despite this success, the range of strapping elements employed to date remains quite limited. Accordingly, we have been working to prepare systems containing "straps" or "caps" that might allow for enhanced anion recognition, lead to greater monitoring sensitivity (e.g., through the use of bridging chromophore or redox active center), or permit the concurrent complexation of a cationic moiety.

In this communication we report the synthesis of the first metalloporphyrin-strapped calix[4]pyrroles **6** and **7**, as well as preliminary studies of their anion binding abilities. The syntheses of the receptors are shown in Scheme 1. Briefly, salicylaldehyde was reacted with 6-bromo-2-hexanone to afford **3** in 82% yield. Then, the resulting aldehyde **3** was condensed with mesityldipyrromethane[14] to afford the dialkoxy-substituted free-base porphyrin **4** as a mixture of atropisomeric forms.

The two atropisomers of free-base porphyrin **4** are easily separated by preparative TLC followed by recrystallization from methanol. The identity of the two isomers was easily assigned on the basis of an analysis of the proton NMR spectra. For example, the *cis*-isomer **4** shows three distinct aromatic methyl signals at 2.62, 1.85 and 1.83 ppm, respectively, whereas in case of the more symmetric *trans*-isomer only two aromatic methyl signals at 2.62 and 1.84 ppm (12 protons) were observed. Quantitative insertion of Ni(II) was possible by treating free-base porphyrin with Ni(OAc)$_2$. Upon treatment of the purified *cis*-isomer with Ni(OAc)$_2$ in boiling DMF, atropisomerization to the *trans*-isomer was observed. As a consequence of this equilibrium, it was decided to use the mixture of the two atropisomers directly in the next step without further purification. The atropisomeric mixture of Ni(II) complex **4** was thus condensed with pyrrole in the presence of a catalytic amount of

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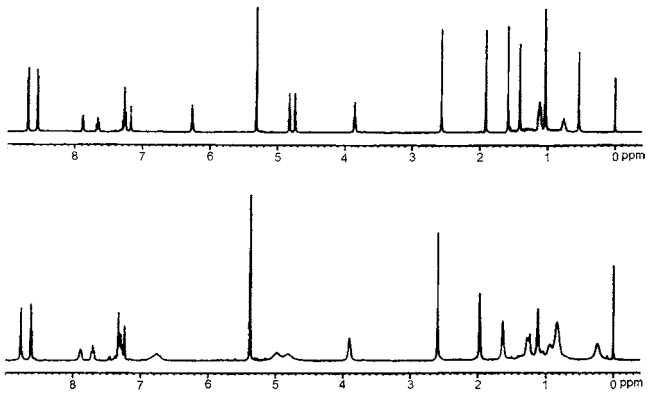

**Figure 1.** Proton NMR spectra of compound **6** in $CD_2Cl_2$ at 25 °C (top trace) and −50 °C (bottom trace).

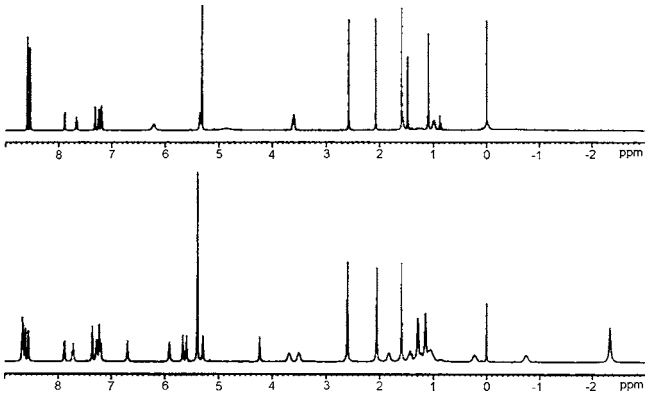

**Figure 2.** Proton NMR spectra of compound **7** in $CD_2Cl_2$ at 25 °C (top trace) and −50 °C (bottom trace).

TFA. This afforded **5** and its corresponding atropisomer, which is of almost identical $R_f$ value with **5** in 72% overall yield. The optimal conditions for effecting this condensation involved using pyrrole as solvent in this case.

Our attempts to synthesize analogues of **5** starting with the free base form of the Ni(II) porphyrin **4** yielded species possessing high polarity that proved sparingly soluble in ethyl acetate and thus could not be characterized properly. Similarly, no isolable product was obtained when the Zn(II) complex of **4** is reacted with pyrrole in the presence of TFA. However, it was then found that the acid-catalyzed condensation of **5** with acetone under conditions of high dilution, afforded the desired receptor **6**, albeit in low yield (5%). Interestingly, the twisted and 1,3-alternate form of calix[4]-pyrrole-strapped porphyrin **7**, species which is isomeric to **6**, was also isolated in relatively higher yield (7%). Receptor **7** has three of the *meso*-methyl groups pointing toward the porphyrin plane.

The identity of the two compounds was confirmed unambiguously by temperature-dependent $^1$H NMR spectroscopic analyses and via anion binding studies (vide infra). The proton NMR spectra of **6** obtained at room temperature shows a single peak at 6.26 ppm corresponding to the calix-[4]pyrrole NH resonance, as well as two multiplets, at 4.82 and 4.74 ppm, respectively, that are ascribed to the $\beta$-pyrrolic protons (Figure 1). Both sets of resonances are shifted upfield compared to those of simple octamethyl calix[4]pyrrole as a result of the diamagnetic ring current effect of the porphyrin. The proton NMR spectra obtained at −50 °C did not show any significant change in these resonances except for a general broadening of the signals and downfield shift of pyrrolic NH signal. The two *meso*-methyl groups of the calix[4]pyrrole were considered to be pointing in toward the porphyrin ring, as inferred from the fact that peaks ascribable to these subunits appeared at 0.54 ppm in the NMR spectrum.

The proton NMR spectral characteristics of receptor **7** were found to differ significantly from those of **6 (**Figure 2). In near analogy to what is seen for **6**, at room temperature the spectrum of **7** is characterized by a NH resonance at 6.31 ppm, which appears as a broad singlet, and two broad singlets at 5.34 and 4.85 ppm corresponding to the calix[4]pyrrole $\beta$-pyrrolic protons. On the other hand, the signals for the two *meso*-methyl groups at the strapping point appeared at −0.43 ppm in the form of a very broad signal, which represents a dramatic upfield shift for this signal compared to what is seen in the case of **6**. Dramatic changes were also observed for all of the resonances when the spectrum was acquired at −50 °C. For example, the calix[4]pyrrole NH resonance was split into two distinct singlets that now appeared at 7.02 and 6.33 ppm. The $\beta$-pyrrolic protons were also split, appearing as four distinct singlets at 5.64, 5.60, 5.27, and 4.19 ppm, respectively. In addition, two sets of resonances were observed for each of the methylene protons in the bridging "strap", while the signal ascribed to the *meso*-methyl groups in the calix[4]pyrrole appearing at −0.43 ppm was found to be shifted to higher field, resonating at −2.23 ppm as a well-defined singlet.

High-temperature proton NMR spectroscopic studies carried out in DMSO-$d_6$/$CDCl_3$ (3/1) showed no sign of interconversion of the two isomers **6** and **7** even at 120 °C. Moreover, all the resonance lines of **6** remain unchanged upon heating to 100 °C, while the structure of **7** becomes more symmetrical at elevated temperature as judged from a sharpening of all $^1$H NMR signals including those ascribed to the $\beta$-pyrrolic protons. All of the above experimental results indicate that the two compounds **6** and **7** are not conformational isomers of each other.

Preliminary solution-phase binding studies of receptor **6** were made using proton NMR spectroscopy in $CDCl_3$. When the tetrabutylammonium salt of fluoride ion (purchased commercially as the purported trihydrate and used without further purification) was added to a $CDCl_3$ solution of **6**, a new set of signals was seen to grow in at the expense of those seen in the case of **6** alone. The fact that two distinct sets of peaks were observed (as opposed to a time-averaged single set) was considered reflective of strong binding with slow complexation/decomplexation kinetics. Near complete conversion to what was presumed to be the bound form was seen upon the addition of ∼1.2 equiv of $F^-$. A Job plot was performed and found to exhibit 1:1 binding ratio with fluoride

anion. Further quantitative estimates of anion affinities could not be made on the basis of these studies because of strong irreversible binding. On the other hand, the very observance of this kind of spectroscopic behavior did provide good qualitative evidence for fluoride ion binding. It also provided evidence for structural changes occurring during the course of binding. For example, titration of receptor **6** with fluoride anion produced a new set of signals for the pyrrole NH protons at 12.53 ppm that were shifted to lower field than what was observed in the absence of anions ($\delta = 6.19$ ppm). Likewise, the $\beta$-pyrrolic CH signals shifted from 4.73 and 4.80 ppm to 5.33 ppm upon the addition of fluoride anion. Since anion binding to the pyrrole NH groups is expected to increase the electron density on the pyrrole ring and engender upfield shifts in the $\beta$-pyrrolic CH signals, the observed spectral shifts are consistent with structural changes that cause the respective protons to move away from the porphyrin plane upon binding to the fluoride ion. The exact nature of these structural changes, however, must await more detailed analysis, either in solution or in the solid state.

Attempted solution-phase binding studies involving the tetrabutylammonium salts of chloride, bromide, and iodide anions did not reveal any evidence of appreciable binding, as judged from the absence of changes in the corresponding $^1$H NMR spectra. Although not a proof, these observations are consistent with the notion that only fluoride anion can fit readily into the cavity and that either the size of this cavity or the conformational flexibility of the calix[4]pyrrole−porphyrin receptor moiety is sufficiently restricted so as to exclude the larger halide anions.

In accord with the notion that structural limitations can play a key role in regulating the anion affinities of strapped or capped calix[4]pyrroles, it was found that receptor **7** showed no affinity for fluoride (or any other halide anion), as judged from the absence of observable changes in its $^1$H NMR spectrum when subject to titrations analogous to those described above. In this instance, it is inferred that the conformational restriction imposed by the twisted junction of the two macrocycles somehow restricts the conformational changes needed to accommodate a bound fluoride anion. Analysis of the single-crystal structure of diester-strapped calix[4]pyrrole reported earlier[12] reveals that the most stable conformation of a strapped calix[4]pyrrole moiety, including those of the present series, is likely to be the twisted 1,3-alternate form in the absence of a bound anion, the result of presumed compensation between the conformational stability of the calix[4]pyrrole moiety and the strain induced by the bridging methylene chain. On the other hand, in analogy to what is seen in most anion-bound forms of calix[4]pyrrole, it is likely that the anion-bound form requires (or at least favors) the cone conformation. A system that is unable to adopt to such conformational changes might thus show very high anion binding selectivities or, as in the case of **7**, prove unable to bind any anionic substrate easily, at least within its central binding cavity.

In conclusion, we have demonstrated that calix[4]pyrrole-capped Ni(II) porphyrins can be prepared readily using a convergent approach. To the best of our knowledge, receptor **7**, bearing a connecting strap with a *trans*-junction relative to the porphyrin plane is unique. Bearing two different kinds of binding elements (calix[4]pyrrole and porphyrin), compounds such as those described here could see utility in the design and synthesis of heteroditopic receptors, as well as Lewis acid assisted anion receptors. Furthermore, because the compounds reported here contain flexible straps that may themselves incorporate additional anion recognition elements (e.g., amides, sulfamides, etc.), additional fine-tuning of the anion binding properties may be envisioned. Finally, the use of the porphyrin moiety as a spectroscopic probe for monitoring the anion binding events suggests itself. Current work is thus devoted to preparing new analogues of **6** and **7** and to studying their molecular recognition properties under a range of experimental conditions.

Another appealing way to modulate the anion binding properties is encapsulation of the parent macrocycle with preorganized H-bonding motif. The system **1** is rather unique in that it contains free-base or metallo-porphyrins as ancillary hydrogen-bonding donors or coordination sites at the proper distance. In addition, the anion could be one of the axial ligands to be trapped inside the cavity.[10] This trapped ligand will stay inside the cavity regardless the nature of the metal ion. This could also serve as a good model for studying metalloporphyrin-catalyzed reactions.

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**Supporting Information Available:** Spectral data for the compounds **1**−**7** and low- and high-temperature NMR studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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