

Review Article

Synthesis and binding pattern of Calix[4]Pyrrole compounds

Debabrata Pal

Assistant Professor, Department of Chemistry, Sreegopal Banerjee College, Bagati, Magra, Hooghly, Pin – 712148, West Bengal, India.

Correspondence should be addressed to Debabrata Pal; debu_magra@yahoo.co.in

Abstract

In this short review, focus has been on the improvisations in the synthetic procedures of the Calix[4] pyrrole type compounds, since their first discovery in the year 1886 and subsequent discussion on their binding pattern towards different chemical species. Calix[4] pyrrole, which is an analogue of hetero calixarenes, is the representative of a group of macrocycles. It has an ability to bind neutral and anionic species. The selectivity towards guest species emerges from the energetics and conformational features of this compound. Different structural modifications and functionalizations have been incorporated in the parent Calix[4] pyrrole moiety in order to achieve better selectivity.

Key Words: Calix[4]Pyrrole, Synthesis, Binding, Selectivity, Energetics

Introduction

Since the discovery of Calix[4] pyrrole by Baeyer in the year 1886,¹ this compound finds an outstanding passage of potential application in diversified dimensions of chemistry and related areas. In the nineties of the past decade, about a hundred years after the discovery, Floriani and coworkers initiate remarkable growth of interest by their extensive work on the metabolism and synthetic chemistry of deprotonated calixpyrroles.² Pioneering work by Sessler and his group triggers the opening of a new domain on these group of compounds,^{3,4} which encompasses an area of developing new methodologies, strategies aiming at elaborate elucidation of functionality, characterization and overall to tune the approach towards multidisciplinary applications. The calix[4]pyrroles are a most venerable class of materials. Calixpyrroles are previously considered as Porphyrinogens, the macrocyclic species composed of four pyrrole rings linked in the α -position via sp^3 -hybridized carbon atoms. Porphyrinogens which carry *meso*-hydrogen atoms are prone to oxidation to the corresponding porphyrin. On the other hand, fully *meso*-substituted porphyrinogens are generally not only stable crystalline

materials but also readily obtainable. While the term porphyrinogen is now widely accepted in the literature, octaalkylporphyrinogens are not *bona fide* precursors of the porphyrins and might, therefore, be better considered as being *calixpyrroles*. Such a renaming, which has precedent in the chemistry of other heterocyclic ring systems, would allow the analogy to calixarenes to be more fully stressed. Interestingly, while functionalized calixarenes have been shown to be capable of binding anions, unmodified calixarene frameworks show no affinity for anionic guests. In the case of the simple octaalkyl functionalized Calix[4] pyrrole, it is found that both fluoride and chloride anion are bound in the solid state and that these two anions, and to lesser extent dihydrogen phosphate, are bound in dichloromethane solution.³ Shortly thereafter, it is discovered that calixpyrroles bind neutral substrates, though weakly.⁴ Since then, much of research have been directed towards the development of systems whose inherent anion binding properties are modified relative to the "parent" Calix[4] pyrrole. Following the course of time, different systems such as calix[*n*]pyrroles,⁵⁻⁸ calixbipyrrole,^{9,10} strapped calixpyrrole,¹¹⁻¹³ calixpyrrole dimer,¹⁴ pentapyrrolic calix[4]pyrrole,¹⁵ and cryptand-like calixpyrrole^{16,17} have been reported. Calix[4]pyrrole adopts four major conformations as in the case of calix[4]arene. While 1,3-alternate conformation is found to be preferred in the absence of a guest, as determined by theory and X-ray method, the cone conformation is observed to be dominant in the presence of an anionic guest by the formation of hydrogen bonding between pyrrolic NH and an anion.³ Apart from conventional binding with anionic and neutral guests, calix[4]pyrrole has recently been reported to function as ditopic ion-pair receptor¹⁸ and also to act as mediators for the selective transport of an ion pair (CsCl) through model phospholipid bilayers.¹⁹ Interaction of calix[4]pyrrole with fullerenes has also been explored recently, where large binding constants has been reported, indicative of strong binding between these species.²⁰ In the context of this review article, the major focus will be on different synthetic pathways, the binding phenomenon and the diversified field of applications.

Synthesis

Baeyer originally synthesized *meso*-octamethylcalix[4]pyrrole **1** as a white crystalline material by condensing pyrrole and acetone in the presence of hydrochloric acid.¹ The reaction has been refined over the following century to a stage where 90% yields of the macrocycle are readily obtainable without the need for any form of templation or for high dilution conditions. Subsequent to the work of Baeyer, Dennstedt and Zimmemann also studied this reaction, using 'chlorzink' as the acid catalyst.^{21,22,23} In the 1950s, Rothmund and Gage reported improved yields by using methanesulfonic acid as the acid catalyst.²⁴ Protic acids (HCl, H₂SO₄), organic

acids ($\text{CH}_3\text{SO}_3\text{H}$) and Lewis acids (BBr_3 and BF_3) have also been used in the synthesis of calix[4]pyrroles.²⁵⁻²⁸ In recent past, M. Radhakishan et al have reported a novel, shape-selective, zeolite-catalyzed synthesis of calix[4]pyrroles by refluxing an equimolar ratio of pyrrole and ketone in dichloromethane over Al-MCM-41,^{29,30} and Co-MCM-41 is found to give maximum yields.³¹ In continuation of their work, efficient evaluation of porphyrins and calix[4]pyrroles by in situ synthesis from pyrrole with aromatic aldehydes and ketones, respectively, over zeolite based molecular sieve catalysts as sorbents in thin layer chromatography (TLC) are accomplished in one step with microwave heating.³² A facile, highly efficient and eco-friendly protocol for the synthesis of calix[4]pyrroles in excellent yields is reported in the meantime, where simple recrystallization techniques instead of tedious column chromatography, has been employed for compound purification yielding better results and leading to multi gram scale synthesis.³³ Another approach, rather a green chemistry approach for the synthesis of calix[4]pyrroles and *N*-confused calix[4]pyrroles in moderate to excellent yields is done by the reaction of dialkyl or cycloalkyl ketones with pyrrole catalyzed by reusable AmberlystTM-15 under eco-friendly conditions.³⁴

Binding phenomenon

Calix[4]pyrroles are effective and selective anion binding agents both in solution and in the solid state. The first ever binding studies have been carried out with *meso*-octamethyl calix[4]pyrrole **1** and tetraspirocyclohexylcalix[4]pyrrole **2**,³ the structures of **1** and **2** are provided in Figure 1. The binding occurs via the interaction of the anion and the pyrrolic H atoms through formation of H bonding.³⁵ The same reasoning can be well attributed during complexation with neutral guests like alcohols, amides etc where the electronegative atoms in the guest molecules are employed in H-bonding. Another point, to be evoked, is the inherent flexibility of calix[4]pyrrole moiety,³⁶ which significantly prompts towards a geometrically favourable local alignment of the core to incorporate the guest in the cavity.³⁷

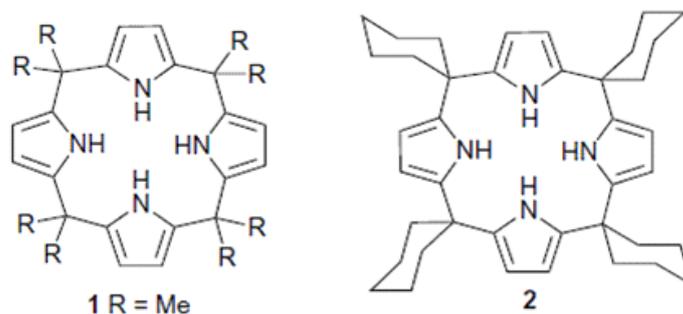


Figure 1: Structure of *meso*-octamethyl calix[4]pyrrole[1] and tetraspirocyclohexylcalix[4]pyrrole[2]

Crystals of the tetrabutylammonium chloride complex of calixpyrrole **1** were obtained by slow evaporation of a dichloromethane solution containing an excess of the chloride salt. Crystals of the tetrabutylammonium fluoride complex of **2** were obtained using a similar procedure.³ X-ray crystal analysis revealed that in both cases the calix[4]pyrrole ligand adopts a conelike conformation such that the four NH protons can hydrogen bond to the halide anion. While these two structures are thus grossly similar, in the case of the chloride complex, the nitrogen-to-anion distances are in the range of 3.264(7)-3.331(7) Å, while for the corresponding fluoride complex they are 2.790(2) Å. (the four pyrrole groups are equivalent by symmetry). As a result, in these two complexes the chloride and fluoride anions reside 2.319(3) and 1.499(3) Å above the N₄ root-mean-square planes of calixpyrroles **1** and **2**, respectively. Thus, fluoride anion appears to be more tightly bound, at least in the solid state. Analyses of the solution phase anion-binding properties of calix[4]pyrroles **1** and **2** have been made using ¹H NMR titrations carried out in dichloromethane-*d*₂. The values of the binding constants are given in table 1 and 2, for anionic and neutral guests respectively, which reveals that both compounds **1** and **2** are not only effective 1:1 anion-binding agents in solution, they are also selective ones; they show a marked preference for F⁻ relative to other putative anionic guests (*Viz.* Cl⁻, Br⁻, I⁻, H₂PO₄⁻, and HSO₄⁻). Thus, the anion-binding behavior displayed by **1** and **2** appears to be a direct consequence of having available for hydrogen bonding a polypyrrolic macrocycle of appropriate size and shape. From this viewpoint it is anticipated that **1** would modify its shape to accommodate different neutral substrates, provided that these can act as hydrogen-bonding acceptors. In accord with this expectation, the calixpyrrole unit in **1**•2(MeOH) is found to assume a 1,3-alternate conformation in the solid state, as judged from single-crystal X-ray diffraction analysis.⁴ Single molecules of the alcohol lie above and below the macrocycle, each one held in place by hydrogen bonds to two pyrrolic NH groups. Further evidence that methanol is bound to **1**, rather than merely occupying space in the lattice, is given by the inward tilt of the pyrroles of **1**•2(MeOH). Complex **1**•2(DMF) [DMF = *N,N*-dimethylformamide] has also been studied by X-ray crystallography. As in the methanol adduct, individual symmetry-equivalent guests are found above and below the host, but in this case each amide is hydrogen bonded to adjacent pyrroles. The conformation of the calixpyrrole is therefore 1,2-alternate. Structurally characterized examples of 1,2-alternate calix[4]arenes are scarce, and **1**•2(DMF) is the first calixpyrrole in this conformation to be unambiguously characterized. The unsaturated portion of the amide lies 3.363(3) Å above the plane of a third pyrrole ring (the planar twist angle between these two moieties is 7.1(1)°), leading to the proposal that a π - π stacking interaction helps to stabilize **1**•2(DMF). From the results of table.

2 it can be said that Calixpyrrole **1** have a measurable affinity for all of the studied substrates except nitromethane, which is a notoriously poor hydrogen-bond acceptor. A trend is evident across both the alcohol and amide series, in which the association constants uniformly decrease with increasing bulk near the substrate oxygen atom. Methanol is therefore bound most strongly among the alcohols, with $K_a=12.7\pm 1.0\text{ M}^{-1}$, the two primary alcohols cluster about $K_a\sim 10\text{ M}^{-1}$, and the secondary alcohols fall near $K_a\sim 7\text{ M}^{-1}$. For the amides, the K_a values are sensitive to changes in substituents on the nitrogen atom and on the carbonyl carbon. Thus, receptor **1** has a higher affinity for a secondary formamide (*N*-formylglycine ethyl ester) than for a tertiary one (DMF) and forms a more robust complex with DMF than with *N,N*-dimethylacetamide. The low K_a value of $2.2\pm 0.1\text{ M}^{-1}$ recorded for 1,1,3,3-tetramethylurea indicates that the presence of *two* sets of *N*-bound methyl groups severely hinders approach of the amide oxygen atom to the calixpyrrole pseudocavity.

Table 1: Stability constants for **1** and **2** with Anionic Substrates in CD_2Cl_2 at 298K

Stability constant (M^{-1})		
anion added	Calix[4]pyrrole 1	Calix[4]pyrrole 2
fluoride	17170(± 900)	3600(± 395)
Chloride	350(± 5.5)	117(± 4.0)
Bromide	10(± 0.5)	
Iodide	<10	
Dihydrogen phosphate	97(± 3.9)	<10
Hydrogen sulfate	<10	

Table 2. Association constants for **1** with Neutral Substrates

substrate added	$K_a(M^{-1})$	substrate added	$K_a(M^{-1})$
methanol	12.7 ± 1.0	<i>N,N</i> -dimethylformamide	11.3 ± 0.8
ethanol	10.7 ± 0.7	<i>N,N</i> -dimethylacetamide	9.0 ± 0.9
benzyl alcohol	9.7 ± 0.7	1,1,3,3-tetramethylurea	2.2 ± 0.1
isopropyl alcohol	7.0 ± 0.4	dimethyl sulfoxide	16.2 ± 1.1
<i>sec</i> -butanol	6.2 ± 0.4	1,2-dimethylimidazole	5.4 ± 0.3
<i>N</i> -formylglycine ethyl ester	13.3 ± 1.0	acetone	2.2 ± 0.2

However, the selectivity among the halides is lost with increasing solvent polarity and thus necessitates the idea of enthalpy-driven interaction to play the major part in the binding process.^{38,39} This view, though seems to be rational concerning the nature of host and guest in the present system, is not quite conceivable if cumulative enthalpy of all processes happening simultaneously in solution is taken into consideration rather than the partial event of the isolated host-guest interaction, e.g., in free space. The results evolve out of Isothermal titration calorimetry (ITC) of calix[4]pyrrole **1** with anionic guests clearly reimburse the fact that in condensed phases selectivity in its thermodynamic sense with competing guests is not a function of the host structure alone but is heavily dependent on the actual solvent used and the fluoride specificity in dichloromethane or in the gas phase, too, is compromised and eventually vanishes totally in more polar solvents such as acetonitrile or DMSO.⁴⁰ Since calorimetry determines the integral heat response of all reactions happening simultaneously in solution it can furnish a detailed mirror image of the molecular events only when the system concerned are ideal in thermodynamic sense without the necessity of making adjustment for competing simultaneous events that run within the same time domain of the measurement process. This situation is quite demanding and practically not attainable considering host-guest interaction in polar solvents and thus the calorimetric study cannot be rendered as a true thermodynamic preview of the interaction process rather it govern most attempts of host design grossly. Retorting to the actual thermodynamic scenario of the intricate host –guest interaction of calix[4]pyrrole **1** with the anions, a nice study by the group of Angela F. Danil de Namor, which is claimed to be the first detailed thermodynamic study on the calix[4]pyrrole-anion complexation process, ascertains the selective recognition of the halides by **1** in polar solvents

like acetonitrile and *N,N*-dimethylformamide.⁴¹ Their approach is quite explanatory in consideration of the fact that host-guest associations in polar solvents are prone to enthalpy-entropy compensation⁴² and the finest of the study is that the selective behavior of the ligand for the anions have been analyzed in terms of the solvation properties of reactants and products in the solvents which is justifiable on the results of ¹H NMR, conductance measurements, and titration calorimetry experiments and thus a relationship between the stability constants and the chemical shift changes of the pyrrole protons has been established redirecting a supportive consequences towards selective recognition of anions by **1**, the notion that has been quite outweighed, rather questioned by the previous Isothermal titration calorimetry study.

Following the track of advancement, sole attention was centered on the anion binding aspect in all respect, the role of the counter-cation in the complexation process remained largely unrevealed, until manifested by the fact that replacement of the quaternary ammonium by the {potassium_cryptand[222]} counter-cation of the guest anion viz fluoride, chloride, bromide and dihydrogen phosphate influences the magnitude of the experimental enthalpy by up to 20%, as reported in the Isothermal titration calorimetry studies of the complexation process with **1** in acetonitrile medium.⁴⁰ This reflects the role of the counter-cation not to be that of an innocent observer, which is already boosted from the results of solid state structural analyses of the complexes formed from a range of presumably similar chloride anion salts, showing the cations of different size, to interact differently with the calixpyrrole bowl.⁴³ Various X-ray crystal structures with variation in the counter cation clearly show differing degrees of encapsulation of the cation into the anion-induced calixpyrrole cup-shaped cavity in the solid state. This substantiates the fact that ion pairing, and hence counter cation-derived effects, could be important under at least some solution-phase conditions. This particular aspect was treated explicitly by Sessler and collaborators.⁴⁴ They focus entirely on the solvation and ion-pairing effect and investigated the variation of solvents and the counter-cation in studying the complexation of **1** with chloride ions by ¹H NMR and ITC method together with crystallographic studies. The results show that in solvents like nitromethane, acetonitrile and DMSO, the effect of countercation is reasonably nil, whereas this is much pronounced in 1,2-dichloroethane and even more in dichloromethane, reflecting the substantial effect of charge density and size of the counter cation on the stability of the ion pair that would form as the result of the cation interacting with the electron-rich walls of the calix[4]pyrrole “bowl”. These effects are anticipated to be masked to a greater extent in a more highly solvating solvent and hence would not necessarily be reflected in observable changes in the calculated affinity constant for anion binding, *K_a*. The effect of the counter cation in the binding process is

subsequently demonstrated by solution binding studies of calix[4]pyrroles with anion (added as tetraalkylammonium salts) investigated using UV–vis spectroscopic techniques.⁴⁵ The observation of red-shift of absorption maximum band of **1** in EtOH in the presence of the tetramethylammonium (TMA⁺) or tetraethylammonium (TEA⁺) salts is indicative of the fact that calix[4]pyrrole receptors linking anionic species through multiple hydrogen bonding interactions are capable of using the periphery electron-rich “walls” for selectively binding electron-deficient tetraalkylammonium cation subunits by cation- π charge–transfer interaction and concomitantly the stability of the calix[4]pyrrole–anion complex is strongly dependent on the nature of the cation. The *meso*-alkyl groups of the calix[4]pyrrole, the affinity for the anion subunits and the structure of tetraalkylammonium cations have considerable effects on the formation of cation- π charge–transfer interaction. Taking in concert, it can be said that apart from the host-designing, the association process is influenced by the solvent and the counter cation, although any apparent correlation between the observed binding behavior and the solvent parameters viz. permittivity, refractive index (polarizability), dielectric constant, donicity, or acceptor strength etc. are yet to be established. The selective recognition of anions by calix[4]pyrroles is substantiated by a recent study on the binding of the macrocycle with fluoro, chloro, bromo, iodo and sulphato anions generated from the corresponding *normal*-TBA salts, investigated by electrospray ionization mass spectrometry (ESI-MS) in dichloromethane–acetonitrile in negative ion mode.⁴⁶ The binding strength is found to be inversely proportional to the size of anion, which is previously interpreted based on the thermodynamic studies referred earlier.⁴¹ The association constants of calix[4]pyrroles and anions obtained from electronic transition studies were in good agreement with that observed from ¹H NMR titration studies.

Applications

The most important application of the calixpyrrole moiety is perceived by utilizing its ability to bind with both anionic and neutral guest species and also by their potency to act as ion-pair receptors. In order to achieve responses with discernible specificity, different redox or fluorescent moieties are incorporated in the parent calixpyrrole skeleton to render the system effective towards discrimination between different guests. Recently a new calix[4]pyrrole-based, dual functional, chemodosimetric sensor is reported and studied as a cyanide selective indicator; where complete color bleaching is observed even in the co-presence of an excess of other anions.⁴⁷ This is quite a land mark in the development of sensors, concerning the toxicity

of cyanide ions. The calixpyrrole is effective in facilitating ion transportation across membranes. The calixpyrrole moiety also finds application in the field of capillary electrophoresis⁴⁸ calixpyrrole and calixpyrrole based materials also find use in fabrication of electrodes and electroanalytical sensors⁴⁹, promoter⁵⁰ and catalysts⁵¹ in different reactions, as well as in the preparation of nanofilms⁵² and selective ion carriers⁵³. The domain of application seems to be increasing in a faster way and thus turning this easy to make simple macrocycle namely calixpyrrole, a very important molecule for the future days to come.

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