

## Ballester Research Group



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### Abstract

Our research aims are mainly focused on the design, synthesis and application of molecular containers. We work in the synthesis of water soluble calix[4]pyrrole structures and the study of their binding processes in aqueous media. This constitutes the starting point for further understanding more complex biological molecular recognition processes. The study of weak non-covalent interactions such as anion- $\pi$  or CH- $\pi$  interactions is another area of our interest. By using calix[4]pyrrole receptors synthesized in the group we evaluate the

strength and nature of these weak intermolecular interactions. The group is also working on the synthesis of unprecedented calix[4]pyrrole and calix[4]arene based uni- and supramolecular receptors whose binding affinity and cargo release can be controlled by external stimuli i.e. light. Finally, we concentrate our efforts to collaborate with other research groups working in the area of sensing devices. We want to apply the receptors prepared in the group for the development of sensing devices that can be used for the detection and quantification of clinically relevant molecules in real biological fluids or in the gas phase.

### Water soluble calix[4]pyrroles

In recent years, the group has been interested in the synthesis of water soluble receptors and in the understanding of molecular recognition processes in aqueous media. We consider that the knowledge gained from the binding studies of simple water-soluble receptors could help in further understanding the operation of more complex biological systems.

In 2009, we reported the first example of a water-soluble aryl-extended calix[4]pyrrole bearing the water solubilizing groups at the upper rim. This specific location of the ionisable groups had several drawbacks: 1) alters the electronic nature of the pristine aromatic cavity and 2) impedes the further elaboration of the aromatic cavity with other functional groups capable of interacting with the included guest.

With the aim to overcome these limitations, during this year, the group has described the synthesis of a water-soluble aryl-extended calix[4]pyrrole receptor bearing the water solubilizing groups at the lower rim. The solubilising groups were installed at the *meso*-alkyl substituents *via* 1,3-Huisgen cycloaddition. They are sufficiently distant to the binding site to avoid any interference in the recognition process.

The receptor forms thermodynamically and kinetically stable complexes with a series of neutral and charged pyridyl *N*-oxide guests in basic aqueous solution with stability constants higher than  $10^4 \text{ M}^{-1}$ . In all the cases, the *N*-oxide moiety engages in hydrogen-bond interactions with the four pyrrole NH's of the calix[4]pyrrole core. Remarkably, the four-fold negatively charged water-soluble receptor is also able to bind an anionic pyridyl *N*-oxide guest equipped with a *p*-substituted carboxylate group with similar binding constant ( $>10^4 \text{ M}^{-1}$ ).

These results demonstrate the ability of the receptor's walls to protect the polar binding site and ensure the establishment of selective hydrogen-bonding interactions even in water solution.

oxide, which is shown as an energy minimized structure (MM3).

### CH- $\pi$ Interactions

We have continued our studies in the use of calix[4]pyrrole receptors as tools for the study and quantification of weak intermolecular interactions i.e. CH- $\pi$  interactions.

We have reported on our efforts to unravel the physical nature and strength of CH- $\pi$  interactions occurring in the inclusion complexes of a series of "two-wall" and "four-wall" aryl-extended calix[4]pyrrole receptors with trimethylamine *N*-oxide ( $\text{Me}_3\text{NO}$ ) and trimethylphosphine *P*-oxide ( $\text{Me}_3\text{PO}$ ).

We demonstrated that the magnitude of the CH- $\pi$  interactions established between the methyl groups of the guests and the aromatic panels of the calix[4]pyrrole receptor did not depend on the electronic nature of the phenyl walls. This observation indicated that electrostatic factors were not very relevant in these interactions, which should be dominated by dispersion forces. In general,  $\text{Me}_3\text{NO}$  produced thermodynamically more stable complexes with aryl-extended calix[4]pyrrole receptors than  $\text{Me}_3\text{PO}$ . Upon guest binding, the receptors adopted a cone conformation and the methyl groups of the included guests engaged in CH- $\pi$  interactions with the aromatic walls. The larger binding affinities determined for the "four-wall" receptors in comparison with the "two-wall" systems supported the importance of CH- $\pi$  interactions on guest complexation. Finally, based on the number of CH- $\pi$  interactions observed in the solid state structure of a four-wall inclusion complex with  $\text{Me}_3\text{NO}$  we estimated the energetic contribution of a single CH- $\pi$  interaction ( $\Delta G \sim 1.1 \text{ kcal}\cdot\text{mol}^{-1}$ ). Our estimate was in complete agreement with other values previously described for "typical" CH- $\pi$  interactions.

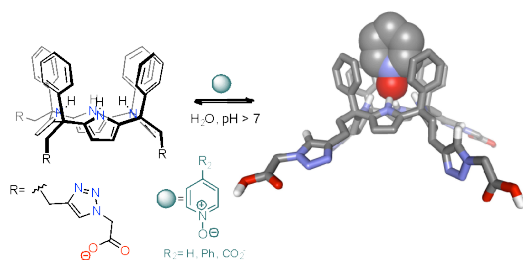


Fig. 1 – Line-drawing structure of the water soluble aryl extended calix[4]pyrrole. Equilibrium involved in the formation of the inclusion complex with pyridine *N*-

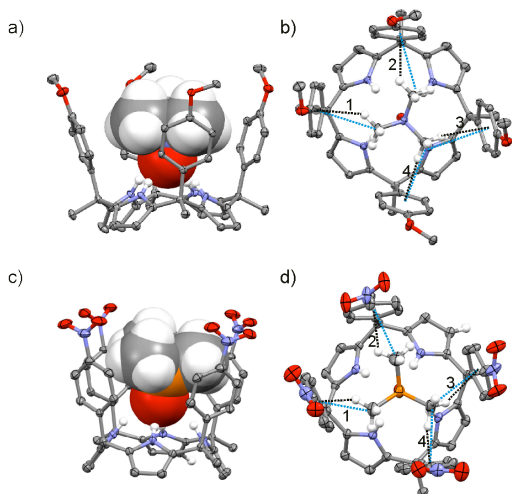


Fig. 2 – Side (a,c) and top (b, d) views of the X-ray structure of two calix[4]pyrrole complexes with  $\text{Me}_3\text{NO}$  and  $\text{Me}_3\text{PO}$ , respectively. Dashed lines indicate CH- $\pi$  interactions.

#### Tetraurea Calix[4]pyrrole Dimeric Capsules

The self-assembly of tetraurea calix[4]pyrroles into dimeric capsule has been widely studied in our group. Related to this topic, during this year we have focused our attention in two main projects: (a) the study of ordered co-encapsulation complexes of chloride with polar neutral guests in a tetraurea calix[4]pyrrole capsule and (b) the reversible light-controlled cargo release of a tetraurea calix[4]pyrrole capsule.

The first project was related to the description of rare examples of ordered encapsulation complexes of a tetraurea calix[4]pyrrole with a polar neutral guest (i.e.  $\text{Me}_3\text{NO}$  or  $\beta$ -alanine betaine) and methyltrioctylammonium chloride (MTOACl) salt. Two different aggregates displaying high kinetic and thermodynamic stability were described showing differences in morphology and stoichiometry. On the one hand, an equimolar solution of tetraurea calix[4]pyrrole, the polar but neutral guest and MTOACl produced a four-particle inclusion complex. On the other hand, a mixture of the same components in a 2:1:1 molar ratio (calix[4]pyrrole:polar guest:MTOACl) induced the formation of a dimeric capsular assembly displaying multiple guests orderly co-encapsulated. The influence of different polar guests and ammonium salts on the self-assembly process was also described. The reported findings evidenced the delicate conditions that operate in reversible supramolecular encapsulation processes

occurring in container systems stabilized by hydrogen-bonding interactions.

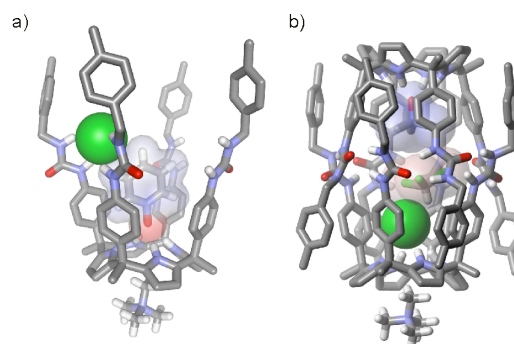


Fig. 3 – a) X-ray structure of the four particle assembly generated from an equimolar solution of tetraurea calix[4]pyrrole, pyridine *N*-oxide and MTOACl. b) Energy minimized structure (MM3) of the capsular assembly obtained from a 2:1:1 mixture of calix[4]pyrrole,  $\text{Me}_3\text{NO}$  and MTOACl.

In the second project, we continued our studies on the light-controlled assembly-disassembly of supramolecular capsules. We reported the synthesis of three different tetraurea calix[4]arenes equipped with four light-responsive terminal azobenzene groups. The thermally equilibrated tetraurea calix[4]arenes with all the azo groups in *trans*-form (all-*trans* isomers) dimerize quantitatively in  $\text{CD}_2\text{Cl}_2$  in the presence of tetramethylphosphonium cation ( $\text{Me}_4\text{P}^+$ ) affording a capsular aggregate. The included cation was detected by  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectroscopy. The light induced *trans*-to-*cis* isomerization of the azo-groups produced a plethora of isomeric *cis*-enriched calix[4]arene dimeric capsules and triggered the partial release of the  $\text{Me}_4\text{P}^+$  cation to the bulk solution. Thermal equilibration in the dark restored the system to the initial equilibrium state. We also demonstrated that we were able to control the amount of released cargo ( $\text{Me}_4\text{P}^+$ ) after isomerization by tuning the extent of substitution of the terminal phenyl in the azobenzene groups. We were able to achieve high level of release (up to 70%) of the encapsulated guest. It is worthy to note that the switching between the thermal equilibrium state and the photostationary state proceeded with no detectable photodegradation, even when it is repeated multiple times.



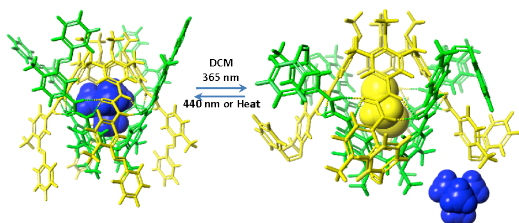


Fig. 4 – Light induced *trans*-to-*cis* isomerization of the capsular assembly based on tetraurea calix[4]arenes equipped with four azobenzene groups. *Trans*-to-*cis* isomerization triggers the release of the encapsulated  $\text{Me}_4\text{P}^+$  cation. Most likely,  $\text{CD}_2\text{Cl}_2$  solvent molecules having a smaller volume than  $\text{Me}_4\text{P}^+$  became competitive encapsulation guests of the *cis*-enriched capsules featuring a reduced internal volume.

### Calix[4]pyrrole for sensing purposes

During this year we also focused on the application of some of the receptors developed by the group (i.e. calix[4]pyrroles and resorcinarenes) for the sensing of clinically relevant neutral and charged molecules. We can divide our studies in three different projects: (a) tetraphosphonate calix[4]pyrrole cavitands as multitopic receptors for ion-pairs, (b) “two-wall” aryl-extended calix[4]pyrroles for the development of chloride-selective electrodes and (c) quinoxaline walled deep resorcin[4]arene cavitands self-assembled on Au-nanoparticles for benzene sensing using resistometric devices. The first project deals with the synthesis, structural characterization, and binding studies of two disatetrameric calix[4]pyrrole-resorcin[4]arene hybrids equipped with four phosphonate groups at the upper rim. The isolated tetra-phosphonate receptors displayed either three (i000) or four (o000) of their P=O groups oriented away from their deep and functionalized cavity. The tetraphosphonate calix[4]pyrrole cavitands exhibited superior binding properties than the previously reported bis-phosphonate counterparts in the complexation of phosphonium and ammonium ion-pairs. We demonstrated that the i000 receptor acted as a multitopic ion-pair receptor by switching the geometry of its 1:1 ion-paired complexes from a receptor-separated to close-contact mode depending on the nature of the organic cation of the chloride salt (i.e., quaternary or primary alkylammonium).

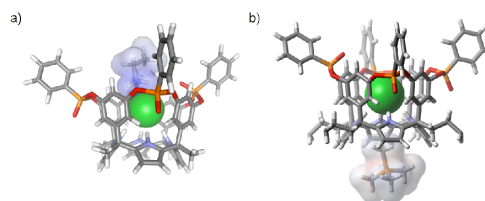


Fig. 5 – Energy minimized structures (MM3) of the 1:1 complexes formed by the tetra-phosphonate receptor i000 displaying close-contact (a) and receptor-separated (b) binding modes.

In the second project of this section we used “two-wall” aryl-extended calix[4]pyrroles to prepare solid-contact ion-selective electrodes (SC-ISEs). Several calix[4]pyrrole receptors decorated with *meso*-phenyl substituents with different electronic properties (i.e. electron-rich, electron-poor or electron-neutral) were incorporated as ionophores in SC-ISEs membranes. The ISEs also incorporated multiwall carbon nanotubes (MWCNTs) as efficient transducers. The “two-wall” calix[4]pyrrole bearing a *p*-nitro electron-withdrawing group on each of the *meso*-phenyl rings, afforded sensors that displayed anti-Hofmeister behaviour against lipophilic salicylate and nitrate anions. Moreover, we demonstrated that this receptor was an excellent ionophore towards chloride anions. The concerted use of hydrogen-bond and anion- $\pi$  interactions in the formation of the complex provided an ISE with excellent selectivity for chloride against common and highly lipophilic anions. The developed sensors were used to measure chloride concentration in real and artificial biological samples of blood, serum, sweat and urine, obtaining excellent recovery.

Finally, in the last project centred on sensing devices we developed, in collaboration with the group of Prof. E. Llobet from the URV, a simple experimental procedure for preparing a resistive gas sensor device. The sensor contained gold nanoparticles (AuNPs) deposited on MWCNTs. In turn, the AuNPs were decorated with a quinoxaline-walled thioether-legged resorcinarene cavitand (cav). The cav-AuNP-MWCNT resistive gas sensor showed outstanding performance toward traces of benzene vapours. The detection of 2.5 ppb of benzene in dry air was demonstrated with a limit of detection (LOD) near 600 ppt. Moreover, the sensor response toward toluene and *o*-xylene was significantly lower, confirming the strong response for benzene.



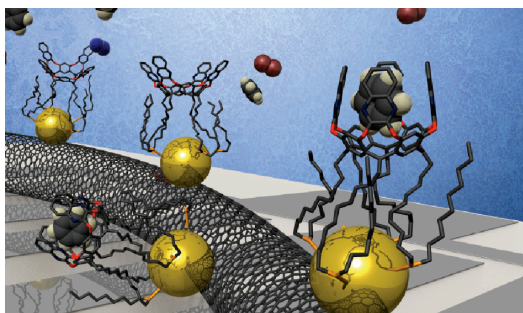


Fig. 6 – Ideally schematized representation of the cavitand immobilized on the AuNP surface that decorate the MWCNTs of the resistive sensor.

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