Ballester Research Group

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 photoresponsive molecule capsules is another area of our interest. By using calix[4]pyrrole and calix[4]arene receptors bearing azo functionalities we are able to control the assembly and disassembly of molecular capsules. We pursue the control of cargo release by external stimuli i.e. light. Finally, we also dedicate some of 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 (e.g. creatinine).

Molecular recognition of polar substrates in water using synthetic receptors represents a challenging and exacting endeavor, aiming to mimic natural protein performance. Encountered difficulties include: 1) the synthesis of receptors that are water soluble and do not aggregate at the concentrations required for conducting NMR binding studies; 2) the incorporation to the receptors’ scaffolds of converging polar groups able to establish hydrogen-bonding interactions with those of the targeted substrates; and 3) burying the receptor’s polar groups in the interior of hydrophobic cavities of sensible dimensions with the aim to reduce water solvation and induce guest inclusion. We and others have demonstrated that the water-soluble tetra-α isomers of aryl-extended calix[4]pyrroles are privileged receptors for the recognition of small polar guest in water (e.g. N-oxides). Previously we have reported water-soluble aryl-extended calix[4]pyrroles bearing the water solubilizing groups either in the upper or the lower rim. The elaboration of the aromatic cavity in synthetic receptors is typically associated with modifications of their binding selectivity and affinity. This year, we have reported the enlargement of the aromatic cavity defined by meso-phenyl substituents in the tetra-α isomers of aryl-extended calix[4]pyrroles affording unprecedented calix[4]pyrroles that we termed “super-aryl-extended” (SAE) (Fig. 1). We reported the binding properties of the prepared SAE-calix[4]pyrrole tetraester towards pyridyl-N-oxides. The binding data revealed the formation of thermodynamically and kinetically highly stable 1:1 complexes. The complexation-induced chemical shifts indicated the formation of hydrogen bonds and aromatic interactions with the calix-core adopting the cone conformation. We quantified the additional interactions established between the four terminal aryl groups and the para-phenyl substituent of 4-phenyl pyridine N-oxide to be in the order of 1 kcalmol⁻¹. Finally, to explore the water solubility of the SAE-calix[4]pyrroles, we appended ionizable groups at their upper rim. Unfortunately, we learnt that four ionizable groups was not enough to gain access to water solubility.

Photoresponsive dimeric capsules

We have continued our studies on light controlled assembly-disassembly of supramolecular capsules. We have described the light-triggered response of a series of dynamic systems based on calix[4]pyrrole-calix[4]arene dimeric capsules bearing photoresponsive azo-groups in only one of their components. The heterodimeric capsule was assembled by the social self-sorting of an all-trans calix[4]arene equipped with four terminal azobenzene units, and a calix[4]pyrrole by encapsulating one molecule of trimethylphosphine oxide or trimethylamine oxide. The trans-to-cis photoisomerisation of the azobenzene groups in all-trans-heterocapsule induced the formation of cis-enriched capsular and non-capsular assemblies that were in equilibria. The process was fully reversible by thermal treatment of the samples (Fig. 2). Addition of bis-(N-oxide-N,N,N',N'-tetramethylamino)hexane to the assembled heterocapsule produced the assembly of a new capsular system in the media, the homocapsule of the calixarene including the added guest. We also showed preliminary results obtained using light-irradiation for controlling the selective assembly of a capsular aggregate in complex systems.
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Fig. 2 – Line-drawing and schematic representation of tetraurea calix[4]arene (orange bowl) and tetraurea calix[4]pyrrole (white vase) photoactive dimeric caspules. Urea groups are represented as blue arrows and azobenzene units as red boxes.

Covalent calix[4]pyrrole containers

Recently, we described the synthesis of macrocycle 1 (Fig. 3), which in turn was used for the preparation of molecular assemblies displaying [2]pseudorotaxane topology exhibiting promising anion recognition properties. Macrocyle 1 was prepared in 60% yield by dimerization of the “two wall” calix[4]pyrrole 2 monomer using Hay reaction conditions. With the aim to extend the range of polar molecular containers based on aryl-extended calix[4]pyrrole scaffolds, this year we wanted to undertook the synthesis of oligomacrocyclic calix[4]pyrrole dimer container 4 using tetraalkynyl derivative 5 as starting material. We expected that the incorporation of two additional aromatic walls to molecular container 4, compared to 1, would increase the thermodynamic and kinetic stability of its encapsulation complexes providing, simultaneously, a complete isolation of the bound guests from the bulk solution. The closed and polar internal cavity featured in container 4 suggested that it may have potential applications as a reactor vessel.

We describe our efforts and results towards the template synthesis of oligomacrocycle 4 using Hay coupling conditions, calix[4]pyrrole 5 and two bipyridine bis-N-oxides, 3 and 6, as templates. On the one hand, we established that bis-N-oxide 3 is not an efficient template for promoting multiple intramolecular coupling reactions between the terminal alkynyl residues at the upper rim of calix[4]pyrrole 5. That is, in the presence of bis-N-oxide 3, calix[4]pyrrole 5 underwent mainly intermolecular oligomerization and polycondensation coupling reactions. On the other hand, bis-N-oxide 6 acted as a positive template favouring three of the four possible alkyne coupling reactions in the dimerization of 5. However, in the presence of 6 the major isolated product was an encapsulation complex of two bis-N-oxide 6 complexes in a tetrameric oligomacrocyclic calix[4]pyrrole. The obtained container is an unprecedented calix[4]pyrrole tetramer, in which the solid state adopts a chiral helical-like conformation resembling “Siamese-Twin porphyrins”. We estimated that the energy barrier for the racemization process of the enantiomeric conformers (P/M), detected in the crystalline packing, was higher than 20 kcal mol$^{-1}$ (Fig. 4).

Fig. 3 – Line-drawing structures of calix[4]pyrrole macrocycles.
Calix[4]pyrrole for sensing creatinine

During this year we have also dedicated our efforts on the pursue of applications of calix[4]pyrrole receptors for sensing clinically relevant neutral guests. Within this arena, we have described an aryl-substituted calix[4]pyrrole with a monophosphonate bridge, that displays remarkable affinity for creatinine and the creatininium cation. The receptor works by including the guest in its deep and polar aromatic cavity and establishing directional interactions in three dimensions. In collaboration with the URV, we were able to incorporate into a suitable polymeric membrane this molecule to act as an ionophore. A highly sensitive and selective potentiometric sensor suitable for the determination of creatine levels in biological fluids, such as urine or plasma, in an accurate, fast, simple, and cost-effective way has thus been developed.

Fig. 5 – Creatinine sensing using monophosphonate bridged calix[4]pyrrole as ionophore.

Articles


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