2017 Annual Scientific Report

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 calix[4]pyrrole structures soluble in both organic and aqueous media. We study their binding processes with biologically relevant molecules (e.g. anions, *N*-oxides). This constitutes the starting point for further understanding more complex biological molecular recognition processes or the mechanism operating in sensing devices.

We pursue the preparation of molecular capsules by using different strategies, including covalent chemistry, dynamic covalent bonds and lately metal-coordination bonds.

The preparation of mechanically interlocked structures is another area of our interest. Rotaxanes and catenanes present unique three-dimensional cavities for anion recognition that resemble the preorganized pocket of anion binding proteins in Nature. That's why we dedicate part of our efforts to synthetize and study the binding abilities of interlocked structures based on calix[4]pyrrole scaffolds.

Finally, we also are proactive in the collaboration 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).

Synthesis of calix[4]pyrrole scaffolds

Our group has been interested in the synthesis of calix[4]pyrrole receptors for many years. The unique properties of the tetra-α isomer of aryl-extended calix[4]pyrroles have been exploited in several applications such as the self-assembly of molecular dimeric capsules, the transport of ions and ion-pairs across lipophilic membranes, and the development of new functional materials.

Aryl-extended calix[4]pyrroles are typically synthesized by the acid-mediated condensation reaction of an aryl methyl ketone with pyrrole. Generally, this reaction produces a mixture of the four different configurational calix[4]pyrrole isomers and a plethora of open oligomers.

Most reported syntheses of aryl-extended calix[4]pyrroles either as pure isomers or isomeric mixtures target compounds with a simple methyl group attached to the mesocarbons. To date and to the best of our knowledge, only two examples featuring four substituents other than methyl groups have been reported. These examples described aryl-extended calix[4]pyrroles with a single type of functional group, either on the upper rim or the lower rim substituents. The condensation reaction of aryl alkyl ketones with pyrrole to produce the corresponding calix[4]pyrroles is significantly less efficient than the reaction with their aryl methyl counterparts, which may explain the limited examples.

We designed an approach based on the simple addition of methyl trialkylammonium chloride salt to the acid-mediated condensation reaction of the aryl alkyl ketone and pyrrole. This methodology is by no means general, but it does provide modest to good yields of calix[4]pyrroles mainly possessing hydroxyl groups at their upper rims and terminal chloro or ester functions on their *meso*-alkyl substituents.

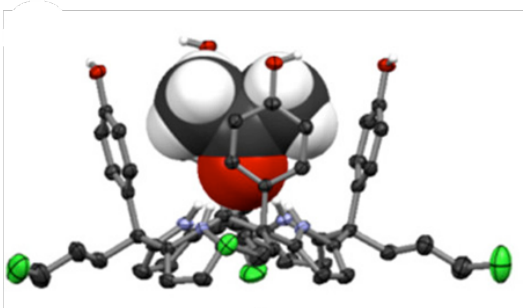

Fig. 1 - *X-ray structure of meso-aryl-meso-chloroalkylcalix[4]pyrrole obtained using the stereoselective synthetic approach described.*

The functional groups incorporated at the lower and upper rims of the calix[4]pyrroles can be further chemically transformed and pave the way for new applications and properties of this family of compounds.

Dynamic covalent capsules

Molecular encapsulation has emerged as an attractive tool in host–guest chemistry to stabilize reactive intermediates, promote or accelerate chemical transformations and even alter their typical regio- and stereo-chemical outcomes.

During the last decade, dynamic covalent bonds have been applied in thermodynamically controlled self-assembly processes of capsules and cages. This strategy combines the strength of covalent bonds with the reversibility and selectivity of non-covalent interactions. However, all the reported examples based on dynamic covalent bonds lack polar functions in their inner cavities.

We have prepared polyimine molecular capsules based on calix[4]pyrrole scaffolds featuring large polar interiors.

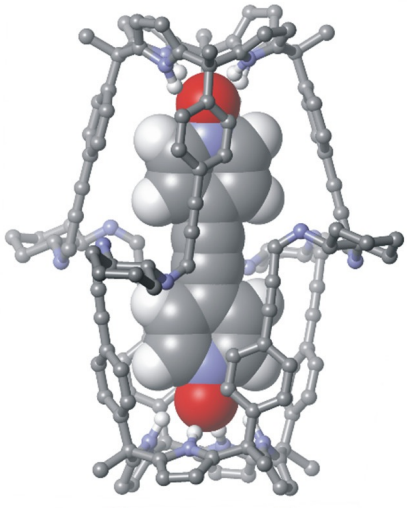

Fig. 2 - *X-ray structure of a chiral polyimine molecular capsule with a bispyridyl-N-oxide guest included in its cavity.*

In brief, an aryl-extended tetraaldehyde calix[4]pyrrole scaffold was condensed with suitable diamines as linkers using templates (i.e. bispyridyl-*N*-oxide derivative) for efficient self-assembly. The capsular complexes were

characterized in solution, gas phase and the solid-state. Unprecedented transfer of asymmetry was observed from a chiral diamine linker to the resulting supramolecular capsular assembly.
Current efforts are directed towards the reduction of the imine bonds to afford fully covalent capsules and the preparation of analogous water-soluble dynamic containers.

Mechanically Interlocked Molecules

Mechanically interlocked molecules such as rotaxanes or catenanes present unique three-dimensional cavities for anion recognition that resemble the preorganized pocket of anion binding proteins in Nature.
The use of anions as templates in the preparation of interlocked structures has been widely described and is known to generate topologically unique cavities for anion recognition. In 2012, we reported the use of polyatomic anions for the quantitative assembly of pseudorotaxane-like architectures without involving ion-pairing in the linear component. Our approach exploited the exceptional recognition properties exhibited by a neutral interwoven self-assembled receptor towards ion-pairs.
Based on this previous findings, at the beginning of this year, we reported our investigations on the synthesis of a [2]rotaxane based on a bis(calix[4]pyrrole) cyclic component and a 3,5-bis-amidepyridyl-N-oxide derivative axle. We isolated the [2]rotaxane in a significant 50% yield through an optimized “in situ” capping strategy using the copper(I)-catalyzed azide–alkyne cycloaddition reaction.

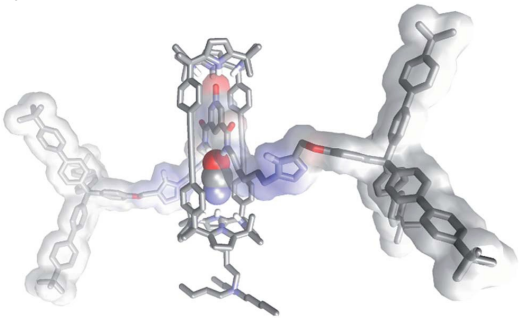

Fig. 3 - *Energy minimized structure (MM3) of the complex between [2]rotaxane and TBA(OCN). The included anion is displayed in CPK representation. Non-polar hydrogens were removed for clarity.*

The synthetic precursor of the [2]rotaxane, featuring [2]pseudorotaxane topology, could be quantitatively assembled in solution in the presence of one equivalent of tetrabutylammonium chloride or cyanate salts producing a four-particle aggregate. However, we observed that the addition of the salt was deleterious not only for the isolation of the [2]rotaxane in its pure form but, more important, for the optimal performance of the copper catalyst. We probed the interaction of the prepared [2]rotaxane with tetraalkylammonium salts of chloride, nitrate and cyanate anions by means of ^{1}H NMR titrations and ITC experiments. We show that in chloroform solution the [2]rotaxane functions as an efficient heteroditopic receptor for the salts forming thermodynamically and kinetically highly stable ion-paired complexes with 1:1 stoichiometry. At millimolar concentration and using ^{1}H NMR spectroscopy we observed that the addition of more than 1 equiv. of the salt induced the gradual disassembly of the 1:1 complex of the [2]rotaxane and the concomitant formation of higher stoichiometry aggregates i.e. 2:1 complexes.
The reported findings augur well for the future application of water soluble analogues of the obtained [2]rotaxane as effective anion receptors in aqueous media.

Metal-based structures

Organic Framework based on calix[4]pyrroles

The preparation of isomeric metal–organic frameworks (MOFs) in which the network topology is controlled by the different covalent connectivity of the organic ligand is an important step forward in the design of new functional materials. In this context, macrocyclic organic ligands able to accommodate suitable guests in their own polar internal cavities are appealing candidates to act as multidentate linkers, which could potentially self-assemble into hierarchical porous structures. Taking this into account, during this year we have reported the first successful attempt to incorporate a tetraaryl-extended calix[4]pyrrole derivative into a transition metal–organic framework by simply

incorporating four terminal carboxylic functional groups at the upper rim of the macrocyclic scaffold. Remarkably, the structures of the metal organic framework and its transition-metal carboxylate clusters (secondary building units, SBU) are governed by the position of the carboxylic substituent in the functionalized *meso*-aryl units of the linker. Only the tetra-α-*meso*-arylextended tetracarboxylic calix[4]pyrrole isomer L1, substituted in a single meta-position of their aryl rings, yields a two-dimensional MOF architecture assembled through complex Cu(II)-carboxylate clusters (SBU). The clusters have higher nuclearity than the $Cu(II)_2$-$(O_2CR)_4$ paddle wheels produced as SBUs during the assembly of the para-substituted counterpart L2. Remarkably, the length of the dialkylformamide used as solvent (DMF or DEF) in the synthesis of the Cu(II)-organic materials derived from L2 played a key role in the structure of the final solid material.

The packing of discrete metal-mediated capsular dimers of L2 switched to that of one-dimensional linear coordination polymers when one methylene unit increased the solvent's alkyl chains. Finally, ligand L3, which featured a longer alkyl spacer between the para-substituted calix[4]pyrrole core and the terminal carboxylic groups than L2, self-assembled, exclusively, into discrete capsular coordination dimers also mediated by Cu(II) paddle wheel units.
The obtained results highlight the strong interplay that exists between molecular recognition, supramolecular isomerization, and solid-state structure. Conformational control of the linker substituents through binding to solvent molecules or other guests prior to self-assembly can give rise to the expected and/or unexpected solid-state architectures that may be further developed for sensing and/or catalysis applications.

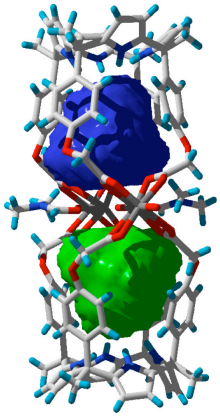

Fig. 4 - *Solid-state structure of the dimeric Cu(II)-capsular assembly obtained with L2 ligand. The included DMF molecules were removed in order to calculate the volumes of the two separate polar cavities of the capsule.*

Ru(II) resorcinarene metallocavitand

The concept of merging molecular recognition with catalysis constitutes an area of growing interest in chemical research. The synthetic availability of resorcin[4]arene cavitands that are not symmetrically substituted allows the incorporation of functional groups at their upper rims that coordinate to catalytic metal centers featuring in this manner a selective binding site in close proximity to an organometallic catalytic site. They constitute a viable strategy to achieve new selectivity and activity in transition metal catalysis.
Inspired by the wide range of oxidative transformations catalyzed by the polypyridyl Ru(IV)=O species, we decided to investigate the feasibility of covalently attaching a heteroleptic terpyridine (tpy) Ru(II) aqua complex at the upper rim of a resorcin[4]arene cavitand.
Therefore, we report the design, synthesis and characterization of a new Ru(II) metallocavitand that is catalytically active in alkene epoxidation reactions. The elaboration of the resorcin[4]arene's aromatic cavity produced a self-folding, deep hexaamide cavitand featuring a single diverging terpyridine (tpy) group installed at its upper rim. The construction of the metallocavitand involved the initial chelation of a Ru(III) chloride complex by the tpy ligand followed by the incorporation of 2-(phenylazo)pyridine (azpy) as an ancillary ligand. The resulting Ru(II) chloro complex was converted into the catalytically active aqua counterpart by a ligand exchange process.

Unfortunately, a limited catalytic activity of the aqua metallocavitand was demonstrated through the epoxidation reaction of simple olefins. The proximity between the catalytic center and the cavitand binding site did not produce a supramolecular catalyst for the epoxidation reaction.

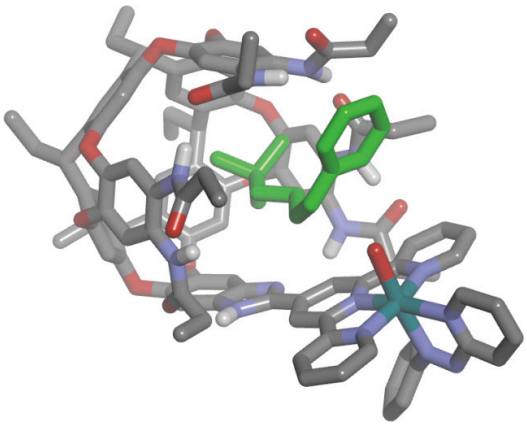

Fig. 5 – *Energy-minimized structure of the complex between 2-(phenylazo)pyridine (azpy), metallo-resorcin[4]arene cavitand trans-1·Ru(II)·(azpy)·OH_2 and a cis-β-alkyl styrene olefin equipped with a terminal trimethylammonium function.*

Calix[4]pyrroles for sensing

Last year, we described an aryl-substituted calix[4]pyrrole with a monophosphonate bridge, that displayed remarkable affinity for creatinine and the creatininium cation. The receptor worked by including the guest in its deep and polar aromatic cavity and establishing directional interactions in three dimensions. Moreover, we reported, for the first time, an Ion-Selective Electrode (ISE) capable of determining creatinine in real samples. During this year, we have dedicated some efforts on providing novel insights regarding the characterization, optimization and analytical performance of this novel sensor, together with the validation through the determination of creatinine in real urine samples. This ISE hinges on the use of a phosphonate-bridged calix[4]pyrrole ionophore that shows excellent selectivity for creatinine. We reported the complex formation constants of the ionophore with the targets in the polymeric membrane, which confirms its superiority compared to the previously reported ionophores. We further demonstrate the influence of the pH on the detection parameters. Lastly, particular emphasis was given to the real sample analysis and on the approach to reduce the matrix interference. Dilution appeared as a crucial way to afford reliable results, so that 50 real urine samples were analyzed using the potentiometric sensor and provided values that correlated excellently with the standard Jaffé's method.

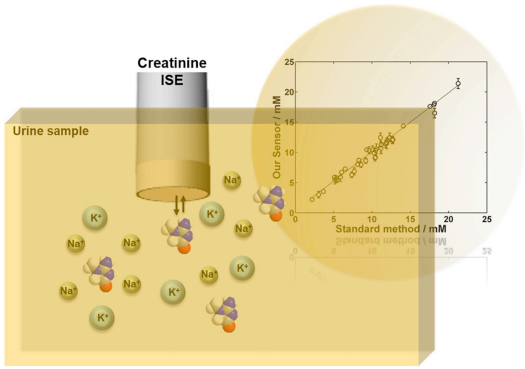

Fig. 6 – *Schematic representation of the ISE sensor used for creatinine sensing including a graphic showing the excellent linear correlation with the standard Jaffé's method.*

Articles

"A Metal Organic Framework Based on a Tetra-Arylextended Calix 4 pyrrole Ligand: Structure Control through the Covalent Connectivity of the Linker."
Crystal Growth & Design (**2017**) *17*(3): 1328-1338 Aguilera-Sigalat, J., C. Saenz de Pipon, D. Hernandez-Alonso, E. C. Escudero-Adan, J. Ramon Galan-Mascaros and P. Ballester

"Light-responsive molecular containers."
Chemical Communications (**2017**) *53*(34): 4635-4652 Diaz-Moscoso, A. and P. Ballester

"Stereoselective Synthesis of Lower and Upper Rim Functionalized Tetra-alpha Isomers of Calix 4 pyrroles."
Organic Letters (**2017**) *19*(1): 226-229 Diaz-Moscoso, A., D. Hernandez-Alonso, L. Escobar, F. A. Arroyave and P. Ballester

"Solid-state inclusion of C-60 and C-70 in a co-polymer induced by metal-ligand coordination of a Zn-porphyrin cage with a bis-pyridyl perylene derivative."
Crystengcomm (**2017**) *19*(33): 4911-4919 Escudero-Adan, E. C., A. Bauza, L. P. Hernandez-Eguia, F. Wuerthner, P. Ballester and A. Fronter

"Template-directed self-assembly of dynamic covalent capsules with polar interiors."
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"Characterization of a new ionophore-based ion-selective electrode for the potentiometric determination of creatinine in urine."
Biosensors & Bioelectronics (**2017**) *87*: 587-592 Guinovart, T., D. Hernandez-Alonso, L. Adriaenssens, P. Blondeau, F. X. Rius, P. Ballester and F. J. Andrade

"Attachment of a Ru-II Complex to a Self-Folding Hexaamide Deep Cavitand."
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"Self-Assembly of Di-N-Heterocyclic Carbene-Gold-Adorned Corannulenes on C-60."
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"Ion-pair recognition by a neutral 2 rotaxane based on a bis-calix 4 pyrrole cyclic component."
Chemical Science (**2017**) *8*(1): 491-498 Ramon Romero, J., G. Aragay and P. Ballester

"Selection and characterization of DNA aptamers against the steroid testosterone."
Microchimica Acta (**2017**) *184*(6): 1631-1639 Skouridou, V., M. Jauset-Rubio, P. Ballester, A. S. Bashammakh, M. S. El-Shahawi, A. O. Alyoubi and C. K. O'Sullivan

“Effects of Nanoconfinement on Catalysis”. Edited by Rinaldo Poli. *(Book review). Springer International Publishing*, (**2017**) pp 266. P. Ballester

“Anion–π Interactions: Theoretical Studies, Supramolecular Chemistry and Catalysis”
Book Chapter In: "Aromatic Interactions : Frontiers in Knowledge and Application", Royal Society of Chemistry (**2017**), pp 39-37. A. Frontera, P. Ballerter

“Preservation of electronic properties of double-decker complexes on metallic supports”
Phys. Chem. Chem. Phys. (**2017**) *19*, 8282-8287

B. Cirera, J. Matarrubia, T. Kaposi, N. Giménez-Aguiló, M. Paszkiewicz, F. Klappenberger, R. Otero, J.M. Gallego, P. Ballester, J.V. Barth, R. Miranda, J.R. Galán-Mascarós, W. Auwärter, D. Ecija