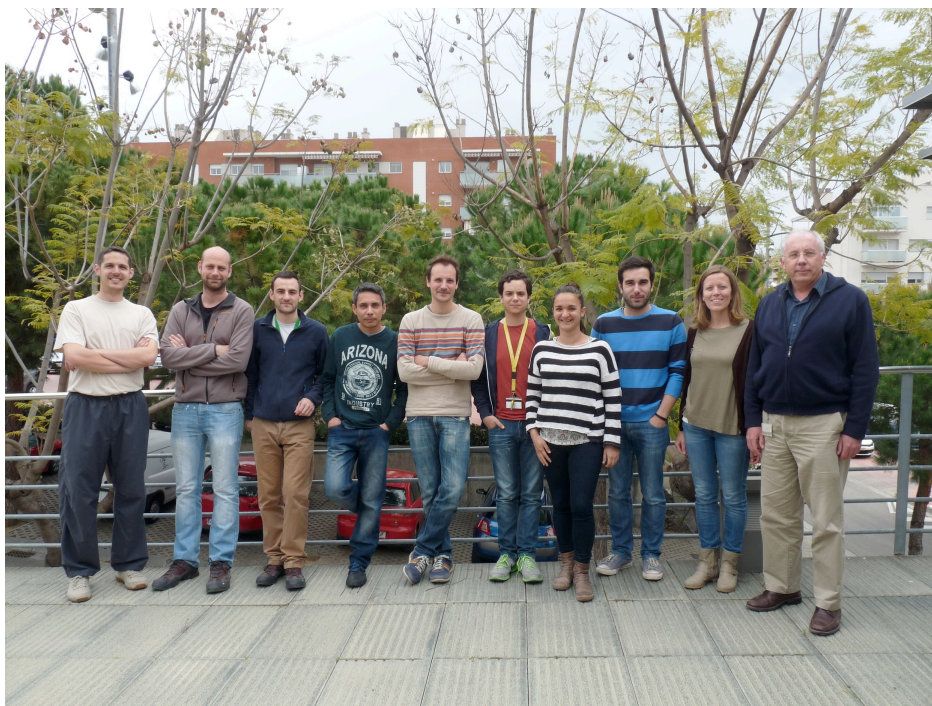


## Ballester Research Group



**Group Leader:** Pau Ballester

**Postdoctoral Researchers:** Gemma Aragay, Louis Adriaenssens (until June), Frank A. Arroyave, Alejandro Díaz-Moscoso ( From Oct. 1)

**PhD Students:** Saša Korom, Albano Galán, Nelson Giménez, Daniel Hernández, José R. Romero

**Visiting Students:** Maria Teresa Mairal (24/02-07/03), Giorgio la Sorella (07/03-02/09), Luis Moreira ( 30/05-01/08), Alessandro Pedrini (30/06-11/07), Cristina García Simón (09-10/07 and 22-23/07), Martina Piccinno (28/10/14-15/03/15).

**Master Students:** Luis Escobar

**Administrative Support:** Beatriz Martin

### Abstract

Our research is mainly focused on the design, synthesis and study of functional multimolecular aggregates. We are interested in the thermodynamic and kinetic characterization of the self-assembly processes that leads to their formation in solution. We are also involved in the study of the applications of unimolecular and supramolecular containers. We investigate the effect that the confinement of molecules and catalyst in nanoscopic spaces may have in the modification of their typical properties expressed in the bulk or free in solution. The group is also

working on the synthesis of new calix[4]pyrrole receptors and supramolecular capsules based on calix[4]pyrrole and/or calix[4]arene scaffolds with the possibility to control their binding affinities and encapsulation properties using external stimuli i.e. light.

Another topic of our interest resides in the study and quantification of weak non-covalent interactions using synthetic receptors as new physical organic chemistry tools.

### Porphyrins and tetraazaporphyrins

For the last decade, the group has been interested in the synthesis and the study of multiporphyrin systems. Within this research area and during the current year we have focused our attention into two different projects: (1) the construction of bimolecular complexes based on cyclopeptides functionalized with a porphyrin and a fullerene unit, and (2) the synthesis of double-decker sandwich complexes of lanthanide cations with tetraazaporphyrins.

In the first project, we described the thermodynamic characterisation of the self-sorting process experienced by two homodimers assembled by hydrogen-bonding interactions established through their cyclopeptide scaffolds. Two different cyclopeptides were decorated by covalently attaching either a Zn-porphyrin substituent or a fullerene unit to their peptidic scaffolds. When mixed in solution the derivatized cyclopeptides were shown to self-assemble exclusively into the heterodimeric aggregate containing one electron-donor (Zn-porphyrin) and one electron-acceptor group (fullerene) close in space. The fluorescence of the Zn-porphyrin unit was strongly quenched upon heterodimer formation.

This quenching phenomenon was demonstrated to be the result of an efficient photoinduced electron-transfer (PET) process occurring between the Zn-porphyrin and the fullerene units of the heterodimeric aggregate.

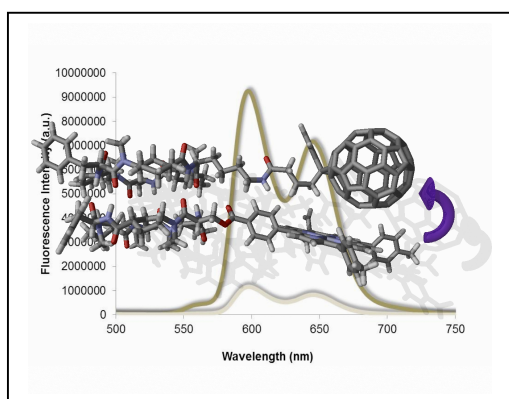


Fig. 1 – Energy minimized molecular structure of the Zn-porphyrin/fullerene cyclopeptide-based heterodimer. The fluorescence spectra depicting the quenching of the Zn-porphyrin unit upon dimer formation are shown in the background of the figure.

The PET occurred in approximately 75% of the chromophores after excitation of both Zn-

porphyrin or fullerene chromophores. Closely related heterodimers, which were previously reported, based on an extended tetrathiafulvalene, instead of the Zn-porphyrin, and the same fullerene component showed a PET process occurring in a significantly reduced extent (33%). We concluded that the strength (stability constant  $K$ ) and the effective molarity (EM) of the intramolecular interaction established between the Zn-porphyrin/fullerene chromophores in the new cyclopeptide-based heterodimers were responsible of a different regioisomeric distribution in the dimer that regulated the high extent of the observed PET process.

In the second project and in collaboration with the group of Prof. J. R. Galán-Mascaros, we described a series of neutral double-decker sandwich complexes of lanthanide cations  $[\text{Ln}(\text{OETAP})_2]$  ( $\text{Ln} = \text{Tb}^{3+}, \text{Dy}^{3+}, \text{Gd}^{3+}, \text{Y}^{3+}$ ; OETAP= octa(ethyl)tetraazaporphyrin). We observed that the  $\text{Tb}^{3+}$  and  $\text{Dy}^{3+}$  derivatives exhibit single-molecule magnet (SMM) behaviour with high blocking temperatures over 50 and 10 K, respectively. These results confirmed that, in double-decker complexes involving  $\text{Tb}^{3+}$  or  $\text{Dy}^{3+}$  cations, the  $(\text{N}_4)_2$  square antiprism coordination mode has an important role in inducing very large activation energies for magnetization reversal.

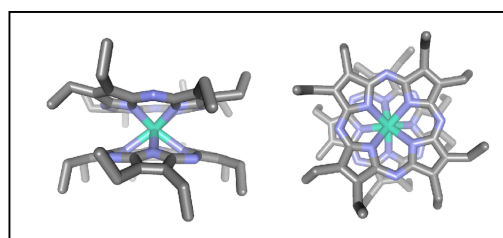


Fig. 2 – X-ray crystal structure of  $[\text{Tb}(\text{OETAP})_2]$  sandwich complex.

In contrast to their phthalocyanines counterparts, the use of tetraazaporphyrin ligands endowed the described  $[\text{Ln}(\text{OETAP})_2]$  complexes with extraordinary chemical versatility. The double-decker complexes that exhibited SMM behaviour were highly soluble in common organic solvents, and easily processable, for example by a sublimation process.

### Encapsulation of organometallic compounds

The group has also been interested in the field of supramolecular catalysis. In particular, we have studied the inclusion of transition metal

catalysts inside unimolecular containers derived from resorcin[4]arene scaffolds. We included a  $Rh^I$  metal center in the cavity of a regioisomeric series of heptaamide cavitands decorated with one pyridyl group at their upper rim. We studied the  $Rh^I$  catalysed hydrogenation of norbornadiene (NBD) using the prepared caviplexes. The different binding geometries exhibited in solution by the  $Rh^I$  cationic complexes of the heptaamide cavitands were used to explain the diverse distribution of products we obtained. For example, the emergence of  $Rh^I$  complexes with *exo* geometry provided an unexpected reaction pathway yielding nortricyclene as the hydrogenation product of NBD.

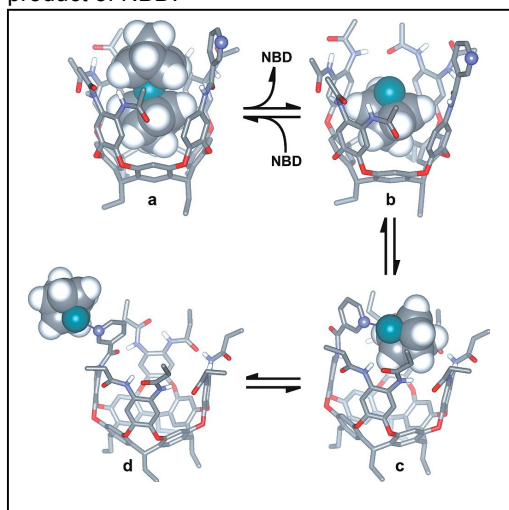


Fig. 3 - Energy-minimized structures of the different metallo complexes (caviplexes) resulting from the interaction of the heptaamide cavitand with a meta-pyridyl substituent at the upper rim with  $[Rh(NBD)]^+$ .

### Anion- $\pi$ interactions

We continued with our studies on the experimental quantification of anion- $\pi$  interactions. We characterized thermodynamically the binding of  $Cl^-$ ,  $Br^-$ , and  $I^-$  anions with a series of “two-wall” calix[4]pyrrole receptors having electronically different aromatic *meso*-phenyl groups “walls”. We detected that halide binding became progressively more attractive as the number and electron withdrawing character of the aromatic substituents increased (more positive ESP value at the centre of the six member ring). This may be considered as evidence for the presence of attractive anion- $\pi$  interactions and the electrostatic nature of those interactions.

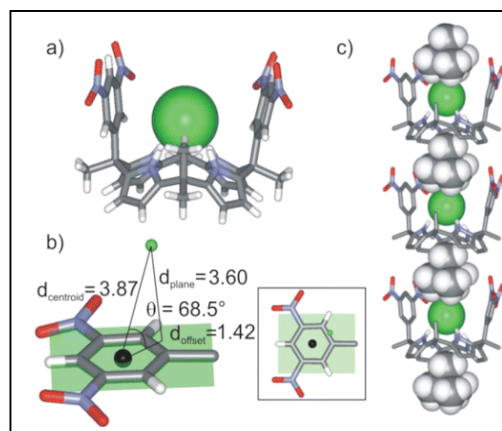


Fig. 4 - (a) X-ray structure of a two-walls  $\alpha,\alpha$ -calix[4]pyrrole complex with  $Cl^-$ . (b) Expansion (side and top views) of the region relevant to the chloride- $\pi$  interaction; important geometrical parameters between the  $Cl^-$  and the aromatic ring are indicated. (c) Partial packing of the X-ray structure of the complex. Distances are indicated in angstroms.

The binding processes were analysed methodically via their enthalpic and entropic terms. Unexpectedly, in acetonitrile solution, the observed increase in free energy of binding ( $\Delta G$ ) for the halides with the receptors having aromatic rings with more positive ESP values was connected to a larger and positive entropic contribution ( $T\Delta S$ ) to binding. In addition, the enthalpic contributions ( $\Delta H$ ) showed a subtle inverted trend with respect to the free energy values ( $\Delta G$ ). We ascribed this unexpected behaviour to strong solvation effects taking place during the binding process.

The use of chloroform, a much less polar solvent, limits the impact of solvation effects revealing the expected existence of a parallel trend between free energies and enthalpies of binding. This result indicated that halide- $\pi$  interactions in organic solvents are mainly driven by enthalpy. However, the typical paradigm of enthalpy-entropy compensation was not observed even in this less polar solvent.

### New insights in calix[4]pyrrole receptors

Calix[4]pyrrole scaffolds have been widely used in our group. During this year we have focused our attention in three main projects related to calix[4]pyrrole receptors: (a) the synthesis of lipophilic cavitands based on a calix[4]pyrrole-resorcinarene hybrid scaffolds, (b) the study of *N*-oxide binding to calix[4]pyrroles in water by

means of surface plasmon resonance (SPR) and (c) the synthesis of a tetraurea-calix[4]pyrrole capsule with appended azobenzene units.

The first project dealt with the synthesis, structural characterization, and binding properties of a series of unprecedented deep cavitands based on a meso-dodecyl-calix[4]pyrrole-resorcin[4]arene hybrid scaffold.

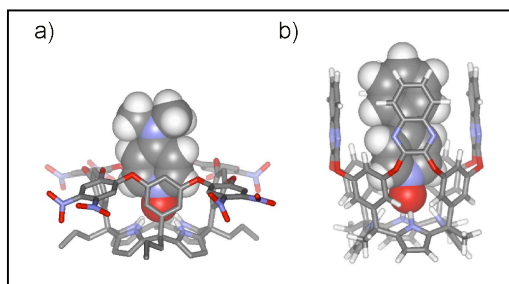


Fig. 5 – (a) Side view of the X-ray crystal structure of the inclusion complex of calix[4]pyrrole-resorcinarene hybrid receptor with 4-dimethylaminopyridine *N*-oxide. (b) MM3 energy minimized structure of the putative complex of the diamino-naphthalene bridged caviatnd in the vase form with 4-phenyl-pyridine *N*-oxide.

The polar interior of the synthesized containers allowed the inclusion of a series of pyridine *N*-oxide derivatives. Kinetically and thermodynamically highly stable 1:1 complexes were formed. In addition, the putative switching process between the *vase* and *kite* forms of the deep cavitands was also investigated. All the results obtained indicated the existence of a remarkable preference toward the *kite* conformation, both in free and bound calix[4]pyrrole-based cavitands.

In the second project of this portion of our research, we demonstrated the use of SPR detection integrated to a microfluidic cell (BIA technology) to monitor and estimate binding events between water-soluble calix[4]pyrroles and *N*-oxide derivatives.

Specific binding between calix[4]pyrrole and *N*-oxide derivatives was observed on the surface of the Biacore CM5 chip. The binding process displayed a thermodynamic behavior close to one measured in solution for the complexes.

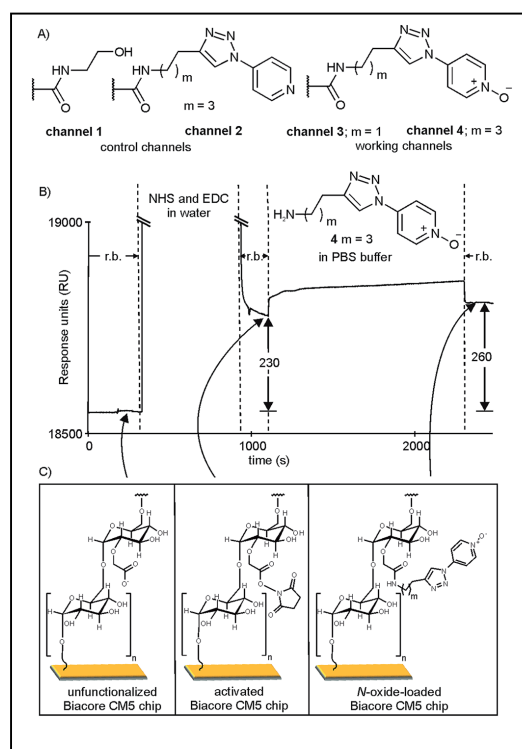


Fig. 6 - (A) Line drawing structures of the substrates immobilized in the different channels of the Biacore chip. Channel 1 and channel 2 represented ethanolamine and pyridine controls respectively. Channel 3 & 4 were functionalized with two pyridine *N*-oxide derivatives (B). Sensogram registered during the functionalization process of channel 4 with a *N*-oxide. (C) Molecular structures of the dextran matrix immobilized on the gold surface of the chip as received (left), after activation (center), and after *N*-oxide functionalization (right).

However, the kinetics of binding and dissociation processes were drastically slower on the surface. They seemed to depend on the position and orientation of the ligand in the surface-bound matrix. We rationalized this observation by considering the barrier that the dextran matrix presented to the analyte in finding and interacting with the *N*-oxide ligand. Finally, we showed that the matrix had a not insignificant effect on the thermodynamics of binding.

In the last project of this section, we aimed to synthesize supramolecular capsular aggregates whose assembly/disassembly processes could be controlled by light irradiation without having to rely on photo-switchable guests. We synthesized a tetraurea aryl extended calix[4]pyrrole with four appended azobenzene groups that dimerized by encapsulating a bis-*N*-oxide acting as a template. The assembly process was detected by  $^1\text{H}$  NMR spectroscopy and it only took place when all eight azobenzene units were in their trans forms. The light-induced trans-to-cis-isomerization of a single azobenzene moiety in the capsular assembly triggered the capsular disintegration from solution, probably through a disassembly process. The reassembly of the encapsulation complex was achieved by cis-to-trans relaxation of the azobenzene photo-switches in the dark.

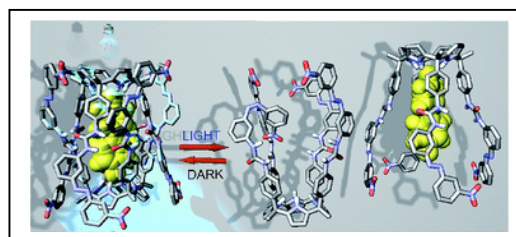


Fig. 7 – Light-induced trans-to-cis-isomerization of the capsular assembly based on tetraurea aryl extended calix[4]pyrroles with four appended azobenzene groups. We hypothesized that trans-to-cis isomerization triggered the disintegration of capsule from solution by disrupting the aggregate. Cis-to-trans relaxation in the dark yielded the all-trans originally assembled capsular system.

## Articles

“Single-Molecule-Magnet Behavior in the Family of  $[\text{Ln}(\text{OETAP})_2]$  Double-Decker Complexes (Ln = Lanthanide, OETAP =

Octa(ethyl)tetraazaporphyrin)”  
*Chem. Eur. J.* (2014), 20, 12817-12825

N. Giménez-Agulló, C. Saenz de Pipaon, L.

Adriaenssens, M. Filibian, M. Martínez-Belmonte, E.C. Escudero-Adan, P. Carretta, P. Ballester, J.R. Galan-Mascaros

“Binding of calix[4]pyrroles to pyridine *N*-oxides probed with surface plasmon resonance”

*Chem. Sci.* (2014), 5, 4210-4215

L. Adriaenssens, J.L. Acero Sanchez, X. Barril, C.K. O’Sullivan, P. Ballester

“Reversible photocontrolled disintegration of a dimeric tetraurea-calix[4]pyrrole capsule with all-trans appended azobenzene units”

*Chem. Sci.* (2014), 5, 4260-4264

L. Osorio-Planes, M. Espelt, M.A. Pericas, Pablo Ballester

“Pyridyl-Decorated Self-Folding Hepta-amide Cavitands as Ligands in the Rhodium-Catalyzed Hydrogenation of Norbornadiene”

*Eur. J. Org. Chem.* (2014), 4276-4282

S. Korom, P. Ballester

“Synthesis, Structure, and Binding Properties of Lipophilic Cavitands Based on a Calix[4]-pyrrole-Resorcinarene Hybrid Scaffold”

*J. Org. Chem.* (2014), 79, 5545-5557

A. Galan, E.C. Escudero-Adan, A. Frontera, P. Ballester

“Self-Sorting of Cyclic Peptide Homodimers into a Heterodimeric Assembly Featuring an Efficient Photoinduced Intramolecular Electron-Transfer Process”

*Chem. Eur. J.* (2014), 20, 3427-3438

G. Aragay, B. Ventura, A. Guerra, I. Pintre, C. Chiorboli, R. Garcia-Fandino, L. Flamigni, J.R. Granja, P. Ballester

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M. Raynal, P. Ballester, A. Vidal-Ferran, P.W.N.M. van Leeuwen

“Supramolecular catalysis. Part 1: non-covalent interactions as a tool for building and modifying homogeneous catalysts”

*Chem. Soc. Rev.* (2014), 43, 1660-1733

M. Raynal, P. Ballester, A. Vidal-Ferran, P.W.N.M. van Leeuwen

## 2014 Annual Scientific Report

“Thermodynamic Characterization of Halide- $\pi$  Interactions in Solution Using "Two-Wall" Aryl Extended Calix[4] pyrroles as Model System”  
*J. Am. Chem. Soc.* (2014), 136, 3208-3218  
L. Adriaenssens, G. Gil-Ramirez, A. Frontera, D. Quiñero, E.C. Escudero-Adan, P. Ballester

“Porphyrin tweezer receptors: Binding studies, conformational properties and applications”  
*Coord. Chem. Rev.* (2014), 258-259, 137-156  
V. Valderrey, G. Aragay, P. Ballester