

Ballester Research Group



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Abstract

Our research is focused in the design, synthesis and study of functional molecular aggregates. We tackle the thermodynamic characterization of self-assembly processes as a methodology to construct large and functional multimolecular architectures. We are also active in the design and synthesis of new synthetic heteroditopic receptors for ion-pairs. Another area of our interest resides in the design and application of

molecular containers. These are molecules or supramolecules which are sufficiently large to include or encapsulate other molecules. We investigate the effect that the confinement of molecules in reduced nanoscopic spaces may have in modifying their chemical reactivity. We are also interested in the synthesis of mechanically interlocked molecules (MIM) i.e. catenanes and rotaxanes, which have potential applications in molecular machinery.

Encapsulation studies of organometallic complexes

As the field of supramolecular catalysis develops, a sound fundamental understanding of the catalytic assemblies employed will be essential. Regarding systems based on transition metal catalysts as guests of supramolecular capsules this basic knowledge is lacking. We have investigated the inclusion behavior of gold complexes based on well-known cationic Au(I) catalysts within a self-assembled hexameric resorcin[4]arene capsule. The reported results shed light on the nature of the encapsulated species, and the way in which those species are encapsulated. We introduced an encapsulation methodology that functions *via* the transient introduction of an excess of water. Finally, by small modifications in the encapsulation methodology, we showed that the inclusion process can be controlled to give different encapsulated species stemming from the same gold (I) precursor.

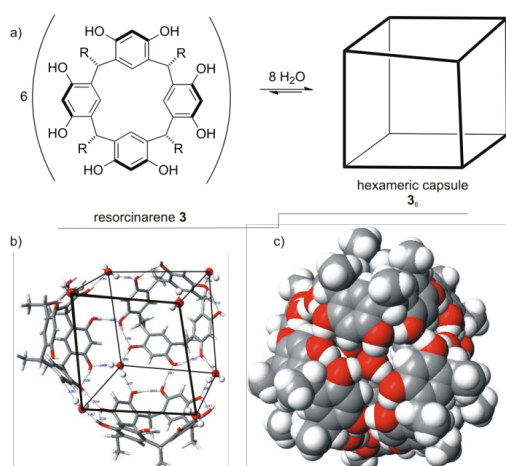


Fig. 1 - a) Schematic representation of the assembly process that yields the hexameric resorcinarene capsule $3_6 \cdot 8H_2O$. Each vertex of the cube represents one molecule of water and each face of the cube represents one resorcinarene unit; b) section of the CAChe minimized structure of the hexamer superimposed with the cubic schematic representation; c) rendering of the hexamer $3_6 \cdot 8H_2O$ as a CPK model.

DOSY experiments revealed that the diffusion coefficient value calculated from the decay of the signals assigned to the *i*-Pr CH_3 protons of the encapsulated gold complex $1-OH_2$ was very similar to the diffusion coefficient calculated from signals belonging to protons of the hexamer (Figure 2). This helps to confirm that the gold complex and the hexamer correspond to the

same supramolecular aggregate. Furthermore, the value calculated for the diffusion coefficient of $[1-OH_2]^+ \cdot 3_6$ ($2.7 \pm 0.2 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$) is in line with that previously reported for the chloroform filled hexameric resorcinarene assembly ($2.8 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$).

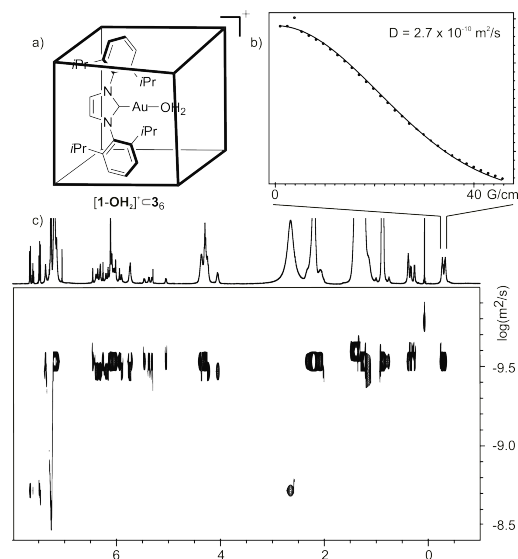


Fig. 2 - a) Schematic representation of the $[1-OH_2]^+ \cdot 3_6$ complex. b): Plot of the DOSY data processing for the signal at - 0.3 ppm corresponding to the *i*Pr CH_3 protons of the encapsulated gold complex. The solid line represents the fit of the data to a single exponential decay. c): 1H pseudo-2D DOSY plot of encapsulation complex $[1-OH_2]^+ \cdot 3_6$.

Using the hexameric resorcinarene capsule 3_6 we were able to encapsulate a variety of cationic gold species stemming from two well-known Au(I) catalyst precursors.

In a related project, we have studied the reaction mechanism of the hydrogenation reaction of norbornadiene (nbd) catalysed by bis-norbornadiene rhodium(I) $[Rh(nbd)_2]^+$ complex, both in the absence and in the presence of a self-folding octamide cavitaand using, DFT based methods.

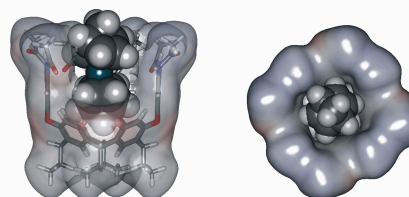


Fig. 3 - Top and side views of the energy minimized structure of complex $Rh(I)(nbd)_2 \cdot \text{octamide}$.

We discussed in detail the formation of three different products, norbornene, nortricyclene and a dimer. The theoretical calculations indicate that when the organometallic Rh(I) complex is encapsulated inside the cavitand, the steric crowding induced by the molecular container around the metal catalyst prevents the formation of the dimer. On the contrary, in the absence of the molecular flask, the dimer is the major product produced in the nbd hydrogenation catalyzed by bis-norbornadiene rhodium(I). Although energy differences between the studied reaction pathways are small, the obtained results serve to explain the changes in regioselectivity observed by experiment.

Anion- π interactions

We have disclosed the results of our investigations regarding the interactions between the biologically relevant nitrate oxoanion and several “two-wall” aryl-extended calix[4]pyrroles **2**.

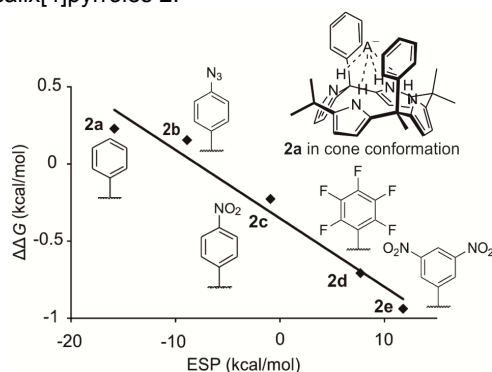


Fig. 4 - Experimental values for the nitrate- π interaction derived from the binding of nitrate with calix[4]pyrroles **2** correlate with the ESP values calculated at the centroid of the aromatic walls.

There exists a clear relationship between the electronic nature of the aromatic walls of the calix[4]pyrroles and the stability of the nitrate-calix[4]pyrrole complex.

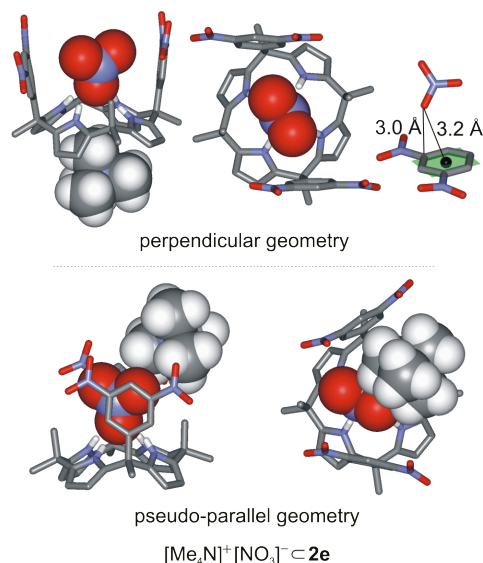


Fig. 5 - Side and top views of the two distinct binding geometries seen in the solid-state structures of $[\text{Me}_4\text{N}]^+[\text{NO}_3]^- \subset \mathbf{2e}$ complexes. The Me_4N^+ cation is omitted from top view of the perpendicular binding geometry, also for clarity. $[\text{Me}_4\text{N}]^+[\text{NO}_3]^-$ is shown in CPK model and **2e** in stick representation.

This suggests that NO_3^- - π interactions have an important electrostatic component. We also provided energetic estimates for the interaction of nitrate with several phenyl derivatives. Additionally, we reported solid-state evidence for the preferred binding geometry of the nitrate anion included in the calix[4]pyrroles.

The “two-wall” aryl-extended calix[4]pyrroles showed excellent activity in ion transport through lipid-based lamellar membranes. Notably the best anion transporters are highly selective for transport of nitrate over other anions.

We also reported experimental evidence indicating that the nature of the interaction established between $\text{HAT}(\text{CN})_6$, a well-known strong electron acceptor aromatic compound, with mono- or polyatomic anions switches from the almost exclusive formation of reversible anion- π complexes, featuring a markedly charge transfer (CT) or formal electron transfer (ET) character, to the quantitative and irreversible net production of the anion radical $[\text{HAT}(\text{CN})_6]^{-\bullet}$ and the dianion $[\text{HAT}(\text{CN})_6]^{2-}$ species.

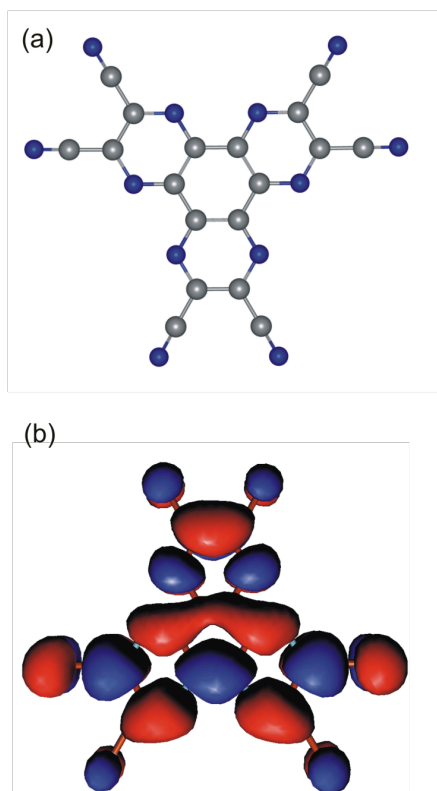


Fig. 6 - Structure of $\text{HAT}(\text{CN})_6$ (a) and its computed LUMO orbitals diagram (b).

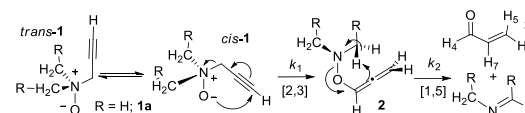
The preferred mode of interaction is dictated by the electron donor abilities of the interacting anion. Thus, weaker Lewis basic anions such as Br^- or I^- are prone to form mainly anion- π complexes. On the contrary, stronger Lewis basic F^- or OH^- anions display a net ET process. The ET process can be either thermal or photo induced depending on the HOMO/LUMO energy difference between the electron donor (anion) and the electron acceptor ($\text{HAT}(\text{CN})_6$). These ET processes possibly involve the intermediacy of anion- π complexes having strong ET character and producing an ion-pair radical complex. We hypothesize that the irreversible dissociation of the pair of radicals forming the solvent-caged complex is caused by the reduced stability (high reactivity) of the radical resulting from the anion.

We have overviewed the experimental efforts to determine the binding energies that can be expected from anion- π interactions in solution with examples that center around the recognition of halides. The studies show that anion- π interactions also exist in solution, and the free energy of binding estimated for these attractive interactions is less than 1 kcal/mol for each substituted phenyl groups. The quantification of anion- π interactions in solution relies on the use of molecular recognition model systems;

therefore researchers need to consider how the structure of the model system can alter the magnitude of the observed energy values. In addition, the recognition of anions in solution requires the use of salts (ion-pairs) as precursors, which complicates the analysis of the titration data and the corresponding estimate of the binding strength. In solution, the weak binding energies suggest that anion- π interactions are not as significant for the selective or enhanced binding of anions but offer potential applications in catalysis and transport within functional synthetic and biological systems.

Kinetic stabilization of organic compounds using molecular containers

Thermally and in non-protic media, tertiary propargyl-amine *N*-oxides undergo a concerted [2,3]-sigmatropic rearrangement to yield *O*-allenyl ethers **2**. In turn, these *O*-allenyl ethers are kinetically unstable and experience a rapid elimination, akin to a [1,5]-hydrogen shift, generating propenal **3** and the corresponding Schiff base **4**. The kinetic stability of the intermediate *O*-allenyl ether **2** depends on the substituents on the nitrogen atom.



Scheme 1 - Proposed mechanism for the thermal decomposition of tertiary prop-2-ynyl *N*-oxides **1**

We have demonstrated that the inherent reactivity of *N*-oxide **1a** affording **3** can be modulated by inclusion/encapsulation in molecular containers **5** and **6**. These containers feature concave, polar interiors based on aryl-extended calix[4]pyrrole scaffolds. *N*-oxide **1a** is encapsulated in *trans*-conformation and forms four hydrogen bonds between its oxygen atom and the pyrrolic NH protons of the container. We derived a kinetic model that quantitatively explains the relationship between the apparent kinetic stabilization of **1a** and the thermodynamic/kinetic stability of the complexes formed with the molecular flasks. The kinetic stabilization does not result of a rate determining dissociation of **1a** from the container but simply from the significant reduction of its concentration free in solution in presence of the molecular containers.

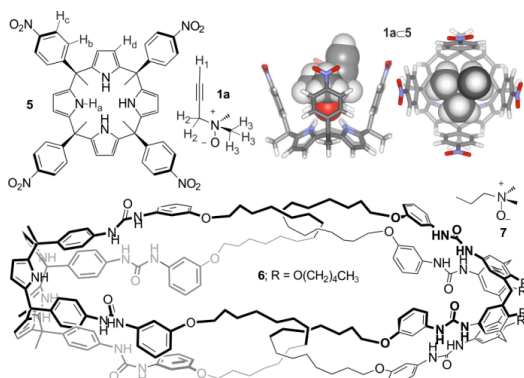


Fig. 7- Molecular structures of *N*-oxides **1a**, **7** and containers **5** and **6**. Top right) Side and top views of the energy minimized complex **1aC5**. Note that **1a** must adopt the *trans*-conformation to fit in the aryl-extended calix[4]pyrrole binding pocket of **5**.

The experimentally measured first half-life for a 2.5 mM solution of free **1a** is 3.8 hours and is extended to > 50 hours in the presence of 1 equiv of **5**. *N*-oxides **1a** and **7** are also nicely encapsulated in the calix[4]pyrrole hemisphere of the mechanically locked capsule **6**, whilst the calix[4]arene hemisphere is occupied by one molecule of chloroform. The series of ¹H NMR spectra acquired during a two month period indicated that the encapsulation complex **1aC6** remained unaltered in solution. Finally, the decomposition of **1a** into **3** was induced by competitive release from the container.

Receptors for ion-pair dimers and ion-quartets

Calix[4]pyrroles and their derivatives are known to function as heteroditopic receptors for ion-pairs. On that basis, we envisaged that receptor **1** having two calix[4]pyrrole binding sites incorporated into a three-dimensional and rigid molecular scaffold could be an ideal candidate for the effective binding of ion-pair dimers through the formation of cascade complexes. We have reported the formation in solution of highly thermodynamically and kinetically stable complexes of ion-pair dimers and quartets of ions with receptor **1**. The resulting complexes constitute unprecedented examples of five particle aggregates. The structures of the aggregates proposed in solution are fully supported by X-ray diffraction results of single crystals. Interestingly, both the cooperativity of the assembly process and the binding geometry of the final aggregates can be controlled by the nature of the cations present in the ion-pair components.

We demonstrated that the bis-calix[4]pyrrole macrocyclic receptor **1** binds two chloride or cyanate tetrabutyl ammonium (TBA) ion-pairs yielding (**2a/b**)₂C**1** complexes through a highly cooperative process ($\alpha > 10^5$). The complexes have a structure with a cascade-like arrangement of the ion pairs. One ion-pair is bound in a close contact geometry while the other in a receptor-separated arrangement. The use of the ion-pair **2c** containing a methyloctylammonium (MTOA) cation instead of TBA cation renders the binding process significantly less cooperative. In the homodimeric complex **2c**₂C**1** both bound ion-pairs feature a receptor-separated binding mode. The equimolar combination of TBA and MTOA salts allows the self-assembly of hetero ion-pair dimer (ion quartet) complexes **2a2c**C**1** and **2b2c**C**1** with cascade arrangement of ion-pairs and by means of cooperative binding processes. Importantly, in these latter complexes the MTOA cation seems to be selectively located in the “out” position.

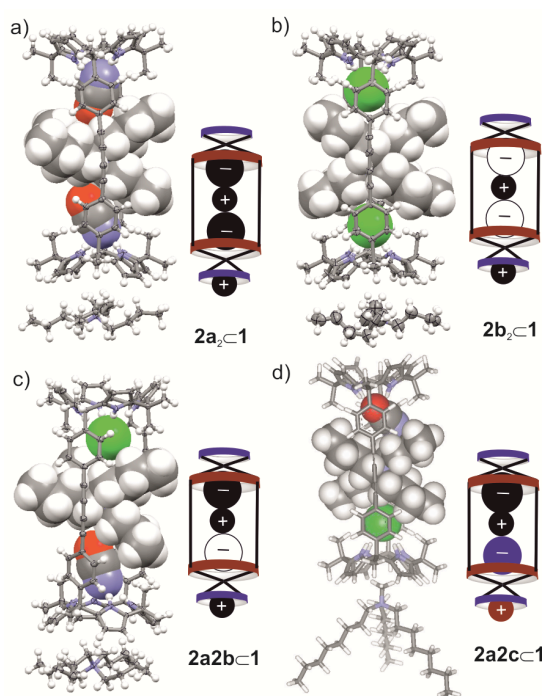


Fig. 8 - X-ray structures of cascade complexes: a) **2a**₂C**1**, b) **2b**₂C**1**, and c) **2a2b**C**1** and d) energy minimized structure of **2a2c**C**1** with their schematic representations. Receptor **1** and the “out” cations are shown in ball-and-stick representations. The anions and the “in” TBA cation included in the cavity of **1** are displayed as CPK representations.

Articles

“Encapsulation Studies of Cationic Gold Complexes within a Self-Assembled Hexameric Resorcin[4]arene Capsule”
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“Different Nature of the Interactions between Anions and HAT(CN)₆: From Reversible Anion- π Complexes to Irreversible Electron-Transfer Processes (HAT(CN)₆ = 2,3,6,7,10,11-hexacyano-1,4,5,8,9,12-Hexaazatriphenylene)”
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“Mechanisms of Catalysis in Confined Spaces: Hydrogenation of Norbornadiene with a Rhodium Complex included in a Self-Folding Cavitand”
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Book Chapter

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In *Comprehensive Inorganic Chemistry II Vol. 6*
(Eds.: J. Reedijk, K. Poeppelmeier), Elsevier, Oxford, **2013**, pp. 457-486.
P. Ballester, P. W. N. M. v. Leeuwen, A. Vidal