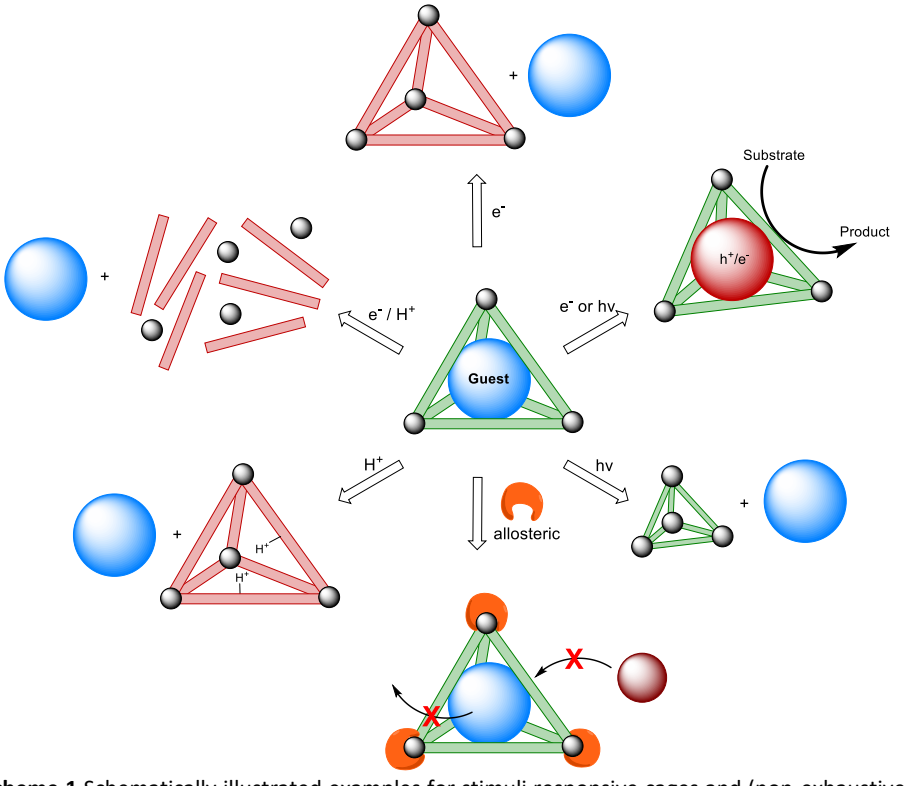
Summary

Nature utilizes enzymes to achieve chemical transformations with both high selectivity as well as high activity. These enzymes consists of a unique long amino acid polymer, folded in a specific way to form a well-defined three dimensional structure. Buried within this structure resides a (metal-containing) active site, which is responsible for the selective conversion of substrate. The so-called 'second coordination sphere' around the active site aids in the pre-organization of the substrate, lowers the activation barrier and results in chemo- and enantioselective reactions.

The supramolecular chemistry field has emerged to mimic the second coordination sphere found in enzymes with synthetic 'cages'. By rationally designing and synthesizing building blocks, a wide range of differently shaped, charged and sized cages are available. Although these cages have been demonstrated to enable reactions to proceed with interesting reactivity and selectivity, often not possible without the second coordination sphere, the cage structures themselves typically act as 'static' capsules. Within the conventional design strategies, there are limited to no options to influence, switch or tune the framework or the interior or ensuing host-guest interactions.

In **Chapter 1** an overview is given of the development in the field of stimuli responsive cages. These cages are constructed by incorporating known stimuli-responsive motifs for triggers such as light, electricity or pH, into the cage building blocks (Scheme 1). The original properties of the building blocks are not always linearly transferred to the supramolecular structure, nor are the structures always stable under 'switching' conditions. The discussed reports show successful strategies for the incorporation of these stimuli-responsive motifs into cages, which change, for instance, the shape, size, charge or available inner volume of the cage. The changes often result in modified encapsulation properties of the cage, making it possible to reversibly encapsulate guests. The guests are often limited to simple ions or small (apolar) molecules and have yet to be extended to more complex structures, such as (active) catalysts.



Scheme 1 Schematically illustrated examples for stimuli responsive cages and (non-exhaustive) possible specific effect(s) of the stimulus on supramolecular properties and/or its reactivity.

Chapter 2 discusses the design and synthesis of three new heteroleptic $M_4L_2L'_2$ supramolecular squares. The squares contain the redox-active Perylene BisImide (PBI) building block **PBI-pyr$_2$** (L), while each square contains different dicarboxylate linkers (L') with increasing spacer length, to modify the dimensions of the resulting overall structure. With increasing size, it was found that the **PBI-pyr$_2$** building block has an increased rotational freedom within the squares (Figure 1). The dynamic behaviour was observed in ^{1}H NMR spectroscopy, displaying upfield chemical shifts and splitting of the signals for the PBI-hydrogens, and was corroborated using variable temperature (VT) NMR.

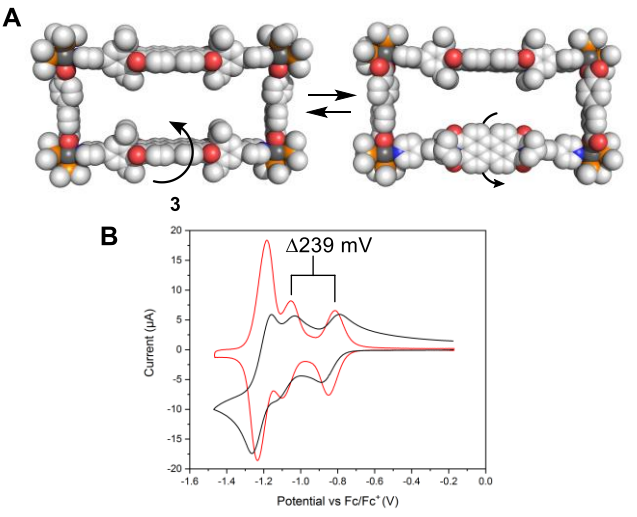


Figure 1 A) Rotation of the **PBI-pyr$_2$** ligand inside square **3**. Light grey = carbon, red = oxygen, orange = phosphorus, dark grey = platinum. B) Cyclic voltammetry (black) and convoluted CV (red) of **3** in DCM, displaying peak splitting of the first reduction event.

DFT calculations showed the smallest linker prevents the dynamic behaviour due to steric clash between the two **PBI-pyr$_2$** ligands, whereas the square bearing the median length linker adopts a perpendicular conformation for the two PBI-building blocks. Investigating the squares with cyclic voltammetry (CV) revealed that the dynamic behaviour, and accompanying desymmetrization of the PBI-ligands results in splitting of the first (overall two-electron) reduction event into two single-electron events. The splitting was most pronounced in the squares with the largest linker and least in the square with the smallest linker. Lastly, the square bearing the smallest linker can form a 1:1 host-guest system with pyrene in CH_3CN ($K = 964\ M^{-1}$). A guest titration coupled to CV measurements showed that the redox properties of the square can be tuned by binding pyrene in the square.

In **Chapter 3** we extend 2D host-guest chemistry to 3D molecular cages for selective guest encapsulation. Two novel phosphine oxide guests, each bearing three pyrene motifs, are designed and synthesized. The three pyrene motifs are electron-rich aromatic surfaces, whereas the M_4L_6 cage has electron-deficient Perylene BisImide (PBI) struts, allowing for intermolecular π-π interactions. The phosphine oxides are shown to easily encapsulate in a one-pot synthesis using both cage building blocks and guest, or by mixing one

equivalent of pre-assembled cage with free phosphine-derived guest, as determined by ^{1}H, ^{31}P and DOSY NMR spectroscopy in addition to High Resolution Mass Spectrometry (HR-MS).

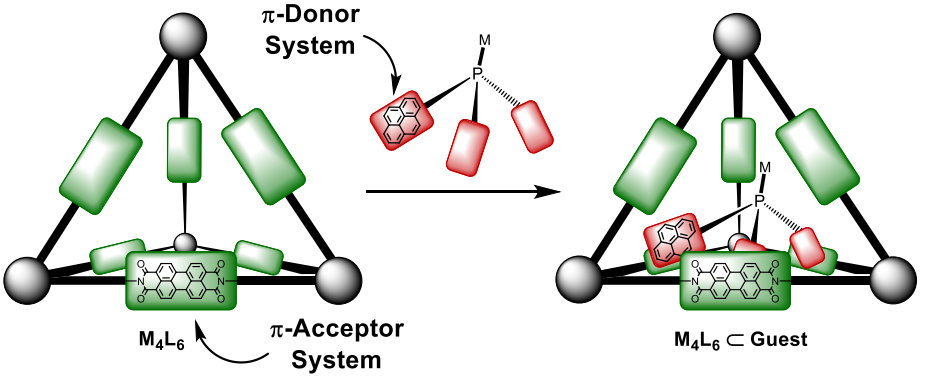


Figure 2 Schematic illustration of the concept. A cage with electron-poor π-systems (acceptor) as walls binds a (metal)phosphine containing multiple electron-rich π-systems (donor).

Subsequently, the phosphine oxides were reduced to their respective phosphine analogues and were coordinated to Rh(I) and Au(I) metal ions. We attempted to encapsulate the metal-phosphine complexes in the cage using similar strategies. In the case of Rh(I), ^{1}H NMR and HR-MS indicated that a complex mixture of products was obtained. Application in exploratory hydroformylation reactions revealed that the Rh-phosphorus ligand complex shows activity toward styrene (derivatives) and 1-octene, albeit no clear supramolecular benefit could be obtained. In the case of Au(I), the phosphine gold chloride complexes were successfully encapsulated, as determined by ^{1}H, ^{31}P and DOSY NMR spectroscopy and HR-MS. Activation of the encapsulated gold catalysts by abstracting the chloride ligand through addition of excess AgOTf proved unsuccessful. The unencapsulated gold catalyst could be pre-activated and was able to catalyse the intramolecular cyclization of 4-hexynoic acid, however addition of empty cage to the reaction mixture stopped the reaction, suggesting that the encapsulated cationic gold complex is no longer active.

In **Chapter 4** a more in-depth study is performed on the host and host-guest system discussed in Chapter 3. We set out to investigate the effect of self-assembly on the properties of composing the building blocks and

subsequently the effect of guest binding within the cavity. The PBI-building blocks have characteristic optical and electrochemical properties, which can be used to track the changes. Additionally, the previously mentioned tris(pyrene) phosphine oxide and a novel tris(pyrene) phosphine-borane guest are used. Both guest molecules contain pyrene and P-X (X = O, BH_3) fragments that can act as distinct spectroscopic handles in (UV-Vis) absorption/emission spectroscopy and IR spectroscopy, respectively. The cage retained up to 39% of its fluorescence emission, compared to the free PBI-building blocks, despite the presence of the Fe^{2+} corner stones. No effect of the guest on the emission of the cage was found, however the emission of the guest molecule was enhanced as a result of encapsulation. The redox-properties of the building blocks were retained, as all oxidation states of the PBI-struts (PBI -> $PBI^{\bullet-}$ -> PBI^{2-}) could be reversibly addressed when the guest was present in the cage. The guest did not influence the redox-properties of the cage. In contrast, upon encapsulation of the guest its reduction event is no longer observed in CV or SEC-UV-Vis. In the FT-IR absorption spectra a new weak absorption was observed upon encapsulation of the phosphine oxide or phosphine borane guest at 1552 cm^{-1}. This new absorption is tentatively assigned to the weakened C=C stretch of the pyrene-motifs of the guest, as a result of binding within the cavity.

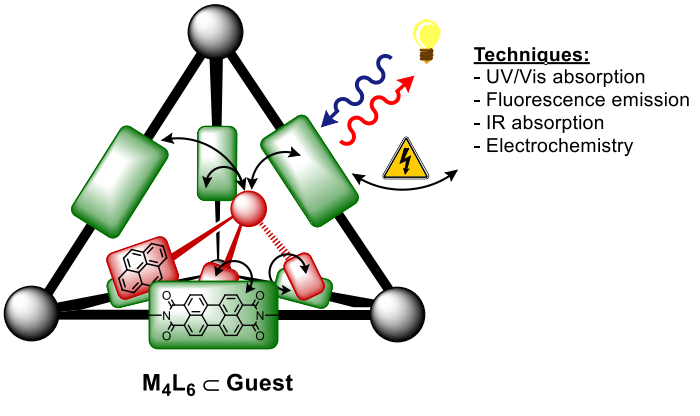


Figure 3 Host–guest system indicating pyrene-PBI interactions and through-space wall effects. Red sphere = spectroscopic handle (*i.e.* P-X, X = O, BH_3).

In **Chapter 5** the well-known M_6L_4 Fujita-type cage is modified to contain redox-active components. The normally redox 'innocent' diamine capping ligands bound to the Pd^{2+} or Pt^{2+} nodes were exchanged for bis(arylimino)-

acenaphthene (BIAN) capping ligands. This type of ligand is well known for its ability to reversibly accept two electrons. This resulted in two novel redox-active cages, based on Pd^{2+} and Pt^{2+}. The BIAN-cornerstones of the Pd-based cage could all be simultaneously reduced, reversibly, by a single electron (BIAN -> $BIAN^{\bullet-}$) resulting in an overall six electron process, confirmed by bulk electrolysis measurements. Further reduction led to the decomposition of the cage, which was also found for the mononuclear bis(pyridyl)Pd model system.

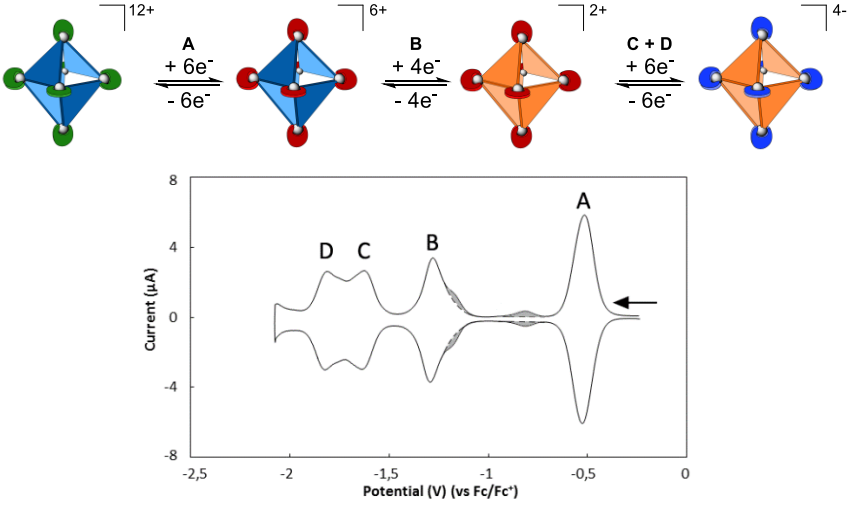


Figure 4 Convolution plot of BIAN-Pt cage in DCM demonstrating full reversibility of the supramolecular assembly. Individual reduction processes A-D are labeled above the waves.

In contrast, all three oxidation states of the BIAN-ligand for the Pt-based cage and for the bis(pyridyl)Pt model system were reversibly accessible. This showed that the intrinsic higher stability of the Pt-N_{py} *vs.* Pd-N_{py} bond is important for the overall stability of the cage upon redox-switching. In the case of the Pt-based cage, it was found that not only the BIAN-cornerstones are reduced in the redox-switching, but also the trispyrydyltriazine (tpt) wall fragments participated. As confirmed by spectro-electrochemical UV-Vis and CV measurements, the four tpt-wall fragments are each reduced by a single electron in addition to the BIAN-ligands, resulting in an overall storage and release of 16 electrons for the Pt-based cage. Both redox-active cages were able to encapsulate the $B_{12}F_{12}^{2-}$ anion, as confirmed by ^{1}H, ^{19}F NMR, and ^{19}F DOSY NMR spectroscopy as well as high resolution mass spectrometry.

This research contributes to the fundamental understanding of the role of the structural components of a supramolecular assembly, through the design and synthesis of the previously described systems. The combined results from the various Chapters show that, depending on the size of the building blocks, intramolecular interactions within the assembly can occur. These interactions may affect the redox properties and, in cases where the cavity is large enough, also the host-guest chemistry of these non-covalent assemblies. Furthermore, the choice of metal ion may influence the optical properties or the stability, which therefore affects the extent of redox-switchability of the cages, for instance in the context of switchable catalysis. These examples illustrate that relative small changes within a supramolecular assembly can result in stark changes in the overall properties. These results are expected to enable the more straightforward, rational design and application of (redox-based) stimuli-responsive cages.