Second coordination sphere effects in [FeFe]-Hydrogenase mimics

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Building charges in $M_{12}L_{24}$ nano-spheres. Does the Faraday principle still hold for molecular objects?
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Introduction

Supramolecular self-assembled cages have attracted considerable interest, as they display interesting properties, especially with respect to objects that have been enclosed in their confined spaces.\(^1\) Molecular reactions can be drastically increased in rate but encapsulated catalysts can also display unusual reactivity or selectivity when reactions are carried out in cages.\(^2\)-\(^8\) Whereas most systems allow the encapsulation of a single catalyst, certain recently developed larger spheres also allow the encapsulation of multiple catalyst molecules.\(^9\)-\(^12\) In particular, the M\(_{12}\)L\(_{24}\) Fujita type of cages based on ditopic bis(pyridine) building blocks and metal-containing corners have been used to create high local concentrations of metal complexes, which can lead to unusual reactivity for several reactions.\(^13\),\(^14\) The ease of functionalization of the standard building block and their relative large size make them suitable for several applications.

In the previous chapter we have explored redox chemistry of molecular components that are enclosed in such M\(_{12}\)L\(_{24}\) cages. The multiple redox processes observed were independent and reflected as a single redox event. The formation of cages with multiple charged species poses the question of the stability of such systems. In fact, the principle of a Faraday cage, a metal cage in which the extra charge resides at the outside and cannot enter the inside, is based on the repulsion of the charges (electrons) that drives them to the outside. The typical M\(_{12}\)L\(_{24}\) cage is based on an aromatic and fully conjugated framework, which to some extent represents the features of a Faraday cage. As far as we are aware, Faraday cages are usually macroscopic, conductive, hollow objects, and molecular analogues thereof have not been reported as yet. If the M\(_{12}\)L\(_{24}\) cages with redox sites would act as molecular Faraday cages, this would imply that the redox centers could not be oxidized or reduced if the charges are not neutralized by the electrolyte used in the electrochemical experiment. According to Faraday’s theory, repulsive electrostatic forces should force the charged objects to the outside of the sphere. In this chapter we set out to investigate whether the functional principles of a macroscopic Faraday cage are still valid for molecular objects such as the M\(_{12}\)L\(_{24}\) supramolecular cages.
Strategy

In order to explore whether supramolecular hollow spheres can behave like macroscopic Faraday cages, we use $M_{12}L_{24}$ supramolecular cages containing redox-active moieties that can be oxidized electrochemically, thus generating positive charges within the hollow cavity of the sphere. If our hypothesis is valid, upon the electrochemical event, a rearrangement of charges originating from electrostatic repulsion of the newly generated positively charged species is expected. A schematic representation is shown in Figure 1.

As this investigation is carried out utilizing voltammetry, which intrinsically requires large amounts of supporting electrolyte, typically a small size salt such as tetrabutylammonium hexafluorophosphate, it is expected that the electrolyte is homogeneously distributed in solution but also present within the cage. Because of the presence of these small ions within the cavity of the cage, we hypothesize that net accumulation of charges in the hollow cavity of the supramolecular assembly is not possible as the electrolyte ions can freely move inside or outside the rim of the cage to balance the electric field generated upon the electrochemical event, Figure 2. Accordingly, voltammograms for a cage sample containing 24 ferrocene moieties in the presence of TBAPF$_6$ as supporting electrolyte display reversible behavior, indicating no significant rearrangement of the charges (Chapter 4, Figure 14).

Figure 1. Schematic representation of the envisioned charge reorganization within the cavity of the $M_{12}L_{24}$ sphere upon electrochemical oxidation.

Figure 2. Schematic representation of a ferrocene containing cage, in the presence of a small sized electrolyte (left) and self-charge balance of the cage interior upon oxidation of ferrocenyl moieties, by rearrangement of the electrolyte ions (right).
In order to surpass this issue and allow charge accumulation inside the hollow cavity of the sphere, we envisioned the application of an electrolyte that cannot cross the cage windows due to its large size. In particular, because the redox process that will be investigated involves the oxidation of ferrocene, thereby generating positive charges inside the hollow cavity of the sphere, it is most important that the anion cannot access the cage interior via diffusion through the cage windows. No particular requirements are posed to its cation. A more practical requirement regarding the design of the electrolyte concerns the scalability of the reactions involved for its preparation. In a voltammetric experiment the supporting electrolyte is typically used in sub-molar concentration; a large amount is thus required for every single experiment. Nanometer-sized salts have been previously reported in literature but the harsh conditions needed for their synthesis render their scalability problematic. Nevertheless, inspired by this work, we opted for an ethynyl-functionalized tetraphenylborate that may be further extended in size via the CuAAC click reaction to obtain the desired size. A preliminary Spartan model of the envisioned anion is depicted in Figure 3, together with a scaled representation of an empty $M_{12}L_{24}$ supramolecular cage, showing that the size of the electrolyte is comparable to the size of the cage windows.

![Figure 3. Left: Spartan model (MMF) of the anion 6. Right: a scaled representation of an empty $M_{12}L_{24}$ supramolecular cage showing that the size of the electrolyte is comparable to the size of the cage windows.](image)

A second approach is to use ferrocenyl sulfonate moieties enclosed in a guanidinium decorated sphere, in combination with the large size electrolyte. The ferrocenyl sulfonates are in principle able to leave the cage if electrostatic repulsion upon the oxidation event becomes
comparable or larger than the binding energy. Although these entities are strongly bound in the interior of the cage by cooperative binding between the guanidinium and sulfonate moieties, among all the ferrocenyl derivatives encapsulated, at least some would be expected to leave the interior of the cage, Figure 4.

**Figure 4.** Schematic representation of ferrocenyl sulfonate encapsulated by a guanidinium cage and possible rearrangement of the redox-active moieties upon oxidation, when in the presence of large size electrolyte TBA6.
Results and discussion

Large size electrolyte synthesis

The synthesis route for the large electrolyte TBA6 is shown in Scheme 1. Its preparation starts with a condensation reaction between tritylmethanol and anilinium chloride in refluxing acetic acid to afford 4-tritylaniline, isolated as its hydrochloride salt. Compound 1 was converted into the corresponding azide by a Sandmeyer reaction in acidic aqueous environment. This procedure has been reported before by Schalley and coworkers on about half a gram scale.\textsuperscript{16} We performed the reaction on a 40 gram scale after having considered possible risks associated with large scale azide reactions in acidic media. The reaction setup and the precautions taken are described in the experimental section. The azide 2 was found to be stable in the solid state at 4 °C for extended time. Parallel to this, intermediate 3 was prepared according to a literature procedure from a palladium catalyzed coupling reaction between 1-bromo-4-iodobenzene and (triisopropylsilyl)acetylene. Treatment of 3 with one equivalent of \textit{n}-butyl lithium and subsequent quenching with BF$_3$∙Et$_2$O affords the modified protected tetraphenyl borate 4 as its lithium salt in moderately high yield. This salt is fairly insoluble in organic solvents unless some THF or diethyl ether is present as co-solvent, in which case, the salt is highly soluble. Removal of the triisopropylsilyl protecting groups is achieved by tetrabutylammonium fluoride treatment of 4. To ensure complete deprotection, 8 equivalents of TBAF and around 60 hours are required, affording 5 in quantitative yield. The excess TBAF can be easily removed by several washings with a 10% sodium chloride solution. Finally, a copper catalyzed \textit{click} reaction affords the electrolyte TBA6. The copper ions can be removed by washing the crude THF/DCM reaction mixture with a 10% sodium chloride solution containing concentrated ammonia. The electrolyte is recrystallized three times from a THF/hexane mixture at -20 °C. TBA6 was found to be highly soluble in DCM and only slightly soluble in THF or acetonitrile.
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Scheme 1. Reaction route for the preparation of the large size electrolyte TBA6.

Single crystals suitable for X-ray diffraction were obtained by slow evaporation of a concentrated DCM/MeCN solution of TBA6. The solid state structure of TBA6 is shown in Figure 5. The unit cell was found to contain several solvent molecules (2.6 dichloromethane molecules and 1.96 acetonitrile molecules) which are here omitted for clarity. The central boron atom displays a tetrahedral geometry around which the four aromatic arms extend with an actual length of roughly 1.7 nm, confirming the anion to be comparable in size to the cage windows (largest cage square window about 1.8 x 1.8 nm).
**Figure 5.** X-ray crystal structure of TBA6. Ellipsoids are set at 50% probability. Crystallization solvent molecules are here omitted for clarity.
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**Samples preparation**

The general literature procedure for the preparation of $M_{12}L_{24}$ cages consist of mixing 24 equivalents of building blocks with 12 equivalents of metal precursor ($Pd^{2+}$ or $Pt^{2+}$). Typically, the metal precursors used are $CF_3SO_3^-$, $BF_4^-$ or $PF_6^-$ salts (other small non-coordinating ions are used as well). Therefore every cage has 24 small anions that are able to move across the cage rim, potentially neutralizing charge accumulation inside the cavity of the cage. It is therefore important to also replace these small anions.

The first approach that comes to mind is the preparation of a palladium or platinum salt of the type $M_6^2$ ($M = Pd$ or $Pt$). Considerable efforts have been spent for the preparation of such salts. Unfortunately salts of the type $MX_6$ ($X =$ coordinating or non-coordinating anion: $Cl^-$, $PF_6^-$, $CF_3SO_3^-$) were obtained as a common end result. It was instead possible to prepare the silver salt, $Ag_6$, which proved to be poorly soluble in all solvents. Combination of this silver salt with $Pd(MeCN)_2Cl_2$ in refluxing acetonitrile afforded a completely insoluble white material from which $AgCl$ could be isolated by soxhlet extraction. The white solid proved to be difficult to analyze and its use for the preparation of cages proved unsuccessful, likely due to its insolubility.

Since salt metathesis proved to be highly problematic, a different strategy employing dialysis was developed. The literature method for cage preparation was used, affording the typical samples of the desired cages with small counter-ions present in solution, e.g. $PF_6^-$. To the cage solution thus prepared, excess TBA6 dissolved in DCM was added. This solution was then dialyzed over the course of 24 hours using a regenerated cellulose membrane and a mixture of DCM and acetonitrile dialysate. During the dialysis process, the small $TBA\cdot PF_6^-$ salt is removed from the sample while the larger molecules (cages and the large anions 6) are retained within the dialysis membrane. The dialysis was monitored by the disappearance of the $^{31}P$ and $^{19}F$ NMR signals of the $PF_6^-$ ions. The excess TBA6 might stay in the sample but this is not considered a problem as it is also the electrolyte for the voltammetric experiment.

During the dialysis process it was noticed that large amount of precipitate was formed inside the membrane tube, likely due to poor solubility of the cage samples in the presence of the large counter-ions 6. To avoid this issue the cage solutions were diluted to a concentration of 0.04 mM in cage (0.96 mM in ferrocene for a cage containing 24 ferrocene functionalized building blocks and 0.48 mM for a cage containing 12 ferrocene functionalized building blocks).
Electrochemistry

Electrochemical experiments on a solution containing only the electrolyte TBA6 revealed an undesired background oxidation event. The voltammograms show a broad oxidation with peak potential at about 1 V vs. Ag/AgCl, Figure 6 (left). This redox event is attributed to the oxidation of the triazole rings present on the anion 6. Addition of ferrocene building block revealed the appearance of a reversible wave just before the oxidation of the electrolyte, Figure 6 (right). Importantly, the redox event is fully reversible, as expected for a ferrocene moiety, indicating that the background reaction of the electrolyte does not pose any concern regarding possible additional reactivity of the ferrocene moiety with the oxidized triazoles. Nevertheless the background electrolyte oxidation partly covers the electrochemical window of interest. This issue is partially circumvented by application of semidifferential electroanalysis to the voltammograms recorded. The theory and advantages of this analysis have been long demonstrated although its application is not often seen.17-19

Figure 6. Left: voltammograms for a solution of TBA6 in dichloromethane. Right: addition of ferrocene building block to a solution of TBA6, the cyclic voltammogram is shown in black and its semidifferential convolution plot is shown in red.

Ferrocene cages

Voltammetric measurements of a ferrocene cage solution, containing 24 ferrocene building blocks, with the large counter-ions, as obtained after dialysis, lead to rather interesting voltammograms featuring a first non-reversible wave with a peak potential at 0.6 V vs. Ag/AgCl. This potential is consistent with the forward oxidative wave of the ferrocene functionalized cage, as seen in the previous chapter. Immediately after this first event, a second sharp
Rise in current is observed, consistent with the background reaction of the electrolyte, Figure 7. Interestingly, at slow scan rates (20-750 mV/s) the peak assigned to the oxidation of ferrocene in the cage it is not reversible, however, at high scan rates of 1 V/s the redox event becomes more reversible.

**Figure 7.** Left: cyclic voltammograms for a cage sample containing 24 ferrocene moieties measured using TBA6 as electrolyte. Right: semidifferential convolution plots showing limited reversibility of the ferrocene couple at slow scan rates.

As mentioned before, because of the electrolyte background, semidifferential convolution analysis is applied to the cyclic voltammograms to obtain waves that are easier to interpret and that can be analyzed quantitatively, Figure 7 (right). The forward and backward peak current obtained from Figure 7 (right) are plotted against the scan speed, as shown in Figure 8 (left). The current of the forward oxidation is found to scale linearly with the scan rate while the back reduction follows an exponential trend, indicating that subsequent to oxidation, a slow follow-up process occurs with the encapsulated ferrocenes. For comparison, similar data are shown for the same cage measured in the presence of TBAPF₆ electrolyte, Figure 8 (right). For a species dissolved in homogeneous solution, the peak current of the cyclic voltammogram scales linearly with the square root of the scan speed according to the Randles–Sevcik equation, Equation 1. When semidifferential convolution analysis is applied to the voltammograms, the peak current of the semidifferential plot scales linearly with the scan rate, according to Equation 2.¹⁸
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The linear oxidative trend shown in Figure 8 (left) thus suggests no absorption of the cage, ferrocene or electrolyte to the surface of the electrode. In line with this, the entire dataset is collected without the need to polish the glassy carbon working electrode, which in case of absorption processes to the electrode would have caused loss of electrochemical signal leading to a non-linear oxidative trend.

To further prove that the loss of reversibility is a result of charge build-up in the cage originating from the use of the large size electrolyte, TBAPF$_6$ was added to the same solution un-

\[ i_p(CV) = 0.4463 \, nFAC \frac{\sqrt{nFvD}}{RT} \]

**Equation 1.** Peak current of cyclic voltammograms as predicted by the Randles–Sevcik equation, where $i_p$ is the peak current, $n$ the number of electrons transferred, $F$ the Faraday constant, $A$ the geometrical surface area of the electrode, $C$ the bulk concentration of the species, $v$ the scan speed, $D$ the diffusion coefficient, $R$ the gas constant and $T$ the temperature.

\[ i_p(SDC) = \frac{n^2F^2ACvD^2}{4RT} \]

**Equation 2.** Predicted peak current for semidifferential convolution plot (SDC), where each factor has the usual meaning as described above for Equation 1.

Figure 8. Left: plot of the semidifferential peak currents against the scan speed for a cage sample containing 24 equivalents of ferrocene measured in the presence of TBA$_6$. Right: cage sample containing 24 equivalents of ferrocene measured in the presence of TBAPF$_6$. 
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Under investigation. The small counter-ions introduced into the solution can enter the cavity of the sphere to compensate the charge build-up. Indeed, cyclic voltammograms of this solution show that the encapsulated ferrocene fragments, after the addition of small size electrolyte, undergo reversible oxidation already at slow scan rates (25 mV/s), thus completely regaining electrochemical reversibility, Figure 9.

![Figure 9](image1.png)

**Figure 9.** Left: cyclic voltammograms for a cage sample containing 24 ferrocene moieties and large size electrolyte to which TBAPF$_6$ was added in solution. Right: semidifferential convolution plots, showing that reversibility of the ferrocene couple is re-established.

A plot of the semidifferential peak current confirms full reversibility of the system at all scan rates measured, Figure 10. The linearity of the trend lines indicate that the cage is in homogeneous solution during the electrochemical processes.

![Figure 10](image2.png)

**Figure 10.** Plot of the semidifferential peak currents against the scan speed for a cage sample containing 24 equivalents of ferrocene after TBAPF$_6$ has been added to the solution.
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The electrochemical data are in agreement with the hypothesis that the small ions can migrate to/from the cavity of the cage effectively, keeping its net charge constant throughout the redox processes that occur with the redox-active moieties in its cavity. In stark contrast, when only electrolyte with a large anion that cannot travel across the cage rim is used, the redox reversibility of the encapsulated ferrocenes is lost. Interestingly, it is still possible to oxidize the encapsulated redox-active moieties. It is proposed that after the electrochemical oxidation of the redox-active moieties inside the cavity of the cage, electrostatic repulsion causes the ferrocene moieties to physically redistribute at the rim of the cage, similar to what happens to charges in a Faraday cage. Redistribution of the ferrocene units towards the rim of the cage could possibly lead to disassembling of the supramolecular structure of the cage. Nevertheless, loss of reversibility of the ferrocene moieties indicates that the cage does not simply disassemble. In fact, if that would be the case, the back-reduction of the ferrocene moieties should be still detectable at a potential similar to that of the free ferrocene building block.

As suggested by the partial loss of reversibility at fast scan rates, this redistribution process is relatively slow, which would be consistent with the physical movement of the ferrocene units, together with the entire aliphatic chain that holds them, towards the rim of the cage. After this first reorganization which would be needed to lower the electrostatic field inside the cavity of the sphere, we propose the existence of a second fast process involving either reactivity of the ferrocenium moieties or a charge transfer from the cage outer-shell or from the palladium ions, to the ferrocenium units, although the formation of palladium(III) or palladium(IV) seems unlikely. Both would lead to non-reversible redox behavior of the ferrocene moieties. Clearly, this second process is caused by accumulation of positive charge.

To further study this effect, a second cage sample containing fewer equivalents of ferrocene building blocks was prepared and measured under similar conditions, expecting gradual increasing redox reversibility when less ferrocene moieties are present within the cavity of the cage. In particular, cage samples containing 12 and 1 equivalents of ferrocene building block were prepared; the latter sample proved to be too diluted (ferrocene concentration 0.04 mM, as result of cage dilution to avoid its precipitation from solution in the presence of TBA6 during dialysis), hampering detection of the ferrocene wave.

Cyclic voltammograms of the cage sample containing 12 ferrocene moieties display increased reversibility compared to the more crowded previously described sample, Figure 11.
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More quantitative information can be obtained from the plot of the semidifferential peak current against the scan speed shown in Figure 12 (left). A reversibility factor can be defined as the ratio of the forward anodic current and the backward cathodic one as $(E^f_p / E^b_p)$. The average reversibility factor obtained from the nine scan speeds recorded is about 0.79. When TBAPF$_6$ is added to this cage solution, the reversibility of the process is fully regained, as indicated by the reversibility factor of 1.08, Figure 12 (right).

**Figure 11.** Left: cyclic voltammograms for a cage sample containing 12 ferrocene moieties measured in the presence of TBA$_6$. Right: semidifferential convolution plots showing reversibility of the ferrocene couple even at slow scan rates.

**Figure 12.** Plot of the semidifferential peak currents against the scan speed. Left: cage sample containing 12 equivalents of ferrocene measured in the presence of TBA$_6$. Right: after addition of TBAPF$_6$ to its solution.
These results are in line with the hypothesis that the additional reactivity of the ferrocenium moieties is an effect of the electrostatic repulsion between the oxidized redox active moieties. When the number of ferrocene units is halved, this effect is drastically reduced likely due a combination of different factors. Assuming a homogenous distribution of the 12 ferrocenes moieties within the cavity of the cage, their relative distance would be roughly doubled compared to the more crowded cage containing 24 units. As a consequence the electrostatic repulsion is lowered by a factor of 4. The lower electrostatic repulsion would provide less driving force for the ferrocene to migrate at the rim of the cage. Nevertheless the effect of the electrostatic repulsion is still evident at slow scan rates.

**Guanidinium Cage**

A sample of guanidinium cage containing PF	extsubscript{6} counter-ions was loaded with 18 equivalents of ferrocenyl sulfonate (as mentioned in chapter 4, addition of higher amounts of ferrocenyl sulfonate causes precipitation of the supramolecular assembly from solution) which gave the solution a distinct yellow color. Excess TBA	extsubscript{6} was added after which this solution was dialyzed as described for the ferrocene containing cages. After 48 hours of dialysis, the yellow color of the solution remained, indicating the presence of the ferrocene derivative within the sample, confirming once more the strong binding of sulfonates to the guanidinium functionalized cage.

After the dialysis, the sample was subjected to electrochemical measurements, revealing the presence of a reversible wave assigned to the oxidation of the ferrocenyl sulfonate. The voltammograms and semidifferential convolution plots are shown in Figure 13. The plot of the semidifferential peak current against the scan speed indicated full reversibility of the event and no deposition of the compounds at the electrode, Figure 14.
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Figure 13. Left: cyclic voltammograms for a guanidinium cage sample containing 18 equivalents of ferrocenyl sulfonate measured in the presence of TBA6 after dialysis. Right: semidifferential convolution plots showing reversibility of the ferrocene couple.

Figure 14. Plot of the semidifferential peak current against the scan speed for a guanidinium cage sample containing 18 equivalents of ferrocenyl sulfonate measured in the presence of TBA6 after dialysis.

The shape and position of the waves measured are compared to those of the free ferrocenyl sulfonate and to those obtained for the encapsulated ferrocenyl sulfonate by the guanidinium cage in the presence of the small size electrolyte TBAPF$_6$. This comparison, shown in Figure 15, evidences the differences in the half-wave potential of the ferrocenyl moiety for the three different situations (in a semidifferential plot, the half-wave potential corresponds to the peak potential. Therefore, for a reversible system, anodic and cathodic waves should have the same peak potential).
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The difference in half-wave potential between the free and the encapsulated ferrocenyl sulfonate, measured in the presence of TBAPF\textsubscript{6}, is about 150 mV. In the previous chapter we described a titration experiment of n-butyl-guanidinium into a solution of ferrocenyl sulfonate (Chapter 4, Figure 12) which shows that the half-wave potential of the ferrocenyl moiety is a reflection of the interaction between the sulfonate and guanidinium groups. This interaction renders the ferrocene moiety less electron-rich and therefore more difficult to oxidize. A sample of the caged ferrocenyl sulfonate measured in the exclusive presence of TBA\textsubscript{6} displays roughly half of the shift, about 60 mV in the same direction. This would suggest a weaker interaction of the two complementary functional groups. This could be due to a loss of the cooperative binding of the guanidinium moieties that could be facing the large cage windows when only the large size anions are present. The experiments suggest also that the ferrocenyl sulfonates do not leave the cavity of the nano-sphere upon oxidation. This is indicated by the single wave detected along the back-reduction trace; if some redox probes would leave the cavity of the cage after the oxidation event, they would be back-reduced at a potential similar to that of the free ferrocenyl sulfonate. Importantly, the full reversibility observed for the redox couple indicates that the ferrocenes do not undergo further reactivity upon the electron transfer.

Figure 15. Left: comparison of voltammograms for a sample of free ferrocenyl sulfonate (blue) and guanidinium cage containing 18 equivalents of ferrocenyl sulfonate in the presence of TBA\textsubscript{6} (back) and in the presence of TBAPF\textsubscript{6} (red). Right: comparison of their respective semidifferential convolution plots.
Conclusions

In this chapter we have explored the redox chemistry of $M_{12}L_{24}$ nanospheres functionalized with 24 redox-active ferrocene units in various electrolyte solutions. In particular, we have prepared electrolyte material with exceptional large anions that in principle cannot pass the windows of the spheres. This implies that upon oxidation of the ferrocene at the inside of the $M_{12}L_{24}$ sphere, an overall net charge is generated. At normal scan speeds, the oxidation was indeed demonstrated to be irreversible, which is not observed in the electrochemical experiment performed in the presence of traditional TBAPF$_6$ electrolyte. Also the addition of this electrolyte during the electrochemical experiment in the solution of the large electrolyte restores the typical reversible oxidation behavior of the ferrocene. Interestingly, at high scan speeds the redox event of ferrocene becomes more reversible, implying that after initial oxidation of the ferrocene units a follow-up reaction is enforced by the electrostatic repulsion that can be slow on the electrochemical time scale. Also, if the number of ferrocene units is reduced to 12, similar effects are observed but to a lesser extend; thus at low scan speed the oxidation is still irreversible. These preliminary results indicate that $M_{12}L_{24}$ supramolecular self-assembled cages have similarities to the macroscopic Faraday cage. The data suggest that charging of the species encapsulated in the cavity of these cages causes electrostatic repulsion among these redox-active fragments and redistribution of the positive charges toward the outer shell of the cage. Details on the follow-up reaction as a result of the repulsion are currently lacking, and more insights by studying related systems are needed to fully elucidate how the processes parallel those found for macroscopic Faraday cages.

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Experimental

Materials and methods

General procedures: all synthetic procedures were carried out under an argon atmosphere using standard Schlenk techniques. All commercially available chemicals were used as received without further purification. Solvents used for synthesis were dried via the most suitable method, distilled and degassed. Column chromatography was performed open to air using solvents as received.

Dialysis: Spectra/Por® 3 dialysis membrane, 3.5 kD, 18 mm flat width was cut into 10 cm pieces, washed with Milli-Q water and let them in Milli-Q water for 30 minutes. The membranes were then rinsed with acetonitrile before they were immersed in acetonitrile for 30 minutes. After a last rinse with a 1:1 mixture of DCM and acetonitrile the membranes were charged with a 5-10 mL of cage solution containing about 50 equivalents of TBA6. The samples were dialyzed with a 1:1 mixture of DCM and acetonitrile dialysate solution (1 L). The first dialysate change was done about 2-3 hours, the second one after about 4-5 hours and the last one prior to leaving the sample to dialyse overnight. Thereafter, the samples were removed from the membrane and filtered through a 200 µm syringe filter. TBA6 was added as a solid to reach a concentration of 50 mM (excluding the already present TBA6 added before dialysis), the solution degassed and used for electrochemical measurements.

Electrochemistry: cyclic voltammetry was performed on 1 mM solutions of analyte (unless otherwise stated) containing 0.1 M tetrabutylammonium hexafluorophosphate or TBA6 as supporting electrolyte. The voltammograms were recorded using a PG-STAT302 N potentiostat at glassy carbon disk electrode (2 mm diameter). A platinum coil was used as auxiliary electrode and a leak-free silver electrode (inner compartment 3 M KCl/Ag).

Mass analysis: mass spectra for all compounds were collected on an AccuTOF GC v 4g, JMS-T100G-CV mass spectrometer (JEOL, Japan).

X-ray crystal structure determination: All reflection intensities were measured at 110(2) K using a SuperNova diffractometer (equipped with Atlas detector) with Cu Kα radiation (λ = 1.54178 Å) under the program CrysAlisPro (Version 1.171.36.32 Agilent Technologies, 2013). The same program was used to refine the cell dimensions and for data reduction. The structure was solved with the program SHELXS-2013 or SHELXS-2014/7 and was refined on F2 with SHELXL-2013 or SHELXL-2014/7. Analytical numeric absorption corrections based on a multifaceted crystal model were applied using CrysAlisPro. The temperature of the data collection was controlled using the system Cryojet (manufactured by Oxford Instruments). The H atoms were placed at calculated positions using the instructions AFIX 43 or
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AFIX 137 with isotropic displacement parameters having values 1.2 or 1.5 times \( U_{eq} \) of the attached C atoms.

X-ray intensities were also measured on a Bruker D8 Quest Eco diffractometer equipped with a Triumph monochromator (\( \lambda = 0.71073 \text{ \AA} \)) and a CMOS Photon 50 detector at a temperature of 150(2) K. Intensity data were integrated with the Bruker APEX2 software.\(^{22}\) Absorption correction and scaling was performed with SADABS.\(^{23}\) The structures were solved using intrinsic phasing with the program SHELXT.\(^{24}\) Least-squares refinement was performed with SHELXL-2013\(^{44}\) against \( F^2 \) of all reflections. Non-hydrogen atoms were refined with anisotropic displacement parameters. The H atoms were placed at calculated positions using the instructions AFIX 13, AFIX 43 or AFIX 137 with isotropic displacement parameters having values 1.2 or 1.5 times \( U_{eq} \) of the attached C atoms.

**Synthesis of compounds**

Synthesis of cage building blocks and cages preparation is reported in Chapter 4 of this thesis.

Compounds 1 and 3 were prepared according to literature procedures.\(^{15,25}\)

Compound 2 was prepared according to a literature procedure.\(^{16}\) Because of the large scale employed in this work a description of the setup is given.

A 4 L beaker was equipped with a cylindrical stirring bar (10 cm diameter, 3 cm tall), a mechanical stirrer and a thermometer. The beaker was placed inside a 20 L plastic bucket filled with ice and salt. A 1 L, 2 M solution of HCl was added to the beaker and 1 (40 g, 0.11 mol, 1 equiv) was added portionwise. The temperature was allowed to drop to \(-5 \) °C before 80 mL of a solution containing NaNO\(_2\) (17 g, 0.25 mol, 2.3 equiv) was added dropwise over the course of 3 hours, being careful to keep the temperature around \(-5 \) °C. It is necessary to keep the temperature of the solution around \(-5 \) °C. This requires the frequent addition of ice and sodium chloride to the plastic bucket. After complete addition, the suspension was stirred for an additional hour. Calcium carbonate (about 100 g) was then added portionwise to the mixture to neutralize the hydrochloric acid solution and the excess unreacted sodium nitrate. CO\(_2\) effervescence and foaming of the suspension render this step time-consuming, nevertheless it is important to check completeness of the neutralization by both pH paper and potassium iodide starch paper to ensure quenching of nitrates. After neutralization a 50 mL solution of NaN\(_3\) (16 g, 0.25 mol, 2.3 equiv) is added dropwise. Again it is of primary importance the temperature of the mixture is kept around \(-5 \) °C for the entire time. After the addition was completed, the mixture was stirred for one hour. The suspension was filtered through...
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Compound 4 was prepared according to a modified literature procedure. An oven-dried round bottom Schlenk flask was charged with 3 (25 g, 74.10 mmol, 1 equiv.) and 300 mL of dry diethylether. The solution was cooled to -78 °C before nBuLi (29.65 mL of 2.5 M solution in hexane, 74.10 mmol, 1 equiv) was added dropwise over the course of 20 minutes. After the addition, the solution was allowed to stir at the same temperature for one hour before BF₃∙Et₂O (2.28 mL, 18.53 mmol, 0.25 equiv) was added. The solution was allowed to warm to room temperature overnight. The solvent was reduced to about 50 mL before 100 mL of dichloromethane were added. The suspension was filtered through a plug of Celite before the volatiles removed under vacuum. The residue was dissolved in DCM containing 5% Et₂O, filtered through a plug of Celite before hexane was added to precipitate white solids. The solids were filtered, washed with hexanes and dried under vacuum (15.9 g, yield 82%). Spectroscopic data are in accordance with the reported values.

Compound 5: compound 4 (15 g, 14.32 mmol, 1 equiv) was dissolved in 200 mL of THF before a 1 M THF solution of TBAF (114.5 ml, 114.56 mmol, 8 equiv) was added. The solution was allowed to stir in the dark, at room temperature for 60 hours before it was transferred to a separatory funnel and washed 10 times with a 10% sodium chloride solution. The organics were dried over MgSO₄ and the volatiles removed under vacuum to afford a waxy solid. The solids were filtered, washed with hexanes and dried under vacuum (9.4 g, quantitative yield). Spectroscopic data are in accordance with the reported values.

Compound TBA6: A round bottom Schlenk flask was charged with compound 5 (9 g, 13.68 mmol, 1 equiv) and compound 2 (20.76 g, 57.43 mmol, 4.2 equiv). The flask was flushed with argon before 300 mL of a degassed 1:1 mixture of DCM and THF was added. To this solution about 300 mg of Cu(OAc)(PPh₃)₂ catalyst, prepared according to literature procedure was added. The solution was stirred in the dark at room temperature overnight before it was transferred to a separatory funnel and washed 5 times with a 10% sodium chloride solution containing concentrated ammonia. The organics were dried over MgSO₄ and the volatiles removed under vacuum to afford a white solid. The residue was dissolved in THF and hexane was added (about 2/3 of the THF volume) and the flask placed in a -20 °C freezer. The solids formed were collected and the process repeated two additional times. Eventually the solids
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were filtered, washed with hexanes and dried under vacuum (21.6 g, 75%). $^1$H NMR ($d_3$-MeCN) δ 8.48 (s, 4H), 7.79 (d, $J = 8.8$ Hz, 8H), 7.64 (d, $J = 7.7$ Hz, 8H), 7.60 – 7.42 (m, 16H), 7.34 (d, $J = 4.3$ Hz, 54H), 7.26 (m, 16H), 3.17 – 3.01 (m, 8H), 1.66 – 1.54 (m, 8H), 1.49 – 1.26 (m, 8H), 1.00 (t, $J = 7.4$ Hz, 12H). $^{13}$B NMR ($d_3$-MeCN) δ 6.49. $^{13}$C NMR ($d_2$-CD$_2$Cl$_2$) δ 149.9, 147.4, 146.4, 136.3, 135.0, 132.2, 131.2, 130.9, 128.0, 127.8, 126.2, 124.1, 123.7, 123.6, 119.3, 116.8, 64.8, 58.7, 23.7, 19.6, 13.4. HR ESI(neg.)-MS found: 1869.7967 expected: 1869.8016 for the anion $C_{132}H_{96}BN_{12}^-$.

Crystallographic details

TBA6: $C_{132}H_{96}BN_{11.89}C_{16}H_{36}N$·$2.607(CH_2Cl)_2$·$1.945(C_2H_2N)$, Fw = 2403.32, colorless block, 0.47 × 0.41 × 0.31 mm, Triclinic, P (No: 2), a = 13.89208 (19), b = 23.6892 (4), c = 24.1682 (3) Å, α = 94.1708 (12), β = 102.7294 (12), γ = 103.9281 (13) °, V = 7463.24 (19) Å$^3$, Z = 2, $D_e$ = 1.069 g/cm$^3$, μ = 1.32 mm$^{-1}$. 94194 reflections were measured up to a resolution of ($\sin \theta/\lambda_{max}$ = 0.616 Å$^{-1}$. 40798 reflections were unique ($R_{int}$ = 0.042), of which 30499 were observed (|I|>2σ(I)). 1756 parameters were refined with 469 restraints. R1/wR2 [I > 2σ(I)]: 0.0607/0.1686 R1/wR2 [all refl.]: 0.0775/0.1820. S = 1.09. Residual electron density between −0.80 and 1.36 e/Å$^3$. 
Appendix

**Figure 16.** Left: voltammograms for a solution of ferrocene in the presence of TBA6 electrolyte. Right: semidifferential convolution plots.

**Figure 17.** Left: voltammograms for a solution of cage containing 12 ferrocene moieties in the presence of TBA6 electrolyte after addition of TBAPF$_6$ electrolyte. Right: semidifferential convolution plots.
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