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# Triggered Exchange of Anionic for Neutral Guests inside a Cationic Coordination Cage

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Supporting Information

**ABSTRACT:** Molecular encapsulation processes under the control of an external trigger play a major role in biological signal transduction processes and enzyme catalysis. Here, we present an artificial mimic of a controllable host system that forms via self-assembly from a simple bis-monodentate ligand and Pd(II) cations. The resulting interpenetrated double cage features three consecutive pockets which initially contain one tetrafluoroborate anion, each. Activation of this host system with two halide anions triggers a conformational change that renders the central pocket susceptible to the uptake of small neutral guest molecules. Thereby, the pentacationic cage expels the central anion and replaces it with a neutral molecule to give a hexacationic species. The cage structures prior and after the halide triggered binding of benzene were examined by X-ray crystallography, ESI MS, and NMR techniques. The kinetics and thermodynamics of the encapsulation of benzene, cyclohexane, and norbornadiene are compared.

Switch-on molecular binding processes are widespread in nature.[1] Quite often, the affinity of an enzyme to its substrate is regulated by phosphorylation, thus by a covalent modification. In other cases, the noncovalent binding of a small molecule such as ATP or a specific messenger substance triggers substrate binding or the interaction between two proteins. The design and examination of artificial systems capable of such controlled binding processes helps to understand the underlying principles of molecular recognition and promises to lead to new functional nanostructures.

In the field of supramolecular chemistry, numerous synthetic host–guest systems have been studied in the past couple of decades.[2] Until recently, the vast majority of these systems consisted of a static host that would bind any appropriate guest in the fashion of a simple equilibrium reaction once the guest is made available to the host.[3] Advanced developments have started to introduce switchable elements to gain control over the encapsulation process.[4] For example, we recently reported a coordination cage consisting of light-switchable ligands based on dithienylethene (DTE) chromophores whose affinity for the uptake of an anionic guest can be smoothly switched back and forth by irradiation with light of different wavelengths.[5]

The present system is based on a self-assembled host[6] that forms in virtually quantitative yields when banana-shaped bis-monodentate pyridyl ligands are combined with square-planar Pd(II) cations in the presence of noncoordinating anionic templates.[7] Following this principle, we reported a series of interpenetrated double cages $[Pd_4L_8]$, all featuring three anion-filled pockets and ligands L of differing size and chemical makeup.[8] These dimers were found to encapsulate halide anions in their outer two pockets according to an allosteric binding mechanism with a strong positive cooperativity.[8a] Furthermore, we showed that the size of the template in the central pocket controls the selectivity for the binding of smaller or larger guests inside the outer pockets via a mechanical relay mechanism.[8c]

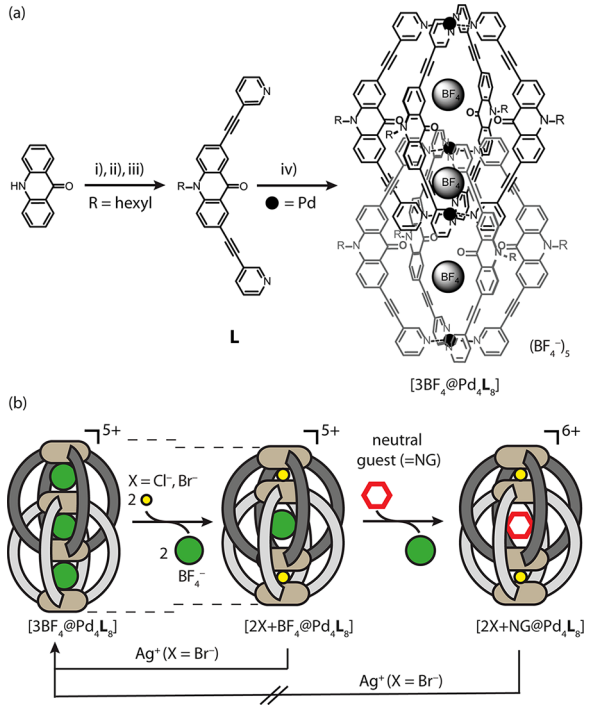


**Figure 1.** (a) Synthesis of ligand **L** and assembly to cage $[3BF_4@Pd_4L_8]$: (i) 1-bromohexane, KO$^t$Bu, THF; (ii) NBS, DMF; (iii) 3-ethynylpyridine, CuI, $[Pd(PPh_3)_2Cl_2]$, $NEt_3$; (iv) $[Pd(CH_3CN)_4](BF_4)_2$, $CD_3CN$; (b) schematic representation of the halide binding in the outer pockets of the double cage that triggers the uptake of neutral guest molecule in the central pocket.

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Compared to our previous studies on interpenetrated double cages, the encapsulation chemistry of the present system differs significantly: The central template is not meant to control guest uptake in the outer pockets, but in contrast, the binding of halide anions in the outer pockets modulates the binding of guests in the central cavity. Neutral guests were found to be encapsulated in the central pocket, despite the fact that the replacement of the central anion turns a pentacationic cage into a hexacationic species.

Ligand **L** was synthesized in three steps starting from acridone by N-alkylation with *n*-hexyl bromide, a subsequent selective bromination with *N*-bromosuccinimide and finally Sonogashira cross-coupling with 3-ethynylpyridine (Figure 1a). Heating the ligand **L** for 24 h at 70 °C in the presence of $[Pd(CH_3CN)_4](BF_4)_2$ in deuterated acetonitrile resulted in the quantitative formation of an interpenetrated coordination cage $[3BF_4@Pd_4L_8]$, as confirmed by $^1$H NMR spectroscopy (Figure 2b) and

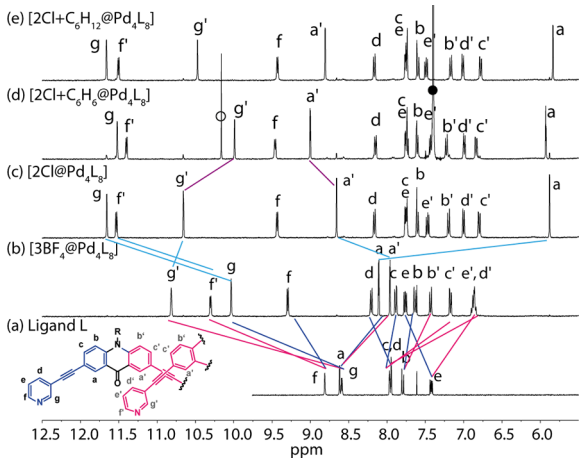


**Figure 2.** $^1$H NMR spectra of (a) ligand **L**, (b) double cage $[3BF_4@Pd_4L_8]$, (c) $[2Cl@Pd_4L_8]$ which forms upon addition of 2.0 equiv of *n*-$NBu_4Cl$, (d) $[2Cl+C_6H_6@Pd_4L_8]$ and (e) $[2Cl+C_6H_{12}@Pd_4L_8]$ which form after addition of 20 equiv of neutral guest (benzene or cyclohexane; 400 MHz, 298 K, $CD_3CN$). Filled circle: free benzene. Empty circle: encapsulated benzene (the cyclohexane signals are out of the depicted range; see the SI).

high-resolution ESI mass spectrometry (Figure 3a). The conversion of ligand **L** into the highly symmetric double cage structure leads to a splitting of all $^1$H NMR signals into two sets of equal intensity, which is in full accordance with the results of our previous studies.[8a,b,f] The $^1$H NMR signals of the pyridine moieties (in particular $H_f$ and $H_g$) undergo a downfield shift, which indicates the coordination of the palladium(II) cations to the ligand. In contrast, the signals of the acridone backbone and the N−$CH_2$ groups of the hexyl chains show an upfield shift in the $^1$H NMR spectra (Figure 2b). The $^{19}$F NMR spectrum at rt shows three signals, which could be assigned to free $BF_4^-$ ($\delta$ = −151.70 ppm) and encapsulated $BF_4^-$ in the inner ($\delta$ = −143.32 ppm) and outer pockets ($\delta$ = −144.85 ppm, Figure SI 25 in the Supporting Information (SI)).

In the high resolution ESI mass spectrum the interpenetrated dimer could be identified as the pentacationic species $[3BF_4@Pd_4L_8]^{5+}$ (Figure 3a). In accordance with the anion binding experiments performed with our previously reported double cages, we probed the capability of the new acridone double cage for the uptake of halide anions.[8a,d,f] Indeed, addition of 2 equiv of halide anions (as their $NBu_4^+$ salts) leads to an exchange of the

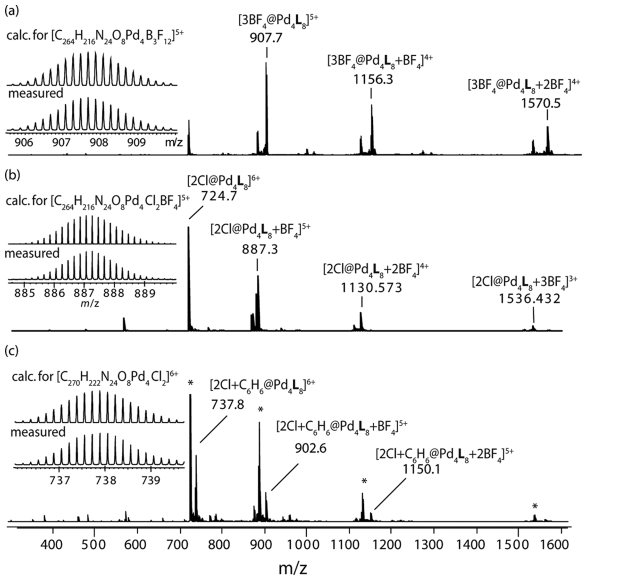


**Figure 3.** ESI mass spectra of (a) $[3BF_4@Pd_4L_8]$, (b) $[2Cl@Pd_4L_8]$, and (c) $[2Cl+C_6H_6@Pd_4L_8]$ (* = free host).

$BF_4^-$ anions in the outer two pockets of the double cage and thus to the formation of a new species $[2X+BF_4@Pd_4L_8]$ (X = $Cl^-$, $Br^-$). The clean formation of these products was confirmed by NMR spectroscopy and high resolution mass spectrometry. The $^1$H NMR signals of the pyridine protons $H_g$ and $H_{f'}$ which are pointing inside the outer, chloride-filled pockets of the double cage undergo a significant downfield shift. The backbone protons $H_a$ and $H_{a'}$ shift up- and downfield, respectively (Figure 2c). According to our previous studies, this observation indicates that halide binding is accompanied by a compression of the double cage structure along the $Pd_4$-axis.[8d] At rt, the $^{19}$F NMR spectrum of $[2Br+BF_4@Pd_4L_8]$ shows two signals, one corresponding to free $BF_4^-$ ($\delta$ = −151.70 ppm) and one representing a tightly encapsulated $BF_4^-$ anion sitting inside the central pocket ($\delta$ = −152.23 ppm). According to a $^{19}$F EXSY NMR experiment, no exchange between free and encapsulated $BF_4^-$ could be detected in this case on a millisecond time scale (Figure SI 29).[9] In contrast, only one signal was found in the $^{19}$F NMR spectrum of $[2Cl@Pd_4L_8]$ (Figure SI 26). The signal at −151.00 ppm corresponds to free $BF_4^-$; thus, tight encapsulation of tetrafluoroborate in the central pocket of the chloride-containing double cage was not observed, but quickly exchanging $BF_4^-$ cannot be excluded.[10] The high-resolution ESI mass spectrum of the halide-filled double cage $[2Cl@Pd_4L_8]$ shows a series of species $[2Cl@Pd_4L_8+nBF_4]^{(6-n)+}$ ($n$ = 0−3) containing a variable number of $BF_4^-$ counteranions (Figure 3b).

Single crystals of $[3BF_4@Pd_4L_8]$ suitable for X-ray structure determination were grown by slow vapor diffusion of benzene into an acetonitrile solution of the double cage. The $C_4$-symmetric structure reveals that the double cage features three pockets, each filled with a $BF_4^-$ anion (Figure 4a). The Pd−Pd distances are 8.24 and 8.26 Å for the outer pockets and 8.44 Å for the inner cavity. These values are similar to the corresponding distances that were found in the X-ray structures of the previously reported dibenzosuberone- and phenothiazine-based double cages.[8a,b] In the interstitial space between the cages, the remaining counteranions and several benzene molecules were found. Furthermore, we were able to obtain an X-ray structure of $[2Cl@Pd_4L_8]$, thus representing the first example of a double cage containing halide anions in its outer pockets that we were


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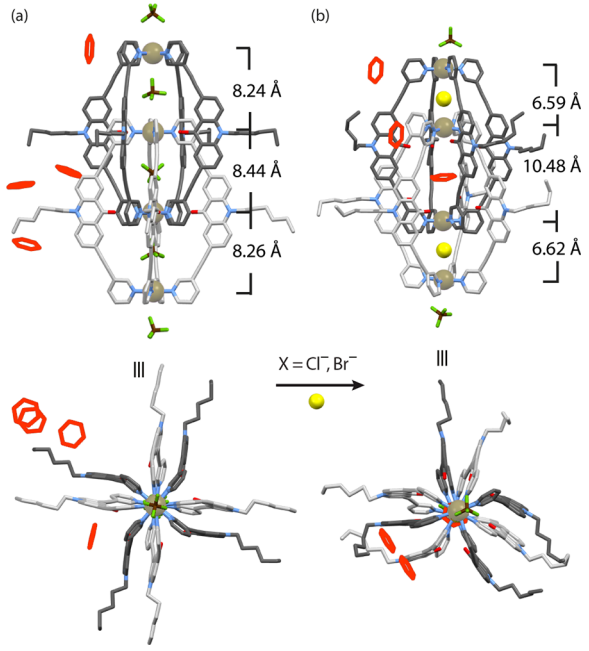


**Figure 4.** X-ray crystal structures of cage (a) $[3BF_4@Pd_4L_8]$ and (b) $[2Cl+C_6H_6@Pd_4L_8]$. Color scheme: C, light/dark gray; N, blue; O, red; Cl, yellow; F, green; B, brown; Pd, tan. For clarity, H atoms and some of the solvent molecules have been removed.

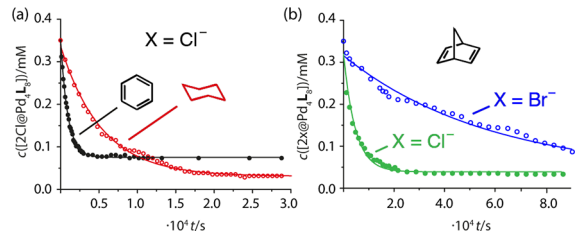


**Figure 5.** Uptake kinetics of (a) $[2Cl@Pd_4L_8]$ with benzene (black) and cyclohexane (red); (b) addition of norbornadiene to $[2Cl@Pd_4L_8]$ (green) and $[2Br+BF_4@Pd_4L_8]$ (blue).

able to crystallize. Again, the crystals were obtained by slow vapor diffusion of benzene into an acetonitrile solution of the cage. Now, however, benzene was not only found in positions outside of the cage's boundaries, but one benzene molecule was found being encapsulated inside the central pocket of the double cage (hereafter named as $[2Cl+C_6H_6@Pd_4L_8]$, Figure 4b). As a result of the halide incorporation, the double cage structure is compressed along the $Pd_4$-axis.[11] Consequently, the Pd−Pd distances of the outer pockets are reduced to 6.59 and 6.62 Å and the distance of the inner pocket is increased to 10.48 Å. Thus, the addition of halide anions seems to activate the double cage's ability to bind benzene in the enlarged central pocket.

We propose, that encapsulation is mainly driven by dispersion interactions with contributions of a solvophobic effect (SI).[12,13]

Viewing the crystal structure of $[2Cl+C_6H_6@Pd_4L_8]$ along the $Pd_4$-axis reveals a very asymmetric arrangement of the eight ligands around the Pd centers. We hypothesize, that this conformational flexibility provides an important prerequisite for the present cage to allow the relatively large neutral guest molecule to enter its central pocket.

Also, we were able to show that the uptake of benzene inside the chloride containing double cage is not only a solid state phenomenon. In solution, the same process was unambiguously verified by NMR spectroscopy and high resolution mass spectrometry. After addition of 20 equiv of benzene to an acetonitrile solution of $[2Cl@Pd_4L_8]$, dramatic changes in the $^1H$ NMR spectra were observed. In particular, the protons pointing inside the central pocket of the double cage were affected, with $H_{g'}$ shifting upfield and $H_{a'}$ shifting downfield. The $^1H$ NMR signal of the encapsulated guest is shifted downfield by 2.8 ppm with respect to the signal of the free benzene. An NOESY NMR experiment revealed contacts between inward pointing cage protons and the encapsulated benzene (see Figure SI 31). In addition, the species $[2Cl+C_6H_6@Pd_4L_8+nBF_4]^{(6-n)+}$ ($n$ = 0−2) were clearly identified by high resolution ESI mass spectrometry (Figure 3c).

Subsequently, we explored the ability of the halide containing cages for the encapsulation of other neutral guest molecules. While the dichlorobenzenes (*o*-, *m*-, and *p*-) and [2.2]-paracyclophane could not be encapsulated, smaller molecules such as cyclohexane, toluene, and norbornadiene were found to form host−guest complexes with the halide containing cages $[2X+BF_4@Pd_4L_8]$ (X = Cl, Br) (Figure 2e; SI). The parental double cage $[3BF_4@Pd_4L_8]$, however, is totally unaffected by the addition of neutral guest molecules. The kinetic and thermodynamic parameters of the encapsulation of benzene and cyclohexane inside the chloride containing double cage were examined by $^1H$ NMR spectroscopy and compared (Figure 5a; SI).[14] The binding constant of benzene ($K = 2.02 \times 10^3$ L mol$^{-1}$) was found to be lower than that of cyclohexane ($K = 3.19 \times 10^3$ L mol$^{-1}$) which hints at a significant contribution of dispersion interactions, since cyclohexane is an unfunctionalized alkane consisting of more atoms than benzene. In contrast, the uptake of benzene was found to be six times faster ($k$ = (1.07 ± 0.02) × $10^{-3}$ s$^{-1}$), than the encapsulation of cyclohexane ($k$ = (1.87 ± 0.04) × $10^{-4}$ s$^{-1}$). These differences in uptake kinetics can be explained by the larger size of cyclohexane as compared with benzene. It was further shown that the uptake of norbornadiene in the chloride containing cage ($K = 2.02 \times 10^3$ L mol$^{-1}$, $k$ = (2.15 ± 0.04) × $10^{-4}$ s$^{-1}$) is thermodynamically favored and 12 times faster than the uptake of the same guest inside the bromide containing cage ($K$ = 1.20 × $10^3$ L mol$^{-1}$, $k$ = (1.73 ± 0.14) × $10^{-5}$ s$^{-1}$) (Figure 5b). A plausible explanation lies in the fact that the central cavity of $[2Cl@Pd_4L_8]$ is larger than that of $[2Br+BF_4@Pd_4L_8]$, since chloride is smaller than bromide.

Finally, we examined the relative binding affinity of the halide anions in the outer pockets prior to and after encapsulation of a neutral guest by a Ag(I) back-titration experiment.[9] While the addition of 2 equiv of $AgBF_4$ to $[2Br+BF_4@Pd_4L_8]$ led to an immediate regeneration of $[3BF_4@Pd_4L_8]$, the chloride anions in $[2Cl@Pd_4L_8]$ could not be removed with Ag(I) cations, even after the addition of 50 equiv of $AgBF_4$ and heating the sample to 70 °C for 24 h. This hints at an enormous binding constant for chloride (SI). Interestingly, the inclusion of a neutral guest inside the central pocket changed the behavior of the bromide containing system, since addition of Ag(I) cations did not result in the immediate removal of the bromide anions. This is a kinetic effect, since subsequent heating of this sample to 70 °C overnight led to a regeneration of cage $[3BF_4@Pd_4L_8]$. This phenomenon is illustrated in Figure SI 24 with a 1:1 mixture of the species $[2Br+BF_4@Pd_4L_8]$ and $[2Br+norbornadiene@Pd_4L_8]$.

In conclusion, we present a self-assembled host that is able to encapsulate a variety of small neutral guest molecules after being


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activated by a chemical signal.[15] The addition of halide anions triggers a mechanical process, a compression of the double cage along the $Pd_4$-axis, that prepares the central cavity for the subsequent inclusion of the guest. Vice versa, the neutral guest kinetically stabilizes the halide anions in the outer pockets.

We expect that the research on chemical signal processing,[16] molecular machines,[17] and reactions inside confined environments[18] will benefit from such self-assembled host systems with fine-tunable switching characteristics.

## ■ ASSOCIATED CONTENT

### Supporting Information

Synthetic procedures, further NMR, MS, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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