Photoswitching

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Light-Triggered Guest Uptake and Release by a Photochromic Coordination Cage**

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The selective encapsulation of guest compounds by discrete, molecular-scale cages has been applied to various separation and purification tasks,[1] the capturing of hazardous chemicals,[2] the stabilization of reactive intermediates,[3] and the realization of sensing systems.[4] A prerequisite for all these applications is strong binding between the host and the particular guest compound. Certain other applications, however, necessitate dynamic control over the strength of the host–guest interaction. In particular, systems designed for the uptake, delivery, and release of cargo[5] (such as drugs or site-specific markers for bioimaging purposes) require temporal and spatial control over the localization of the guest molecules either inside or outside of the host cavity. Furthermore, the action of such control mechanisms may help to overcome one central limitation imposed on the field of supramolecular catalysis in confined cavities, that is, product inhibition.[6,7] A desirable strategy would be one in which the cage itself is enabled to control the presence or absence of guests inside its interior, most preferably triggered by a waste-free external stimulus, such as light.[8]

We[9] and others[10] have previously demonstrated that light can be used to reversibly control encapsulation processes of guests whose structure is based on photoswitchable compounds, such as azobenzene.[11] This approach, however, is of rather limited benefit for the aforementioned tasks, as it requires specially designed guest molecules. Equipping the host with a light-switchable structural element, however, allows the application of the principle of light-triggered guest uptake and release to a broader scope of guest species.[12] Pioneering work in this field was conducted by Irie,[13] Shinkai,[14] and Erlanger.[15] Later examples include hosts such as calixarenes,[16] cyclodextrines[17] as well as (supra)-molecular ring compounds[18] and tweezers.[19] Light-switchable coordination cages, however, have not yet been realized to the best of our knowledge.[20]

Herein we introduce a new metal–organic cage[21] composed of two square-planar-coordinated Pd^{2+} ions and four bis-monodentate pyridyl ligands[22] based on a dithienylethene (DTE) photoswitch.[23]

Ligand *o*-**L** was synthesized from perfluoro-1,2-bis(2-iodo-5-methylthien-4-yl)cyclopentene[24] and 3-ethinylpyridine by a Sonogashira cross-coupling reaction. The ligands can be reversibly interconverted between a conformationally

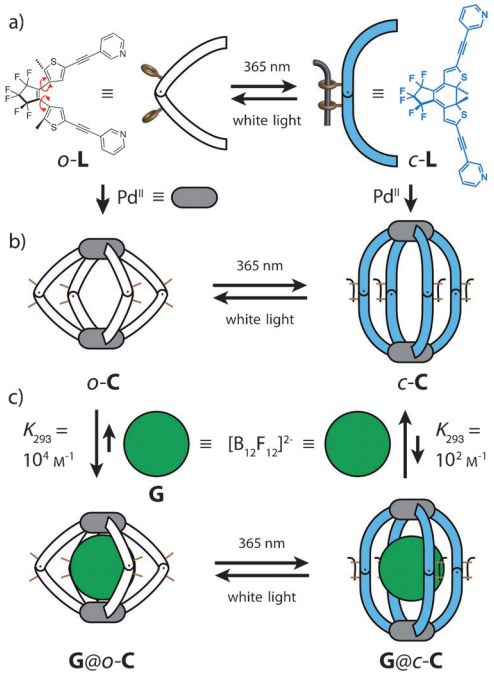

Figure 1. a) The conformationally flexible bis-monodentate pyridyl ligand *o*-**L** based on a dithienylethene (DTE) photoswitch is converted into its rigid closed-ring isomer *c*-**L** upon irradiation at 365 nm. The process can be fully reversed by irradiation with white light. b) Addition of stoichiometric amounts of Pd^{II} leads to quantitative formation of coordination cages *o*-**C** = $[Pd_2(o\text{-}L)_4](BF_4)_4$ and *c*-**C** = $[Pd_2(c\text{-}L)_4](BF_4)_4$, which again can be interconverted by the described photochemical processes. c) Both cage isomers can encapsulate the spherical guest **G** = $[B_{12}F_{12}]^{2-}$. Complex **G**@*o*-**C** is formed by the dynamic host *o*-**C** with much higher yield than **G**@*c*-**C** is formed from the rigid host *c*-**C**. Thus, irradiation of the host–guest complexes results in the reversible uptake and release of the guest.

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flexible open-ring form (*o*-**L**) and a rigid closed-ring form (*c*-**L**) by irradiation with UV light (365 nm) or white light, respectively (Figure 1a). ^{1}H NMR monitoring of the photocyclization in CD_3CN shows that the conversion of the pale yellowish *o*-**L** isomer into the intensely blue-colored *c*-**L** isomer is high yielding and that *o*-**L** can be fully regenerated by irradiation with white light (Figure 2). Upon formation of the closed-ring isomer *c*-**L**, the signal of the thiophene proton H_e undergoes an upfield shift ($\Delta\delta = -0.73$ ppm) whereas the methyl signal H_f shifts downfield ($\Delta\delta = 0.20$ ppm; Supporting Information).

By heating a 2:1 mixture of either ligand *o*-**L** or *c*-**L** with $[Pd(CH_3CN)_4](BF_4)_2$ in CD_3CN, the cage complexes $[Pd_2(o\text{-}\mathbf{L})_4](BF_4)_4$ (*o*-**C**) and $[Pd_2(c\text{-}\mathbf{L})_4](BF_4)_4$ (*c*-**C**) were formed quantitatively, as confirmed by ^{1}H NMR spectroscopy (Figure 2). All of the ^{1}H NMR signals of the ligand pyridine

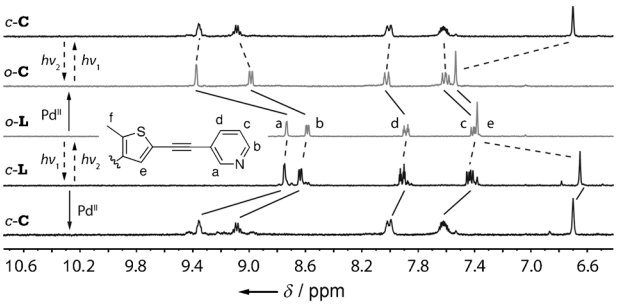

Figure 2. ^{1}H NMR spectra (300 MHz, CD_3CN, 293 K) of ligands *o*-**L**, *c*-**L** and cages *o*-**C**, *c*-**C**.

and thiophene rings were significantly shifted downfield upon complexation with the Pd^{2+} ions in both cases. The FTICR ESI mass spectrum of *o*-**C** exhibits a series of peaks corresponding to the species $[o\text{-}\mathbf{C}]^{4+}$, $[o\text{-}\mathbf{C} + BF_4]^{3+}$, and $[o\text{-}\mathbf{C}+2BF_4]^{2+}$, all of which show experimental isotopic patterns in perfect agreement with the calculated isotope distributions (Figure 3a). In accordance with the free-ligand photochemical behavior, the cage complexes *o*-**C** and *c*-**C** could also be reversibly interconverted by irradiation with UV and white light, respectively. Again, ^{1}H and ^{19}F NMR spectroscopy confirmed the smooth isomerization without observing any signs of photodegradation (Figure 2 and Supporting Information), as did the UV/Vis spectroscopic characterization (Figure 4a).[25]

Further to the significant chemical shifts observed upon the formation of cage compound *c*-**C**, a splitting of each of the pyridyl signals H_a, H_b, H_c, and H_d into three sets of integral ratio 1:2:1 was observed in the ^{1}H NMR spectrum (Figure 2 and Supporting Information). Furthermore, the ^{13}C NMR spectrum allowed the differentiation of at least five peaks for some of the pyridine carbon atoms (Supporting Information). The splitting of the ^{1}H NMR signals is small and only observable in case of the rigid cage photoproduct *c*-**C** but not for the conformationally flexible compound *o*-**C**, even at a spectrometer frequency of 900 MHz. Semiempiric (PM6) as well as DFT (B3LYP/LANL2DZ) gas-phase geometry optimizations of all four possible cage diastereomers (two *meso*-

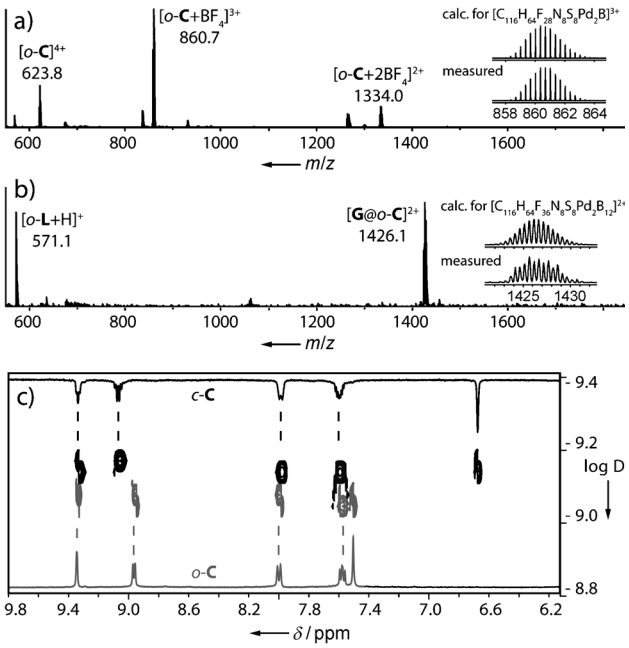

Figure 3. ESI mass spectra of a) *o*-**C** and b) [**G**@*o*-**C**]. c) Superimposed DOSY spectra show the size difference between *o*-**C** and *c*-**C**.

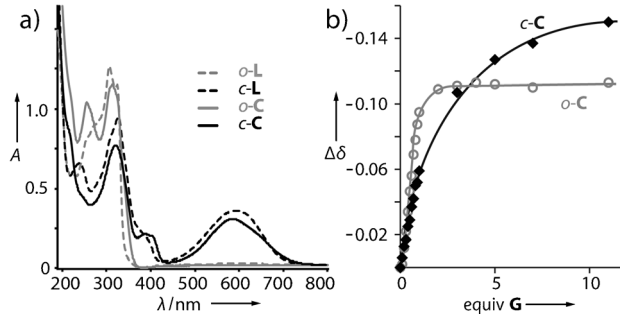

Figure 4. a) UV/Vis spectra of *o*-**L**, *c*-**L**, *o*-**C**, and *c*-**C**. b) Binding isotherms at 293 K of the encapsulation of $[B_{12}F_{12}]^{2-}$ (**G**) by *o*-**C** and *c*-**C**.

forms *PPMM* and *PMPM* and two pairs of enantiomers *PMMM*/*MPPP* and *PPPP*/*MMMM*) that differ in the chirality (*P* or *M*) of the C_2-symmetric ligands *c*-**L** occupying the four positions around the two metal centers indicate that all tetracationic isomers of *c*-**C** are energetically comparable within about 3 kJ mol^{-1}. Similar results were obtained for the corresponding isomers of *o*-**C**. We thus assume that *o*-**C** consists of a mixture of all possible stereoisomers being in fast exchange with respect to the NMR timescale. Since de- and re-coordination of the pyridine ligands to the palladium cations is a process that operates on a timescale of several minutes in acetonitrile at room temperature,[26] we suggest that equilibration takes place by rotations around the C–C bonds connecting the thiophene rings with the central cyclopentene ring in *o*-**C** (red arrows in Figure 1a). Upon irradiation with UV light, the photocyclization reaction transforms the complete set of isomers into their closed-ring forms *c*-**C** in which isomerization by bond rotation is no longer possible. Thus, the individual cage isomers become

distinguishable in the NMR spectra. Although the resolution at 900 MHz does not allow a signal assignment to all the isomers, a plausible explanation for the occurrence of the observed splitting patterns, NOESY contacts, and HSQC relationships could be derived based on statistical considerations (Supporting Information).

Solvent diffusion of *o*-dichlorobenzene into an acetonitrile solution of *o*-**C** led to the isolation of yellowish crystals suitable for single-crystal X-ray structure determination, which allowed us to unambiguously prove the constitution of cage *o*-**C** prior to irradiation (Figure 5 and Supporting Information). Surprisingly, the solid-state structure represents only one of the four postulated stereoisomers, as confirmed by the coincident results obtained from the crystallographic examination of two individual crystalline samples of *o*-**C**. The found form is the *meso*-isomer *PPMM* of overall C_{2h} symmetry consisting of both of the enantiomeric ligands. The resulting cage structure is not chiral and thus the crystallization proceeds under conditions of chiral self-discrimination.[27] The four BF_4^- counterions per cage are located near to either side of the {Pd(pyridine)$_4$} planes (minimal Pd–F distance = 3.08 Å), which is in good accord with our previous findings for related cage structures.[22] One of the side-views of the structure (Figure 5b) clearly shows that the overall shape of the cage is skewed in the sense that the normal vectors of the two {Pd(pyridine)$_4$} planes are parallel but not congruent. This tilted conformation might be the result of crystal packing effects, but it also indicates the conformational flexibility of the backbone structure of ligand *o*-**L**. This is further supported by an analysis of the dihedral angles between the two cyclopentene–thiophene *C*–*C* bonds in each of the four ligands that differ between 42 and 48° in the X-ray structure. In contrast, the DFT-optimized structure of the corresponding rigid, closed-ring isomer *PPMM*-*c*-**C** is not skewed, meaning that the Pd–Pd axis is orthogonal to both of the {Pd(pyridine)$_4$} planes (Supporting Information).

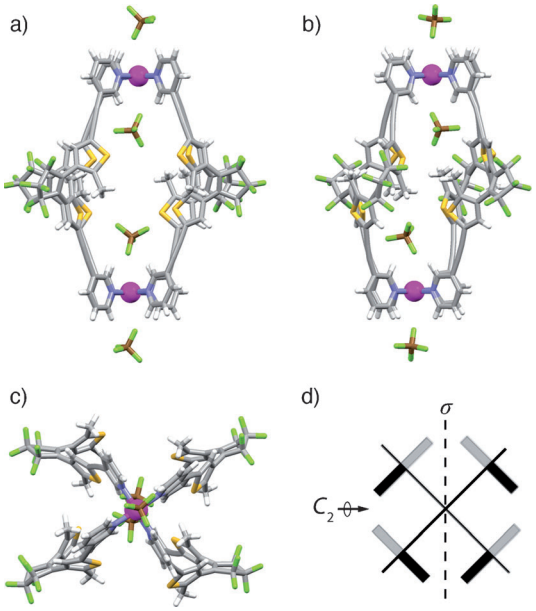

Figure 5. a)–c) X-ray structure of cage *o*-**C** shown from different perspectives (C gray, H white, N blue, B brown, F green, S yellow, Pd purple; solvent molecules have been omitted). d) Depiction of the stereochemical relationships between the four ligands viewed from the top (black/gray bars: close/remote methyl groups).

Next, we performed diffusion-ordered spectroscopy (DOSY) NMR measurements to gain insight into the solution structure of the photoisomers *o*-**C** and *c*-**C** in terms of their hydrodynamic radii r_h. Figure 3c clearly demonstrates that the two isomeric species differ significantly in size ($r_{h,o\text{-}\mathbf{C}}$ = 7.04 Å, $r_{h,c\text{-}\mathbf{C}}$ = 8.67 Å) as a result of the photocyclization of the four ligand backbones. Intriguingly, the open-ring cage *o*-**C** is smaller than its closed-ring isomer *c*-**C**, an observation that can be explained again by the conformational flexibility of *o*-**C** in contrast to the rigid and stretched structure of *c*-**C** (compare the representations in Figure 1).

The ability to reversibly switch between two different cage sizes prompted us to study the anion encapsulation capabilities of the cationic cages *o*-**C** and *c*-**C** by ^{1}H and ^{19}F NMR titrations in CD_3CN. We chose the dodecafluorododecaborate anion **G** ($[B_{12}F_{12}]^{2-}$) as a guest molecule owing to its appropriate size, spherical shape, and negative charge.[28] Indeed, the stepwise addition of **G** to *o*-**C** or *c*-**C** resulted in significant signal shifts of the cage protons in both cases. In particular, the inward-pointing protons H_a were shifted significantly upon guest encapsulation. The observed upfield shift is surprising in comparison with the downfield shifts reported for the pyridine H_a protons of similar cage compounds upon binding of halide[22i] or sulfonate anions[29] near their {Pd(pyridine)$_4$} planes. We assume that the replacement of hydrogen-bonded acetonitrile solvent molecules by the large spherical $[B_{12}F_{12}]^{2-}$ anion carrying two delocalized charges is responsible for the upfield shifts observed in this case. In the ^{19}F NMR spectra of **G**@*o*-**C**, the encapsulated guest shows slow exchange with a resonance signal at −264.2 ppm, which is 5.2 ppm downfield from the signal of free $[B_{12}F_{12}]^{2-}$ and of similar magnitude than our previously reported value for the ^{19}F NMR downfield shift of encapsulated BF_4^-.[22i] Furthermore, the largest peak in the high resolution ESI mass spectrum of a mixture of **G** and *o*-**C** can be unambiguously assigned to $[\mathbf{G}@o\text{-}\mathbf{C}]^{2+}$, which further supports the formation a 1:1 host–guest complex (Figure 3b).

Next, we determined the association constants of the host–guest complexes **G**@*o*-**C** and **G**@*c*-**C** from the titration data by non-linear regression methods (Figure 4b and Supporting Information).[30] Most interestingly, cage *o*-**C** shows a much stronger affinity for **G** ($K_{293} = 3.2 \times 10^4\,M^{-1}$) than cage *c*-**C** ($K_{293} = 6.7 \times 10^2\,M^{-1}$). Furthermore, the described photoswitching was also found to be possible in the host–guest system, thereby allowing us to reversibly control the mole fraction of the bound guest by using light as an external stimulus. One plausible explanation for this significant difference in guest binding strength is based on the structural flexibility of cage *o*-**C**, which is thought to be able to closely surround guest **G** in the fashion of an induced fit (thereby minimizing the Pd^{2+} anion distance), whereas the rigid cage *c*-**C** is not able to structurally adapt to the guest. Van't Hoff analysis of the temperature-dependence of the

association constants between 273 and 333 K, however, showed that the encapsulation process is entropy-driven ($\Delta S°_{o\text{-}\mathbf{C}} = 187\ \mathrm{J\,K^{-1}\,mol^{-1}}$, $\Delta S°_{c\text{-}\mathbf{C}} = 56\ \mathrm{J\,K^{-1}\,mol^{-1}}$) and endothermic ($\Delta H°_{o\text{-}\mathbf{C}} = 30\ \mathrm{kJ\,mol^{-1}}$, $\Delta H°_{c\text{-}\mathbf{C}} = 0.6\ \mathrm{kJ\,mol^{-1}}$) in both cases, which indicates that the effect of solvent release from the interior of the cages indeed governs the driving force of the encapsulation processes.

In summary, we have shown that a photochromic coordination cage, which quantitatively self-assembles from four ligands based on a DTE photoswitch can be smoothly interconverted between a structurally flexible form *o*-**C** and a rigid form *c*-**C** by irradiation with UV or white light, respectively. The associated modulation of the affinity for anionic guests might find applications in fields such as supramolecular catalysis, drug delivery (for example in boron neutron-capture therapy, BNCT)[31] and functional constructs that are based on the control by external stimuli such as switchable receptors and molecular machines.[32] Currently, we are studying the effects of varying the solvent and counterions as well as the structure of the cage and the guests on the encapsulation thermodynamics.

Experimental Section

The synthesis of ligands *o*-**L** and *c*-**L** is described in the Supporting Information. Cage complex *o*-**C** was quantitatively obtained by treating ligand *o*-**L** (6.85 mg, 12 μmol, 1 equiv) with $[Pd(CH_3CN)_4](BF_4)_2$ (2.67 mg, 6 μmol, 0.5 equiv) in acetonitrile at 70 °C for 1 h. Photocyclization was carried out by irradiating the solution of *o*-**L** and *o*-**C** with UV light of 365 nm until NMR analysis indicated completion of the reaction. Reconversion into the open-ring forms was achieved using white light ($\lambda > 600$ nm). Single crystals of *o*-**C** (BF_4^- salt) suitable for X-ray structure determination were obtained from acetonitrile solution by *o*-dichlorobenzene diffusion. CCDC 900746 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data are available in the Supporting Information. The host–guest complexes were prepared by titrating a CD_3CN solution of the guest **G** (30 mM $(NBu_4)_2B_{12}F_{12}$) into 600 μL of the cage solutions (1 mM) of *o*-**C** and *c*-**C**, respectively.

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