Chiral Self-Discrimination and Guest Recognition in Helicene-Based Coordination Cages

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Abstract: Chiral nanosized confinements play a major role for enantioselective recognition and reaction control in biological systems. Supramolecular self-assembly gives access to artificial mimics with tunable sizes and properties. Herein, a new family of [Pd₂L₄] coordination cages based on a chiral helicene backbone is introduced. A racemic mixture of the bis-monodentate pyridyl ligand L¹ selectively assembles with Pd⁺ cations under chiral self-discrimination to an achiral meso cage, cis-[Pd₂L¹⁺](BF₄)₂. Enantiopure L¹ forms homochiral cages [Pd₂L¹⁺]M. A longer derivative L² forms chiral cages [Pd₂L²⁺]M with larger cavities, which bind optical isomers of chiral guests with different affinities. Owing to its distinct chiroptical properties, this cage can distinguish non-chiral guests of different lengths, as they were found to squeeze or elongate the cavity under modulation of the helical pitch of the helicenes. The CD spectroscopic results were supported by ion mobility mass spectrometry.

Nanomized cages based on metal-supramolecular self-assembly have become major players in host-guest chemistry owing to their structural and functional variability and modular composition. Recent design-based approaches allow the positioning of multiple building blocks by thermodynamically controlled integrative self-sorting. In biological host-guest systems, enantioselective recognition plays a pivotal role because of the inherent homochirality of most natural compounds. Hence, the formation of synthetic chiral hosts for enantioselective guest binding is not only of fundamental interest, but provides the basis for the development of selective sensors, transporters, and catalysts.

Numerous chiral hosts based on covalent macromolecular molecules such as cyclodextrins, cyclophanes, and calixarenes have been reported. Chirality has also been reported to facilitate the assembly of hydrogen-bonded organic cages. More recently, chiral metallo-supramolecular self-assembled rings and cages have been introduced as selective receptors and enzyme-like nanoreactors based on chiral backbones, auxiliaries, the inherent chirality of stereogenic metal centers, or the overall architecture. Upon metal coordination, racemic mixtures of ligands may undergo chiral self-sorting, leading to homochiral or heterochiral assemblies. Beyond their use in enantioselective recognition, chiral cages based on luminescent metal centers have been shown to exhibit unique chiroptical properties. With respect to mechanically interlocked coordination cages, covering the implementation of homochirality are still scarce, with Hardie’s dimer of cyclotrimeravatrylene-based coordination cages serving as a notable example.

Since their discovery in 1912, helicenes have been widely studied for properties related to their helical chirality. While helicenes have shown appearance in several supramolecular systems, they have never been used in the construction of coordination-driven cages. We herein demonstrate that despite their highly twisted appearance, helicene-based bis-monodentate ligands can be used to assemble discrete [Pd₂L₄] coordination cages exhibiting chirality-driven effects on their assembly and guest binding. We further report the first example of a homochiral inter-penetrated [Pd₂L₄] dimer, comprising eight interlocked helicenes.

Ligands L¹ and L² were synthesized by Sonogashira cross-coupling reactions from literature-known 2,15-dibromo[6]helicene (Figure 1) to yield racemic products, which were separated into the enantiomers by chiral HPLC (see the Supporting Information, Figure S23). Following our previously reported routines, the bis-monodentate ligands were tested for the formation of self-assembled products using [Pd(CH₃CN)₄](BF₄)₂ as the metal source in different polar organic solvents. Interestingly, in deuterated dimethyl sulfoxide (DMSO), the racemic mixture of ligand L¹ was found to quantitatively assemble under chiral self-sorting into the achiral meso cage cis-[Pd₂L¹⁺L¹⁺] (CIₚₘeso), containing both ligand enantiomers in a 1:1 ratio, as confirmed by ¹H NMR spectroscopy (Figure 4b). For all herein described cages, the ¹H NMR signals of the pyridine moieties (i.e., protons Hₐ and H₉) undergo a downfield shift upon coordination to the palladium(II) cations. The formation of the meso cage leads to splitting of all ¹H NMR resonances into two sets of equal intensity. All resonances could be assigned with the help of 2D NMR techniques (COSY, NOE, HSQC), indicating that the upper and lower halves of ligand L¹ have ended up in a different surrounding upon cage formation (see the Supporting Information). The resonance splitting can be explained by symmetry considerations. The halves of the P-helicenes and the halves of the M-helicenes facing each other have the same chemical surrounding, which results in the same chemical shifts for...
would offer two C axes perpendicular to the major C axis going through both Pd centers, which would allow converting the upper half of each ligand into its lower part (Figure S7).

In contrast, assembly with the enantiopure ligand L², in either its P or M form, leads to a homochiral cage with no splitting of the ¹H NMR signals (Figure 2c). In their high-resolution ESI mass spectra, cage C¹⁺⁺⁺⁺ (Figure S9) and the enantiopure cages C¹⁺⁺⁺ (Figure S11) could be identified as tetracationic [Pd₄L²⁺⁺⁺⁺]⁺⁺⁺⁺.

Next, chiral guest discrimination of C¹ was tested with (1R)- and (1S)-camphorsulfonate anions (G¹R and G¹S); however, no evidence for uptake of the guests was found (Figure S21). The most probable reason is the limited size of the cavity, known as a critical factor for guest binding.[10] To permit guest encapsulation, the ligand structure was extended by including 1,4-phenylene linkers on both sides to give ligand L². The elongation of the ligands nearly doubles the Pd–Pd distance in the modeled structures (DFT oB97XD/def2SVP, PCM solvent: DMSO) of C²⁻⁻⁻⁻ (20.1 Å; Figure 4d) compared to C¹⁺⁺⁺⁺ (10.4 Å; Figure 4c). In case of racemic L², cage formation leads to the splitting of all ¹H NMR resonances into several sets, which is indicative of a lack of chiral self-sorting under formation of a statistical mixture of isomeric species (Figure 2d). This picture is supported by the clean appearance of the high-resolution ESI mass spectrum of this mixture, showing only peaks assignable to the tetracationic [Pd₄L²⁺⁺⁺⁺]⁺⁺⁺⁺ species, which is superimposable with the spectrum of the homochiral cage C²⁺⁺⁺⁺ (Figure S14). The absence of chiral self-discrimination upon cage formation from racemic L² can be explained with the increased distance between the helicene backbones (based on the calculated structures of cages C¹ and C², the closest H–H distance between two neighboring backbones has increased from 2.39 Å to 6.20 Å).

In contrast to the results obtained in DMSO, heating the enantiopure ligand L² with palladium(II) cations in acetonitrile was found to lead to a splitting of all NMR resonances into two sets of equal intensity, thus indicating the formation of a chiral interpenetrated cage DC²⁺⁺⁺⁺ (Figure 2g). In addition, the high-resolution ESI mass spectrum contained signals for the dimeric species [3BF⁴@Pd₂L²⁺⁺⁺⁺]⁺⁺⁺⁺ (Figure 3c).

Further structural insight was obtained by X-ray diffraction methods. Crystals of enantiopure L² (second HPLC fraction eluted from a Chiralpak IC column) suitable for X-ray structure analysis were obtained by crystallization from DMSO (Figure 4e). The asymmetric unit contains twelve individual helicene ligands, all of which are highly intertwined in a remarkably unordered fashion (Figure S25). The absolute configuration was unambiguously determined as the P enantiomer using the method of Parsons[29] as implemented in SHELXL,[31] yielding an enantiopurity-distinguishing parameter of χ = 0.079(8). This assignment is in agreement with the recorded circular dichroism (CD) spectra of this compound as compared to published data on similarly substituted [6]helicenes and DFT-calculated CD bands.[32,33]

Single crystals of the dimeric cage species [2PF⁶@Pd₁L¹M⁺] (DC¹M⁺, based on the M ligand enantiomer eluting first from the chiral column) that were suitable for X-ray structure analysis were obtained by slow diffusion of diethyl ether into an acetonitrile solution of the cage containing PF⁶⁻ counter-
anions (Figure 4f). Synchrotron radiation was required to obtain diffraction data that could be solved with direct methods using SHELXT.\textsuperscript{[24]} Again, the absolute configuration could be unambiguously determined, yielding an enantiopurity-distinguishing parameter of $\delta = 0.02(2)$. The CD data were found to be in agreement with the literature-reported absolute structure assignment of comparable helicenes.\textsuperscript{[22,23]}

The structure reveals that the double cage features three consecutive pockets, with the two outer ones filled with a PF$_6$ anion each. The Pd–Pd distances are 8.66 Å for the outer pockets and 10.33 Å for the inner cavity.

With the large cavity of monomeric C$_2$P/M, chiral guest discrimination could be shown for the enantiopure cages by $^1$H NMR titration experiments by stepwise addition of camphorsulfonates G$_1^R$ and G$_1^S$ as their tetrabutylammonium salts. Characteristic downfield shifts for the inside-pointing proton resonance Ha were observed (Figure S22), and the results were summarized as a comparison of binding isotherms (Figure 5c). Pleasingly, both guest enantiomers showed different binding behavior when exposed to the same chiral cage; however, the combination G$_1^R$@C$_2^P$ showed the same behavior as the enantiomeric system G$_1^S$@C$_2^M$, with binding constants of around 560 M$^{-1}$.\textsuperscript{[25]} The diastereomeric combinations to this, G$_1^R$@C$_2^M$ and G$_1^S$@C$_2^P$, showed a stronger extent of NMR signal shifting and a binding constant of approximately 1010 M$^{-1}$. In the high-resolution ESI mass spectra, the host–guest complexes could be identified as the triple cationic species [G$_1$@Pd$_2$L$_2$]$^{3+}$ (Figure 3b).

**Figure 3.** ESI mass spectra of: a) cage C$_1^M$, b) cage C$_2^M$ after addition of (1R)-camphorsulfonate G$_1^R$, and c) double cage DC$_2^P$.

**Figure 4.** a) DFT-calculated structure of C$_1^meso$. b) NOESY NMR detail of the C$_1^meso$ cage supporting the cis ligand arrangement. c, d) Calculated structures of C$_1^P$ and C$_2^P$. e) One of twelve L$_2$P molecules in the asymmetric unit of its solid-state structure with the found minimum/maximum helical pitches. f) X-ray crystal structure of DC$_2^P$, side and top view along the Pd$_4$ axis. Pd gray, N blue, C green (M enantiomer) and red (P enantiomer), P orange, F light green.

**Figure 5.** a) Circular dichroism spectra of ligands L$_2$P/M and cages C$_2^P$. b) Difference CD spectra (free host CD spectra subtracted from the host–guest CD spectra) of G$_2$@C$_2^P$ and G$_3$@C$_2^P$ as well as G$_4^{trans}$@C$_2^P$ and G$_4^{cis}$@C$_2^P$ (all in DMSO). c) Comparison of the binding isotherms for all four diastereomeric host–guest combinations G$_1$@C$_2^P/M$ showing two “matched” and two “mismatched” cases. d) Superposition of the mobilograms obtained by trapped ion mobility ESI-TOF mass spectrometry for host–guest complexes G$_2$@C$_2^P$ (mobility 1/K$_c$: 1.736 Vs cm$^{-2}$, CCS: 701 Å$^2$ at m/z 1615.4) and G$_3$@C$_2^P$ (mobility 1/K$_c$: 1.745 Vs cm$^{-2}$, CCS: 705 Å$^2$ at m/z 1627.9).
Furthermore, CD spectra were compared for L\textsuperscript{PM} and C\textsubscript{1}P\textsubscript{M} (Figure S24) and L\textsuperscript{PM} and C\textsubscript{2}P\textsubscript{M} (Figure 5a), showing strong circular dichroism for the ligands and the cages with a positive Cotton effect for the \textit{P} enantiomers. We next set out to investigate the potential utilization of the strong CD effect as an indicator for the discrimination of achiral guests. As the cages consist of four helicenes arranged like parallel springs around two connecting Pt\textsuperscript{4} cations, we envisioned that charged guests encapsulated between these electrostatic anchors should modulate the helical pitch of the ligand backbones. First, we compared the effect of binding short 2,7-naphthalenedisulfonate G\textsubscript{2} and long 4,4'-biphenyldisulfonate G\textsubscript{3} on the CD spectra of C\textsubscript{2}P\textsubscript{M}. Difference spectra revealed that encapsulation of the shorter guest led to a decrease in the intensity of the CD band at approximately 360 nm while binding of the longer guest increased the intensity of the same band (Figure 5b). The assumption that such an effect is caused by tuning of the helical pitch of the helicenes was predicted by theoretical work of Morii, Inoue, and Nakai.\textsuperscript{[22]} We were able to confirm this hypothesis by calculating the relative CD signal intensities of unsubstituted [6]helicene under variation of its helical pitch within the limits found in the twelve individual ligands contained in the solid-state structure of L\textsubscript{1} (Figure S26 and Figure 4e).

Furthermore, direct evidence for a shrinking and expansion of the cages upon addition of the short and long guests, respectively, came from trapped ion mobility ESI-TOF mass spectrometry (timsTOF), which indicated a smaller gas phase collisional cross-section for L\textsubscript{PM} and [Pd(CH\textsubscript{3}CN)\textsubscript{4}][(BF\textsubscript{4})\textsubscript{2}] (0.5 equiv) to the corresponding ligands (racemic or enantiopure) in DMSO at 23°C. Cage DC\textsubscript{2} was formed after heating C\textsubscript{2} in MeCN at 75°C for 2 weeks. Single crystals suitable for X-ray structure determination were grown for L\textsubscript{2}P and DC\textsubscript{2}P by slow diffusion of Et\textsubscript{2}O into a mixture of L\textsubscript{PM} and [Pd(CH\textsubscript{3}CN)\textsubscript{4}][(PF\textsubscript{6})\textsubscript{2}] in MeCN at 7°C. CCDC 1585206 (L\textsubscript{2}P) and 1581540 (DC\textsubscript{2}P) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** anion recognition · chirality · host–guest chemistry · interpenetration · supramolecular chemistry

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