Design of Metal-Organic Assemblies via Shape Complementarity and Conformational Constraints in Dual Curvature Ligands


DOI
10.31635/ccschem.023.202302940

Publication date
2023

Document Version
Final published version

Published in
CCS Chemistry

License
CC BY-NC

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (https://dare.uva.nl)
Design of Metal–Organic Assemblies via Shape Complementarity and Conformational Constraints in Dual Curvature Ligands

Cui-Lian Liu1, Eduard O. Bobylev2, Sébastien Dauriac1, Brice Kauffmann3, Koen Robeyns1, Yann Garcia1, Joost N. H. Reek2 & Michael L. Singleton1*

1Institute of Condensed Matter and Nanosciences, Université catholique de Louvain, Louvain-la-Neuve 1348, 2Van’t Hoff Institute for Molecular Sciences, University of Amsterdam, Amsterdam 1098 XH, 3Université de Bordeaux CNRS, INSERM, UMS3033, Institut Européen de Chimie et Biologie (IECB), 33600 Pessac

*Corresponding author: m.singleton@uclouvain.be

Cite this: CCS Chem. 2023, 5, 2506–2518
DOI: 10.31635/ccschem.023.202302940

While common in biological systems, building blocks with low symmetry and flexibility pose numerous problems for synthetic self-assembly, such as the formation of isomers of assemblies that are difficult to distinguish and purify. In this work, three aromatic amide-based ligands (L1–L3) with a central 1,8-diazatriptycene core were designed and used for self-assembly with Pd2+. While hundreds of stereoisomers based on the conformational flexibility around the amides and the unsymmetrical nonplanar structure of the core are possible upon coordination with the metal, the constraints designed into the ligands direct the self-assembly toward only a single Pd2L4 cage (L1) or Pd4L8 double-walled metallomacrocycle (L2) structure, even in mixtures of the ligands. This structural approach and the modularity of the ligand synthesis affords ready access to deep cavitands with endohedral functionalization (L3). These results highlight the potential of this new design strategy and open the door to selectively functionalized cavity-based architectures for numerous applications.

Keywords: metal–organic cageopis, isomer selectivity, low-symmetry ligands, self-sorting, self-assembly

Introduction

Self-assembly and folding play essential roles in the complexity and function of proteins. In recent decades, the possibility of generating synthetic molecules with similar complexity and functions has inspired significant progress in the design of self-assembled cavitands. While numerous strategies for the self-assembly of such structures have been developed, the combination of organic ligands and metal ions for the formation of metal–organic architectures has emerged as a highly promising approach. Notably, the combination of Pd2+ or Pt+ with ditopic ligands for the formation of MnL2n structures has attracted substantial attention and led to some of the largest well-defined systems. A wide range of applications related to their cavities has been reported, including sensing, catalysis, drug delivery, storage, and molecular recognition.

Unlike synthetic building blocks, the folding of peptides leads to subunits for self-assembly that have not only complex electrostatic potential surfaces but also a wide diversity of shapes. The resulting high
complementarity between different subcomponents allows for the selective self-assembly of different units into complex asymmetric architectures. By contrast, the majority of synthetic strategies for coordination-driven self-assembly rely on rigid ligands with high, often planar, symmetry. This can be readily seen in $\text{M}_n\text{L}_2^n$ assemblies. The ligands are most commonly curved organic molecules where $N$-heterocyclic donor groups are connected by flat aromatic or alkyne spacers, the rigidity of which allows the angle between coordination sites, the bend angle, to be well-defined. This offers numerous advantages, such as allowing good prediction of the final self-assembled structures and clean formation of single species. Still, the use of lower symmetry ligands allows additional shape complementarity between ligands to help direct self-assembly, ultimately leading to new design strategies and more complex structures. In the last decade, a number of elegant approaches relying on enhanced shape complementarity for controlling self-assembly have been described, such as combining two different ditopic ligands with compatible convergent and divergent bend angles or the use of coordination sphere engineering. The latter uses additional functional groups included near the coordination sites on the ligands to provide complementarity through interligand steric or electrostatic interactions. However, these approaches still largely rely on rigid or symmetric building blocks, with at least one of these properties usually being constrained to help direct self-assembly. Indeed, self-assembly with low symmetry and flexible building blocks is more challenging but represents an important approach to obtaining more complex and functional structures. For example, unprecedented topological nanostructures have been afforded through cooperative peptide self-folding and metal-induced self-assembly.

Recently, we succeeded in using heteroaromatic amide-based ligands for the self-assembly of multiple $\text{Pd}_n\text{L}_2^n$ ($n = 2, 6, \text{or } 12$) metal–organic cages capable of neutral guest discrimination. The latter uses additional functional groups included near the coordination sites on the ligands to provide complementarity through interligand steric or electrostatic interactions. However, these approaches still largely rely on rigid or symmetric building blocks, with at least one of these properties usually being constrained to help direct self-assembly. Indeed, self-assembly with low symmetry and flexible building blocks is more challenging but represents an important approach to obtaining more complex and functional structures. For example, unprecedented topological nanostructures have been afforded through cooperative peptide self-folding and metal-induced self-assembly.

Figure 1 | (a) Design of aromatic amide-based dual curvature ligands for coordination-driven self-assembly via Diels–Alder reaction with diazaanthracenes. This breaks the ligand symmetry and introduces additional shape complementarity as seen in the DFT-calculated structures of (b) flat versus dual curvature ligands. (c–e) The structure of ligands $\text{L}_1$–$\text{L}_3$ and their self-assembled products. For (c), the cartoon for isomer A corresponds to the crystal structure shown in Figure 2e. The potential competitive interactions of the endohedral carboxylic acid are shown in the inset.

DOI: 10.31635/ccschem.023.202302940
Citation: CCS Chem. 2023, 5, 2506–2518
Link to VoR: https://doi.org/10.31635/ccschem.023.202302940
ligands are predominately flat and offer only limited interactions between ligands for the self-assembly of metal-organic cages. In fact, this is seen in the majority of ligands used for M₄L₄–₈ assemblies. Modification of the surface of the flat aromatic units to include perpendicularly interacting units is a challenge. However, this can be the fastest way to direct groups toward other ligands for designing interligand interactions and shape complementarity. We have recently shown that the large diazaanthracene₆¹ units used for our ligands are amenable to modification via the Diels–Alder reaction, leading to diazaanthracene or triptycene units.₆² These motifs are intriguing for incorporating additional shape complementarity aspects, remote from the coordination sites, into heteroaromatic amide ligands for self-assembly. In effect, the reaction of the central ring in the diazaanthracene bends the attached N-heterocyclic rings toward each other, a change which, in the ligand structure, adds an additional curvature perpendicular to the curvature that defines the bend angle (Figure 1a,b).

The design of such ligands with multiple curvatures for added shape complementarity has not been reported as a bottom-up strategy for metal-organic assemblies, and yet this approach could open up an opportunity for controlling self-assembly with even more complex components. Herein, we demonstrate that this dual curvature, combined with the electrostatic interactions that dictate the bend angle, can direct self-assembly towards a single M₂L₄ cage or M₄L₈ double-walled metallacrowate out of the myriad possible stereoisomers that result from different combinations of amide conformation and triptycene unit orientation (Figure 1b–e and Supporting Information Figures S1–S3 and S10). Importantly, this high isomer selectivity and self-sorting remain applicable, even when the ligands contain lateral functional groups that are competitive for metal binding or hydrogen bonding, allowing the further synthesis of deep cavities with endohedral functionalization.

### Experimental Methods

#### General experimental details

Unless otherwise stated, all chemicals and solvents were purchased from commercial companies and used without further purification. Fully detailed synthetic procedures for ligands L₁–L₃ are described in the Supporting Information. ¹H and ¹³C NMR spectra were recorded on a Bruker BioSpin GmbH (Rheinstetten, Germany) AVANCE 500 MHz spectrometer or Avance II 300 MHz spectrometer at the Institute of condensed matter and nanosciences at the Université Catholique de Louvain. Electrospray ionization time-of-flight mass spectrometry (ESI-TOF-MS) was collected on an HR-ToF Bruker Daltonik GmbH (Bremen, Germany) Impact II, an ESI-TOF-MS capable of a resolution of at least 40,000 full width at half maximum, which was coupled to a Bruker cryo-spray unit. Detection was in positive-ion mode, and the source voltage was between 4 and 6 kV. The machine was calibrated before every experiment via direct infusion of a sodium trifluoroacetate solution, which provided the m/z range of singly charged peaks up to 3500 Da in both ion modes. Data analysis was conducted with the Bruker Daltonik GmbH (Bremen, Germany) Data Analysis software, and simulations were performed with the Bruker Daltonik GmbH (Bremen, Germany) Isotope Pattern software. All computational models were constructed using initial semi-empirical calculations at the PM6 level with Gaussian 09 to optimize geometries of all structures before optimization using density functional theory (DFT). The resulting geometries were optimized with DFT calculations at the B3LYP/6-31G(d) level of theory for organic ligands and B3LYP/def2-SVP level of theory for metal-organic cages using Gaussian 09 package.₆³

#### Synthetic procedures

**Self-assembly of Pd₂(L₁)₄(BF₄)₄**

A suspension of ligand L₁ (130.8 mg, 0.2 mmol, 1.0 equiv) and Pd(CH₃CN)₄(BF₄)₂ (44.4 mg, 0.1 mmol, 0.5 equiv) in 10 mL CH₃CN or dimethylformamide (DMF) was heated at 40 °C for 4 h. The turbid suspension of ligands gradually turned clear to give a yellow solution that was characterized by NMR to show formation of complex Pd₂(L₁)₄(BF₄)₄. Diethyl ether was added to precipitate the isolated product Pd₂(L₁)₄(BF₄)₄. ¹H NMR (500 MHz, CD₃CN) δ 10.15 (s, 2H), 9.26 (ddd, J = 8.8, 2.2, 1.1 Hz, 2H), 8.57 (d, J = 2.3 Hz, 2H), 7.94 (d, J = 5.0 Hz, 2H), 7.64 (s, 2H), 7.50–7.44 (m, 4H), 7.05–7.01 (m, 1H), 6.90 (t, J = 8.1 Hz, 1H), 6.41 (s, 1H), 4.01 (dd, J = 21.3, 6.4 Hz, 4H), 2.76 (s, 3H), 2.22–2.19 (m, 2H), 1.12 (dd, J = 6.7, 2.2 Hz, 12H). ESI-TOF-MS for Pd₂(L₁)₄(BF₄)₄: The following picked signals are those at the high intensities. m/z calcd for [M-2(BF₄)²⁺]⁺, 1502.5026; found, 1502.5026; calcd for [M-3(BF₄)³⁺], 972.6657; found, 972.6660; calcd for [M-4(BF₄)⁴⁺], 707.7482; found, 707.7484.

**Self-assembly of Pd₄(L₂)₈(BF₄)₈**

A solution of ligand L₂ (130.8 mg, 0.2 mmol, 1.0 equiv) and Pd(CH₃CN)₄(BF₄)₂ (44.4 mg, 0.1 mmol, 0.5 equiv) in 10 mL DMF or dimethyl sulfoxide (DMSO) was heated at 40 °C for 4 h to give a yellow solution that was...
characterized by NMR to show formation of complex Pd$_4$(L$_2$)$_8$(BF$_4$)$_8$. Diethyl ether was added to precipitate the isolated product Pd$_4$(L$_2$)$_8$(BF$_4$)$_8$ from its DMF solution. $^1$H NMR (500 MHz, DMSO-d$_6$) δ 10.83 (s, 2H), 9.10 (s, 4H), 8.12 (s, 4H), 7.50–7.58 (m, 4H), 7.15 (s, 2H), 6.28 (s, 1H), 4.02 (s, 4H), 2.65 (s, 3H), 2.01 (m, 2H), 1.05 (d, J = 4.8 Hz, 2H), 4.03 (s, 4H), 2.36 (s, 2H), 2.24 (s, 2H), 2.11 (s, 2H), 1.04 (d, J = 6.2 Hz, 2H), 7.99 (m, 1H), 7.55 (m, 4H), 7.14 (s, 2H), 6.24 (s, 1H), 5.16 (s, 2H), 4.03 (s, 2H), 2.36 (s, 2H), 2.11 (s, 2H), 1.04 (d, J = 6.5 Hz, 12H). ESI-TOF-MS for Pd$_4$(L$_2$)$_8$(BF$_4$)$_8$: The following picked signals are those at the high intensities. m/z calcld for [M-3(BF$_4$)$_3$]$^+$, 1732.5550; found, 1732.5381; calcld for [M-5(BF$_4$)$_5$]$^+$, 1368.8432; found, 1368.8322; calcld for [M-6(BF$_4$)$_6$]$^+$, 1126.2020; found, 1126.1941; calcld for [M-7(BF$_4$)$_7$]$^+$, 953.0297; found, 953.0235. ESI-TOF-MS for Pd$_4$(L$_3$)$_{10}$(BF$_4$)$_{10}$: m/z calcld for [M-7(BF$_4$)$_7$]$^+$, 1212.9668; found, 1212.9580.

**Self-assembly of Pd$_4$(L$_3$)$_8$(BF$_4$)$_8$**

A solution of ligand L$_3$ (153.8 mg, 0.2 mmol, 1.0 equiv) and Pd(CH$_3$CN)$_2$(BF$_4$)$_2$ (44.4 mg, 0.1 mmol, 0.5 equiv) in 10 mL DMF or DMSO was heated at 40 °C for 4 h to give a yellow solution that was characterized by NMR to show formation of complex Pd$_4$(L$_3$)$_8$(BF$_4$)$_8$. Diethyl ether was added to precipitate the isolated product Pd$_4$(L$_3$)$_8$(BF$_4$)$_8$ from its DMF solution. $^1$H NMR (500 MHz, DMSO-d$_6$) δ 10.99 (s, 2H), 9.17 (s, 4H), 8.26 (s, 4H), 7.91–7.99 (m, 1H), 7.55 (m, 4H), 7.14 (s, 2H), 6.24 (s, 1H), 5.16 (s, 2H), 4.03 (s, 2H), 2.36 (s, 2H), 2.11 (s, 2H), 1.04 (d, J = 6.7 Hz, 12H). ESI-TOF-MS for Pd$_4$(L$_3$)$_8$(BF$_4$)$_8$: The following picked signals are those at the high intensities. m/z calcld for [M-4(BF$_4$)$_4$]$^+$, 1502.5018; found, 1502.5008; calcld for [M-5(BF$_4$)$_5$]$^+$, 1184.7991; found, 1184.7991; calcld for [M-6(BF$_4$)$_6$]$^+$, 972.8326; found, 972.8315; calcld for [M-7(BF$_4$)$_7$]$^+$, 821.4273; found, 821.4265.

**X-ray crystallographic details**

The X-ray diffraction studies for complex Pd$_4$(L$_1$)$_4$ and complex Pd$_4$(L$_2$)$_8$ were carried out on a Rigaku (Rigaku Europe SE, Neu-Isenburg, Germany) FRX rotating anode (2.9 kW) diffractometer at the European Institute of Chemistry and Biology (Bordeaux, France) X-ray facility. Cu-K$_{α}$ radiation monochromated with high flux Osric Varimax mirrors were used for data collection. The X-ray source was equipped with a Dectris Ltd. (Baden-Dättwil, Switzerland) EigerM detector and partial chi goniometer. All crystals were kept at 130 K during data collection. CrysAlis$^*$$^{65}$ was used to index and integrate data with a multiscan absorption correction. Structures were solved with the ShelXT$^6$ structure solution program using Intrinsic Phasing and the structures were refined with the ShelXL$^6$ refinement package using Least Squares minimization within Olex2$^6$. Only non-H atoms were refined with anisotropic displacement parameters. H atoms were positioned geometrically and constrained depending on their riding-model approximation, with Uiso(H) = 1.2Ueq (CH, CH$_2$, NH). DFIX, AFIX, and RIGU restraints were applied to model geometry of the molecules and thermal motion parameters. The X-ray diffraction study for complex Pd$_4$(L$_3$)$_8$ was carried out at a MAR345 image plate using Mo-K$_{α}$ radiation generated by an Incoatec Microfocus source (focusing Montel multilayer optics ELM33) at UCLouvain. Prior to data collection, the crystals were flash-frozen to 120 K. Data integration and reduction were performed by CrysAlisPRO$^{67}$ and the implemented absorption correction was applied. The structures were solved by SHELXT$^{65}$ and refined against $^F$ by SHELXL-2018/3.$^{68}$ All nonhydrogen bonds were refined anisotropically, and hydrogen atoms were added in calculated positions and refined in riding mode, with temperature factors 1.2 times higher than their parent atoms. A full set of distance and angle restraints were used for the ligand, as well as planary restraints on the diazaanthracene units. Isotropic and rigid bond restraints were used on all nonmetal atoms. The crystal was found to be twinned by inversion with the twin ratio close to 50%. The crystal contained voids (61%) which were treated by the squeeze algorithm. Crystal data and structure refinement details are shown in the Supporting Information Table S1.

**Results and Discussion**

**Ligand design and synthesis**

Diazatriptycne ligands L$_1$ and L$_2$ were synthesized in three steps from the reported 1,8-diazaanthracene-2,7-dicarboxylate ester$^{59}$ (Scheme 1 and Supporting Information Figures S31–S33 and S66–S90), starting with a [4 + 2] cycloaddition between in situ generated benzene. Subsequent saponification and amide coupling with either 3-aminopyridine or 4-aminopyridine gave ligands L$_1$ and L$_2$ in 68% and 87% yield, respectively. The Diels–Alder reaction with benzene bends the ligands introducing the second curvature of ∼120° between the planes of the amide groups based on the calculated structures (Figure 1a). Additionally, it adds a large benzene ring on one face of the ligand, which is expected to act as a source of steric hindrance between ligands to help control the self-assembly.

**Self-assembly with L1 and L2**

Complexation of L$_1$ with Pd$^{2+}$ (NO$_3$$_{-}$, BF$_4$$_{-}$, CF$_3$SO$_3$$_{-}$, or PF$_6$$_{-}$ salt) in a 2:1 molar ratio in CD$_2$CN or DMF-$d_7$ at 40 °C results in a clear yellow solution. After 2 h, the $^1$H NMR spectrum shows a single sharp set of signals with the same number of resonances as the starting ligand (Figure 2a,b and Supporting Information Figures S4–S7, S91, and S92). Compared to L$_1$, significant shifts of several resonances are observed. Notably, protons H$_a$
and H₆ of the pyridine groups appear further downfield, implying coordination of pyridine to Pd²⁺. These observations suggest the formation of a single symmetric species derived from the complexation of L₁ with Pd²⁺ ions. Based on the expected parallel coordination vectors of the ligand, this was proposed to be an M₂L₄ structure. Consistent with this, diffusion-ordered ¹H NMR spectroscopy (DOSY) showed that all the proton resonances had the same diffusion coefficient of D = 6.99 × 10⁻¹⁰ m²/s, which, based on the Stokes–Einstein equation, indicates a small structure with a radius of 8.3 Å (Figure 2c and Supporting Information Figure S25). ESI-TOF-MS further supported this assignment; a series of isotopic patterns corresponding to [Pd₂(L₁)₄(BF₄)₄]⁺ (n = 2–4) were observed (Figure 2d and Supporting Information Figures S34–S37).

For this species, the symmetry and single set of signals observed by NMR are interesting because the different syn/anti orientations around the amides or cis/trans orientations of the ligand backbones lead to at least 528 possible stereoisomers (Figure 3 and Supporting Information Figures S8–S10). These nevertheless appear to converge to a single stable species, and time-dependent NMR studies of the self-assembly of L₁ did not show any clear signs of other isomers forming as intermediates (Supporting Information Figure S5). Within 10 min of mixing the ligand with Pd²⁺ ions, the ¹H NMR of the solution exhibited relatively broad signals with low intensity. ESI-TOF-MS analysis of the solution mainly found Pd₂(L₁)₄(BF₄)₄, suggesting the composition of this mixture was predominately the M₂L₄ cage with possibly some oligomers and intermediates from the self-assembly. After 1 h, only a single sharp set of resonances, as observed above, emerges and becomes the significant species by ¹H NMR. In the presence of dimethyl sulfone as an internal standard, the observed signals account for >90% of the ligand used for self-assembly (Supporting Information Figure S7).

Figure 2 | ¹H NMR spectra (500 MHz, CD₃CN, 298 K) of ¹H NMR spectra of (a) L₁ and (b) its self-assembly product Pd₂(L₁)₄. (c) The DOSY spectra of Pd₂(L₁)₄. (d) ESI-TOF-MS for Pd₂(L₁)₄ as its BF₄⁻ salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum. (e) X-ray crystal structure of Pd₂(L₁)₄ with views perpendicular to (left) and along (right) the Pd-Pd axis. Protons, solvent molecules, and counterions are omitted for clarity.
Relative to the possibility of different conformations, DFT computational studies (B3LYP/6-31g*) support that the anticonformation (L1A) between the amides of ligand L1 (possible ligand isomers, L1A, L1B, and L1C) should be favored by almost 30 kJ/mol in the self-assembly solvent (CH3CN) (Figure 3a). Similar studies (B3LYP/def2SVP) on the M2L4 cage also suggest that this preference should be maintained in the complex (Figure 3b). Still, the lack of planar symmetry in the ligands could result in four different Pd2(L1)4+ isomers (A–D) with different cis/trans relationships between the 9,10-bridging groups (Figure 3c). However, the dual curvature designed into the ligands should allow for good shape complementarity that directs single isomer formation in order to avoid steric interactions between neighboring ligands. Indeed, additional DFT studies comparing the four isomers estimated that isomer A, where the curves of the ligands are oriented in the same direction, should be the most stable by ~40 kJ/mol. Based on the calculated structures, the higher energy for the three other isomers likely results from steric interactions between nearby benzene rings in the diazatriptycene backbones.

Further support for the formation of isomer A came from its solid-state structure. Single crystals of Pd2(L1)4(BF4)4 could be obtained and were studied by X-ray diffraction (Figure 2e). The crystal structure of the complex shows two palladium ions, each in a square planar N4 coordination environment, bridged by four

Figure 3 | DFT-calculated structures and relative energies (B3LYP/6-31g* for ligands and B3LYP/def2SVP for cages) of (a) three possible conformations of ligand L1 (L1A, L1B, and L1C), (b) Pd2(L1)4 cage with representative ligand syn/anti amide conformations, and (c) four possible diastereomers of Pd2(L1)4 cage based on triptycene orientation.
units of L1 with a Pd$^{2+}$-to-Pd$^{2+}$ distance in the cage of 12.3 Å. In accordance with the solution observations and computational results, the benzene rings on the ligands are all oriented in the same direction around the fourfold symmetry axis, and the amide carbonyls are all anti to the endocyclic nitrogens of the diazatriptycene units. Relative to our previously reported M$_2$L$_4$ cage, which had overall $D_{4h}$ symmetry, the directionality of the triptycene units used for Pd$_4$(L1)$_4^{4+}$ leads to a decrease in the symmetry of the cage to $C_{4h}$.

Motivated by the high selectivity observed with ligand L1, we next looked to see if the self-assembly of larger structures using the reduced symmetry ligands could still be controlled by the dual curvature effects. Ligand L2 was reacted with 0.5 equiv of Pd$^{2+}$ (NO$_3$)$^-$, BF$_4^-$, CF$_3$SO$_3^-$, or PF$_6^-$ salt in DMSO-$d_6$ or DMF-$d_7$. Similar to self-assembly with L1, the $^1$H NMR spectrum showed a single set of resonances distinct from the starting ligand (Figure 4a,b and Supporting Information Figures S11–S14).

S93, and S94). Again, using an internal standard indicates that >90% of [L2] is represented by this new species (Supporting Information Figure S14). As expected, DOSY studies on this species suggested the formation of a larger structure ($D = 7.32 \times 10^{-3}$ m$^2$/s; $r = 13.8$ Å) (Figure 4c and Supporting Information Figure S26). However, as opposed to the M$_6$L$_{12}$ or M$_{12}$L$_{24}$ cages obtained previously with the analogous planar ligand, ESI-TOF-MS analysis showed isotopic patterns consistent with the formation of an M$_4$L$_8$ assembly with the formula Pd$_4$(L2)$_8$(BF$_4$)$_8$ (Figure 4d and Supporting Information Figures S38–S44). The M$_4$L$_8$ composition was further confirmed by X-ray diffraction studies. The crystal structure shows a deep crown-like double-walled metallomacrocycle (Figure 4e). The four palladium ions are found in the same plane and can be seen as occupying the four corners of a square. Each palladium has square-planar coordination, with two ligands, one above and one below the plane, bridging between each pair of adjacent metal ions. This gives a structure with cavity dimensions of 20.5 Å between opposite palladiums and 23.8 Å between the top and bottom faces. All of the ligands are oriented in the same way, with the benzene ring of the diazatriptycene units in each bridging pair pointing away from each other toward either the top or bottom of the structure. This also results in the 9-position group on the diazatriptycene units of the ligands converging towards the center of the cavity.

Interestingly, the bend angle for the ligands in the crystal structure of Pd$_4$(L2)$_8^{4+}$ is ∼70°, while the same bend angle in the DFT optimized structure of the free ligands was found to be ∼60°. Previously, we observed that the partial flexibility in the amide bonds could allow changes of almost 30° in the bend angle, making it possible to transition from a smaller cage structure to a larger one. For example, M$_6$L$_{12}$ and M$_{12}$L$_{24}$ structures, which require ideal bend angles around 90° and 120°, respectively, could be formed with the same aromatic amide ligand in a stepwise manner. With this in mind, we attempted to push the self-assembly of Pd$_4$(L2)$_8^{4+}$ toward a larger Pd$_6$(L2)$_{12}^{12+}$ octahedron. However, even after extending the time for self-assembly up to 2 weeks or increasing the temperature to 120 °C, no other apparent species were observed by NMR or ESI-TOF-MS analysis. The cube-like structures in most M$_6$L$_{12}$ octahedra contain eight adjacent threefold symmetry axes. With the dual curvature ligand L2, it is impossible for the ligands to be arranged in a way where they are all pointing away from each other, something that can occur with Pd$_4$(L2)$_8^{4+}$ (Figure 4e). Interestingly, no close contacts of the complementary shapes, as seen in the iso- mers of Pd$_4$(L1)$_4^{4+}$, are observed in a PM6 model of a Pd$_6$(L2)$_{12}^{12+}$ octahedron (Supporting Information Figure S15). Thus, it is suspected that a combination of unfavorable ligand orientation and significant distortions in the torsion angles around the amides may limit the stability of the M$_6$L$_{12}$ structure.

Figure 4 | $^1$H NMR spectra (500 MHz, DMSO-$d_6$, 298 K) of $^1$H NMR spectra of (a) L2 and (b) its self-assembly product Pd$_4$(L2)$_8^{4+}$. (c) The DOSY spectra of Pd$_4$(L2)$_8^{4+}$. (d) ESI-TOF-MS for Pd$_4$(L2)$_8$ as its BF$_4^-$ salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum. (e) X-ray crystal structure of Pd$_4$(L2)$_8^{4+}$ with side (left) and top (right) views. Protons, solvent molecules, and counterions are omitted for clarity.
Self-sorting studies

To look at how strongly the noncovalent interactions present in the ligand structures control their bend angle, self-sorting studies were performed. In theory, changes in the torsion angles around the amides, at the expense of weakening the noncovalent interactions, should permit both ligands to achieve the same bend angles. While this could potentially allow the self-assembly of structures containing both ligands \(L_1\) and \(L_2\), this does not appear to be favored, Figure 5a. Indeed, upon reacting a 1:1 mixture of \(L_1\) and \(L_2\) with \(\text{Pd(CH}_3\text{CN)}_4(\text{BF}_4)_2\) in D MF-\(d_7\), two distinct sets of signals corresponding to the \(M_2(\text{L}_1)_4^{4+}\) and \(M_4(\text{L}_2)_8^{8+}\) species as described above were observed by \(^1\text{H NMR (Figure 5b,c and Supporting Information Figures S20 and S28–S30). ESI-TOF-MS analysis, Figure 5d and Supporting Information Figures S51–S65, also showed only a mixture of \(M_2L_4\) and \(M_4L_8\) species. These observations indicate that, despite the weak nature of the noncovalent interactions that direct the ligand conformation, they still provide sufficient control to allow self-sorting based on the bend angle, something only previously reported for more ridged ligands.\(^{69–71}\)

Figure 5 | (a) Narcissistic self-sorting of \(M_2L_4\) and \(M_4L_8\) architectures from mixed ligands. (b) \(^1\text{H NMR spectra (500 MHz, DMF-\(d_7\), 298 K), (c) the DOSY spectra, and (d) ESI-TOF-MS of self-sorting outcomes showing a mixture of \(M_2(\text{L}_1)_4\) and \(M_4(\text{L}_2)_8\) species.}

Cage functionalization

This shape complementarity strategy combined with the defined orientation of the diazaanthracene 9-position and modularity of the ligand design can facilitate the endohedral functionalization of the structure.\(^{72}\) This enables us to look at the applicability of our strategy for self-assembly with a functional group that is potentially competitive with the metal coordination and noncovalent interactions important for the conformational stability. This can be especially interesting as there are still no reported examples of endohedral functionalized \(M_nL_{2n}\) type double-walled metallomacrocycles, mainly due to the fact that they require self-assembly from ditopic ligands with bend angles smaller than 90°, which limits endohedral functional sites. To this end, ligand \(\text{L}_3\) bearing a carboxylic acid function was synthesized, as shown in Scheme 2. Following reported procedures, the

Scheme 2 | Synthetic procedures for ligands \(\text{L}_3\).

DOI: 10.31635/ccschem.023.202302940
Citation: CCS Chem. 2023, 5, 2506–2518
Link to VoR: https://doi.org/10.31635/ccschem.023.202302940
9-methyl in the precursor 1,8-diazaanthracene-2,7-dicarboxylate ester could be easily functionalized into a Boc-protected 9-methylamino diazaanthracene derivative. Next, triptycene formation and installation of the pyridine coordination sites were performed in a manner analogous to \( \text{L2} \). Subsequent amine deprotection and reaction with succinic anhydride allowed the incorporation of the carboxylic acid group in \( \text{L3} \).

Despite potential for the endohedral carboxylic acid to compete with metal-pyridine interactions or to act as a hydrogen bond acceptor and donor with the amides and thus limit the conformational constraints, self-assembly with \( \text{L3} \) proceeded without any problems. Upon reaction of \( \text{L3} \) with \( \text{Pd}^{2+} \) (NO\(_3\)\(^-\), BF\(_4\)\(^-\), CF\(_3\)SO\(_3\)\(^-\), or PF\(_6\)\(^-\) salt), in a 2:1 molar ratio in DMSO-d\(_6\) or DMF-d\(_7\), similar changes as for self-assembly with \( \text{L2} \) that is, a single set of signals shifted relative to the free ligand, are observed by \( ^1\text{H} \) NMR (Figure 6a,b and Supporting Information Figures S16–S19, S95, and S96). Given the similar bend angles expected for \( \text{L2} \) and \( \text{L3} \), self-assembly with the functionalized ligand should also lead to an \( \text{M}_4\text{L}_8 \) structure. This was supported by DOSY studies (\( D = 7.55\times10^{-11} \) m\(^2\)/s; \( r = 13.4 \) Å), which suggested the formation of a complex with a size similar to parent \( \text{Pd}_4(\text{L2})_8^{8+} \) (Figure 6c and Supporting Information Figure S27). The \( \text{Pd}_4(\text{L3})_8(\text{BF}_4)_8 \) formula was further confirmed by ESI-TOF-MS, though some low-intensity signals for an \( \text{M}_5\text{L}_{10} \) structure could also be observed (Figure 6d and Supporting Information Figures S44–S50). The presence of the more bulky group on the 9-position of \( \text{L3} \) relative to \( \text{L2} \) may lead to this minor formation of some of the larger macrocycles. Still, the species observed by NMR represents >90% of ligands used for self-assembly. Additionally, the X-ray crystal structure of the product showed \( \text{Pd}_4(\text{L3})_8^{8+} \) and was highly similar to the \( \text{M}_4(\text{L3})_8^{8+} \) structure (Figure 6e). The 9-position substituents are still found pointing into the cavity and oriented toward each other such that they occupy the cavity windows formed by the pairs of bridging ligands. This also leads to short distances between neighboring carboxylic acid groups (O–O distances of 2.3–2.7 Å), suggesting potential hydrogen bond formation between these groups. Such interactions might be expected to lead to some preference for self-sorting. However, self-assembly with mixtures of \( \text{L3} \) and \( \text{L2} \) resulted in statistical mixtures of \( \text{M}_2(\text{L1})_4^{4+} \) and \( \text{M}_4(\text{L3})_8^{8+} \) based on the different bend angles (Figure 7a,b and Supporting Information Figures S21–S24).

**Conclusion**

We have provided an effective strategy for controlling palladium-based self-assembly with flexible and nonplanar ligands by combining endohedral noncovalent
interactions in aromatic amides with additional shape complementarity brought by a dual curvature in the ligand. Three asymmetric diazatryptypene amide-based ligands were synthesized and used for self-assembly with Pd²⁺. Impressively, the constraints designed into the ligands provide high stereoselectivity for the self-assembly process, leading to only a single M₂L₄ cage (L₁) or M₄Lₘ double-walled metallomacrocycle (L₂ or L₃) out of all of the possible stereoisomers. Moreover, we show that despite the flexibility around the amide groups in the ligands, the noncovalent interactions arranged on the ligand backbone provide excellent control over the ligand bend angle, allowing narcissistic self-sorting in mixtures of ligands with different bend angles. This demonstrated level of structural control and the high modularity afforded by the amide connectivity can allow rapid access to libraries of diversely functionalized ligands for applications in sensing and catalysis. To highlight this versatility, we show that this strategy can be used to generate endohedrally functionalized M₄(L₃)ₘ structures with deep cavities lined with competitive functional groups. These results provide promising new design strategies for coordination-driven self-assembly where additional shape complementarity between dually curved ligands can be used for the formation of asymmetric functionalized cavities of interest for diverse applications.

Supporting Information

Supporting Information is available and includes full experimental details, including synthetic procedures and spectroscopic data for ligands L₁–L₃ and their corresponding cages. CCDC 2121219 Pd₂(L₁)₄, 2121220 Pd₄(L²)ₘ, and 2111410 Pd₄(L₃)ₘ contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Conflict of Interest

There is no conflict of interest to report.

Funding Information

This research was supported in part through the Concerted Research Action (ARC16/21-074) and the China Scholarship Council (pre-doctoral fellowships for C.-L.L.). Computational resources were provided by the supercomputing facilities of the Université catholique de Louvain (CISM/UCL) and the Consortium des équipements de Calcul Intensif en Fédération Wallonie Bruxelles (CPCI) funded by the Fond de la Recherche Scientifique de Belgique (F.R.S.-FNRS) under convention 2.5020.11. We thank Dr. S. Ouk for his generous financial support through the Fondation Louvain.

Preprint Statement

Research presented in this article was posted on a preprint server prior to publication in CCS Chemistry. The corresponding preprint article can be found here: (10.26434/chemrxiv-2021-4z45w-v3; https://chemrxiv.org/engage/chemrxiv/article-details/629fb272e6269c3f07a518f).

Acknowledgments

The authors wish to acknowledge Dr. Gabriella Barozzino for help with NMR measurements.

References


44. Li, R.-J.; Marcus, A.; Fadaei-Tirani, F.; Severin, K. Orientation-Self-Sorting: Formation of Structurally Defined


