

Design of metal-organic assemblies via shape complementarity and conformational constraints in dual curvature ligands

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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 usually difficult to distinguish and purify. We herein report a design and synthesis strategy relying on shape complementarity and conformational constraints in dual curvature ligands that effectively promotes high selectivity during self-assembly and self-sorting of metal-organic assemblies. 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 non-planar structure of the core are possible upon coordination with the metal, the constraints designed into the ligands direct the self-assembly towards only a single Pd₂L₄ cage (**L1**) or Pd₄L₈ double-walled metallomacrocyclic (**L2**) structure, even in mixtures of the ligands. We further demonstrate that this structural approach and the modularity of the ligand synthesis affords ready access to the first deep endohedral functionalized double-walled Pd₄L₈ cavitands (**L3**). These results highlight the potential of this new design strategy and open the door to selectively functionalized cavity-based architectures for numerous applications.

Introduction

Self-assembly and folding play essential roles in the complexity and function of proteins.^[1] Over the past decades, the possibility of generating synthetic molecules with similar complexity and functions has inspired significant progress in the design of self-assembled cavitands.^[2] 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 risen as a highly promising approach.^[3] Notably, the combination of Pd²⁺ or Pt²⁺ with ditopic ligands for the formation of M_nL_{2n} structures has attracted substantial attention and led to some of the largest well-defined systems.^[4] A wide range of applications related to their cavities has been reported, including sensing, catalysis, drug delivery, storage, and molecular recognition.^[5]

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.^[6] 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.^[7] This can be readily seen in M_nL_{2n} 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.^[4b, 8] 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 could allow additional shape complementarity between ligands to help direct self-assembly, ultimately leading to new design strategies and more complex structures.^[9] 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.^[10] The latter uses additional functional groups included near the coordination sites on the ligands to provide complementarity interligand steric or electrostatic interactions.^[11] 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 and represents an important goal in this area.

Recently, we succeeded in using heteroaromatic amide-based ligands for the self-assembly of multiple Pd_nL_{2n} (n=2, 6, or 12) metal-organic cages capable of neutral guest

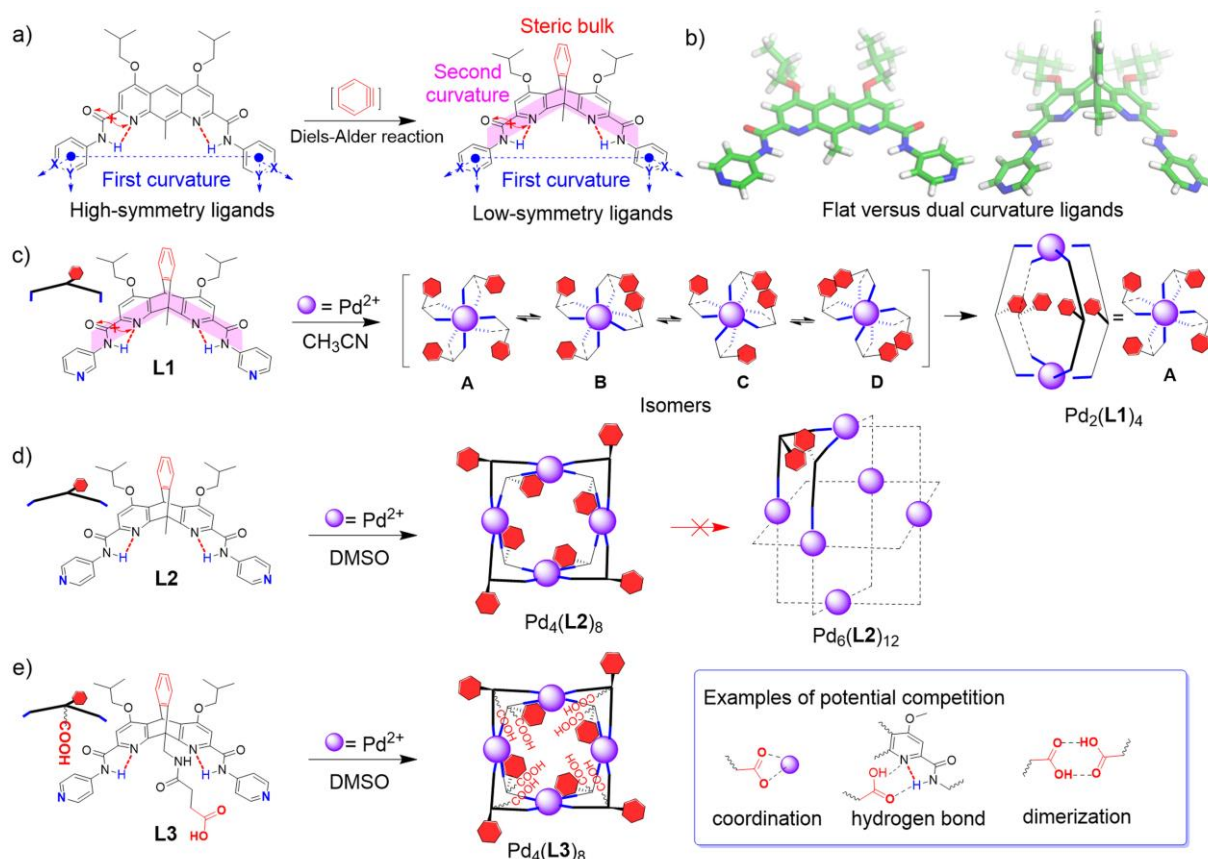


Figure 1. a) Design of aromatic amide-based dual curvature ligands for coordination-driven self-assembly via Diels-Alder reaction with diazaanthracenes. This breaks the ligand symmetry and introduces additional shape complementarity as seen in the density functional theory (DFT) calculated structures of b) flat versus dual curvature ligands. c-e) the structure of ligands **L1-L3** and their self-assembled products. The potential competitive interactions of the endohedral carboxylic acid are shown in the inset.

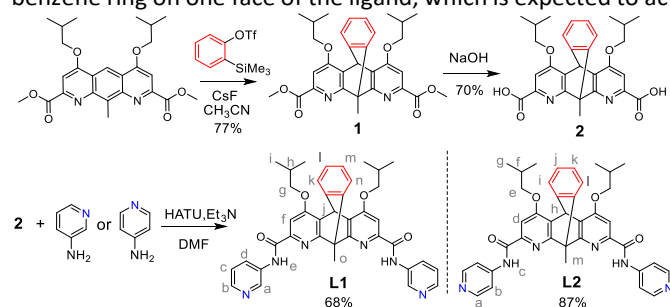
discrimination.^[12] Despite the flexibility around the amide bonds, non-covalent interactions in the ligands lead to preferential curved conformational states that orient the coordination sites and allow sufficient control over the bend angles of the ligands to direct self-assembly. Nevertheless, these 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 the self-assembly of M_nL_{2n} assemblies.^[4] Modification of the surface of the flat aromatic units to include perpendicular interactions is a challenge. However, this can be the fastest way to direct groups towards other ligands for designing interligand interactions and shape complementarity. We have recently shown that the large diazaanthracene units used for our ligands are amenable to modification via Diels-Alder reaction leading to diazaptycene or triptycene units.^[13] 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 towards each other, a change which, in the ligand structure, adds an additional curvature perpendicular to the curvature that defines the bend angle, Figure 1a.

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 M_2L_4 cage or M_4L_8 double-walled metallomacrocyclic out of the hundreds of possible stereoisomers that could result from different combinations of amide conformation and triptycene unit orientation, Figures 1 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 endohedral functionalized cavities.

Results and discussion

Ligand design and synthesis - Diazatriptycene ligands **L1** and **L2** were synthesized in three steps from the reported 1,8-diazaanthracene-2,7-dicarboxylate ester,^[13b] Scheme 1, starting with a [4+2] cycloaddition between in situ generated benzyne. Subsequent saponification and amide coupling with either 3-aminopyridine or 4-aminopyridine gave ligands **L1** and **L2** in 68 and 87% yield, respectively. The Diels-Alder reaction with

benzyne bends the ligands introducing the second curvature of $\sim 120^\circ$ 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



Scheme 1. Synthetic procedures for ligands **L1** and **L2**.

as a source of steric hindrance between ligands to help control the self-assembly.

Self-Assembly with L1 and L2 - Complexation of **L1** with Pd^{2+} (NO_3^- , BF_4^- , CF_3SO_3^- , or PF_6^- salt) in a 2:1 molar ratio in CD_3CN or $\text{D}_7\text{-DMF}$ at 40°C results in a clear yellow solution. After two hours, the ^1H NMR spectrum shows a single sharp set of signals with the same number of resonances as the starting ligand, Figure 2a-b and Figure S4-S7. Compared to **L1**, significant shifts of several resonances are observed. Notably, protons H_a and H_b of the pyridine groups appear further downfield, implying coordination of pyridine to Pd^{2+} . These observations suggest the formation of a single symmetric species derived from the complexation of **L1** with Pd^{2+} ions. Based on the expected parallel coordination vectors of the ligand, this was proposed to be an M_2L_4 structure. Consistent with this, diffusion-ordered ^1H NMR (DOSY) showed that all the proton resonances had the same diffusion coefficient of $D = 6.99 \times 10^{-10} \text{ m}^2/\text{s}$, which, based on the Stokes-Einstein equation, indicates a small structure with a radius of $8.3 \text{ \AA}$, Figure 2c. Electrospray ionization time-of-flight mass spectrometry (ESI-TOF-MS) further supported this assignment; a series of isotopic patterns corresponding to $[\text{Pd}_2(\text{L1})_4(\text{BF}_4)_{4-n}]^{n+}$ ($n=2-4$) were observed, Figure 2d.

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 could lead to hundreds of possible stereoisomers, Figure 3 and Figure 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, Figure S5. Within ten minutes of mixing the ligand with Pd^{2+} ions, the ^1H NMR of the solution exhibited relatively broad signals with low intensity. ESI-TOF-MS analysis of the solution mainly found $\text{Pd}_2(\text{L1})_4(\text{BF}_4)_4$ suggesting the composition of this mixture was predominately the M_2L_4 cage with possibly some oligomers and intermediates from the self-assembly. After one hour, 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, Figure S7.

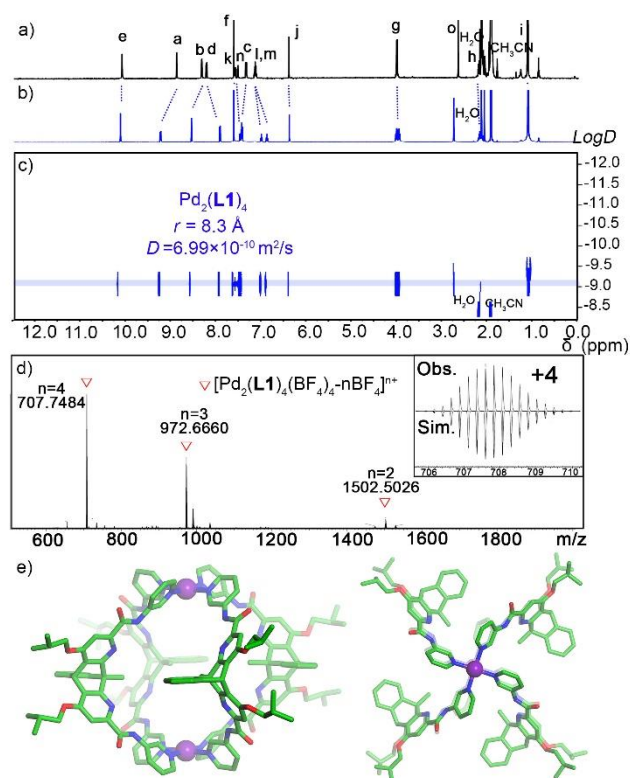


Figure 2. ^1H NMR spectra (500 MHz, CD_3CN , 298 K) of ^1H NMR spectra of a) **L1** and b) its self-assembly product $\text{Pd}_2(\text{L1})_4^{4+}$, c) the DOSY spectra of $\text{Pd}_2(\text{L1})_4^{4+}$, and d) ESI-TOF-MS for $\text{Pd}_2(\text{L1})_4^{4+}$ as its BF_4^- salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum. e) X-ray crystal structure of $\text{Pd}_2(\text{L1})_4^{4+}$ 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, density functional theory (DFT) computational studies (B3LYP/6-31g*) support that the *anti*-conformation(**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 (CH_3CN), Figure 3a. Similar studies (B3LYP/def2SVP) on the M_2L_4 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 $\text{Pd}_2(\text{L1})_4^{4+}$ 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 $\sim 40 \text{ kJ/mol}$. 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.

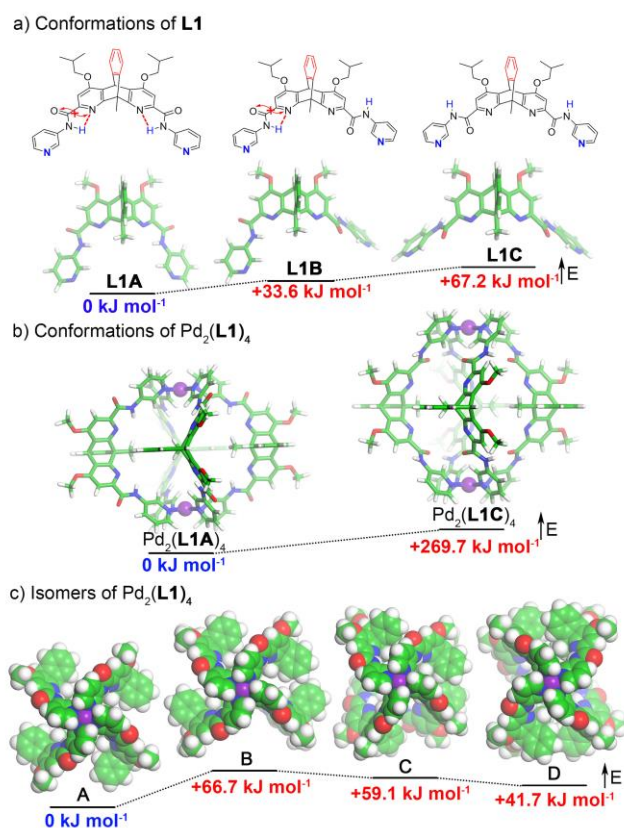


Figure 3. Density functional theory (DFT) calculated structures and relative energies (B3LYP/6-31g* for ligands and B3LYP/def2SVP for cages) of a) three possible conformations of ligand **L1** (**L1A**, **L1B** and **L1C**), b) $\text{Pd}_2(\text{L1})_4$ cage with representative ligand *syn/anti* amide conformations, and c) four possible diastereomers of $\text{Pd}_2(\text{L1})_4$ cage based on triptycene orientation.

Further support for the formation of isomer A came from its solid-state structure. Single crystals of $\text{Pd}_2(\text{L1})_4(\text{BF}_4)_4$ 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 N_4 coordination environment, bridged by four 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 four-fold symmetry axis, and the amide carbonyls are all *anti* to the endocyclic nitrogens of the diazatriptycene units. Relative to our previously reported M_2L_4 cage,^[12] which had overall D_{4h} symmetry, the directionality of the triptycene units used for $\text{Pd}_2(\text{L1})_4^{4+}$ 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 equivalents of Pd^{2+} (NO_3^- , BF_4^- , CF_3SO_3^- , or PF_6^- salt) in D_6 -DMSO or D_7 -DMF. Similar to self-assembly with **L1**, the ^1H NMR spectrum showed a single set of resonances distinct from the starting ligand, Figure 4a-b and Figure S11-S14. Again, using an internal standard indicates that >90% of [**L2**] is represented by this new species, Figure S14. As expected, DOSY studies on this

species suggested the formation of a larger structure ($D = 7.32 \times 10^{-11} \text{ m}^2/\text{s}$; $r = 13.8 \text{ Å}$), Figure 4c. However, as opposed to the M_6L_{12} or $\text{M}_{12}\text{L}_{24}$ cages obtained previously with the analogous planar ligand,^[12] ESI-TOF-MS analysis showed isotopic patterns consistent with the formation of an M_4L_8 assembly with the formula $\text{Pd}_4(\text{L2})_8(\text{BF}_4)_8$, Figure 4d. The M_4L_8 composition was further confirmed by X-ray diffraction studies. The crystal structure shows a deep crown-like double-walled metallomacrocyclic, 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 towards 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.

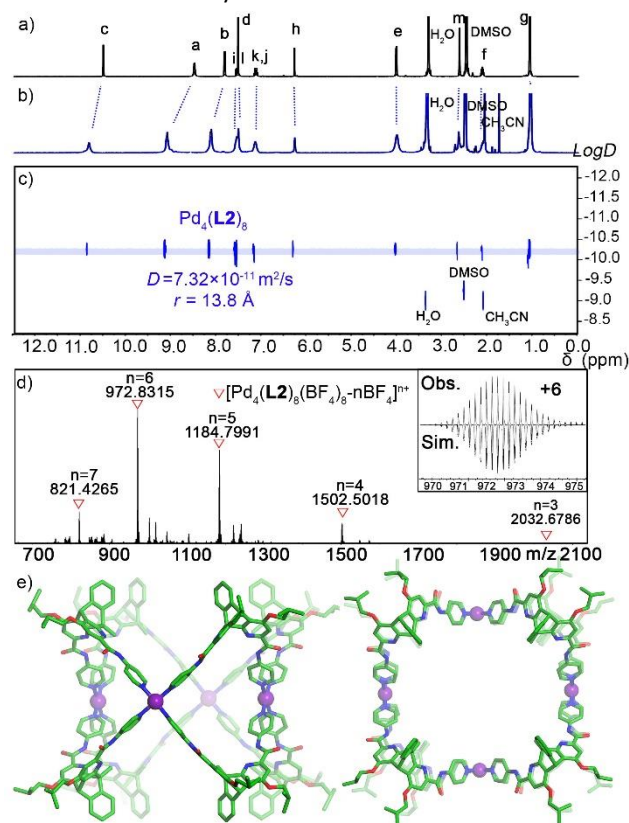


Figure 4. ^1H NMR spectra (500 MHz, DMSO-d_6 , 298 K) of a) **L2** and b) its self-assembly product $\text{Pd}_4(\text{L2})_8^{8+}$, and c) the DOSY spectra of $\text{Pd}_4(\text{L2})_8^{8+}$. d) ESI-TOF-MS for $\text{Pd}_4(\text{L2})_8^{8+}$ as its NO_3^- salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum. e) X-ray crystal structure of $\text{Pd}_4(\text{L2})_8$ with side (left) and top (right) views. Protons, solvent molecules and counterions are omitted for clarity.

Interestingly, the bend angle for the ligands in the crystal structure of $\text{Pd}_4(\text{L2})_8^{8+}$ is $\sim 70^\circ$, while the same bend angle in the DFT optimized structure of the free ligands was found to be $\sim 60^\circ$. 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.^[12] For example, M_6L_{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 step-wise manner. With this in mind, we attempted to push the self-assembly of $Pd_4(L_2)_8^{8+}$ towards a larger $Pd_6(L_2)_{12}^{12+}$ octahedron. However, even after extending the time for self-assembly up to two weeks or increasing the temperature to 120 °C, no other apparent species were observed by NMR nor ESI-TOF-MS analysis. The cube-like structures in most M_6L_{12} octahedra contain eight adjacent 3-fold 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 $Pd_4(L_2)_8^{8+}$, Figure 4e. Interestingly, no close contacts of the complementary shapes, as seen in the isomers of $Pd_2(L_1)_4^{4+}$, are observed in a PM6 model of a $Pd_6(L_2)_{12}^{12+}$ octahedron, 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_6L_{12} structure.

Self-Sorting Studies - To look at how strongly the non-covalent 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 non-covalent interactions, should permit both ligands to achieve the same bend angles. While this could potentially allow the self-assembly of structures containing both ligands **L1** and **L2**, this does not appear to be favored. Indeed, upon reacting a 1:1 mixture of **L1** and **L2** with $Pd(CH_3CN)_4(BF_4)_2$ in D_7 -DMF, two distinct sets of signals corresponding to the $M_2(L_1)_4^{4+}$ and $M_4(L_2)_8^{8+}$ species as described above were observed by 1H NMR, Figure 5 and Figure S20. ESI-TOF-MS analysis also showed only a mixture of M_2L_4 and M_4L_8 species. These observations indicate that, despite the weak nature of the non-covalent interactions that direct the ligand conformation, they still provide sufficient control to allow self-sorting based on bend angle, something only previously reported for more ridged ligands.^[14]

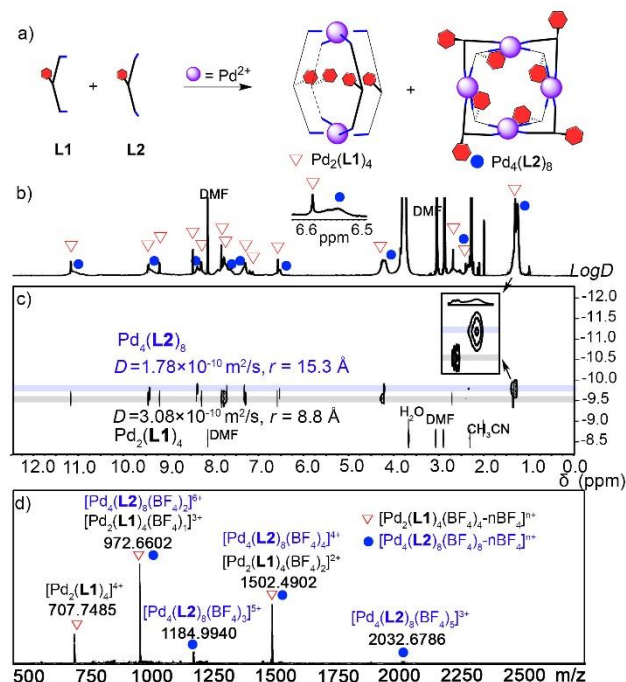
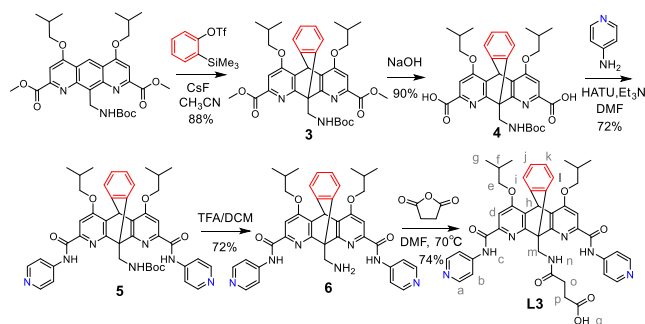


Figure 5. a) Narcissistic self-sorting of M_2L_4 and M_4L_8 architectures from mixed ligands. b) 1H NMR spectra (500 MHz, $DMF-d_7$, 298 K), c) the DOSY spectra and d) ESI-TOF-MS of self-sorting outcomes showing a mixture of $M_2(L_1)_4$ and $M_4(L_2)_8$ species.

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. 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 non-covalent 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 **L3** bearing a carboxylic acid function was synthesized, as shown in Scheme 2. Following reported procedures, the 9-methyl in the precursor 1,8-diazaanthracene-2,7-dicarboxylate ester could be easily functionalized into a Boc-protected 9-methylamino diazaanthracene derivative.^[15] Next, triptycene formation and installation of the pyridine coordination sites were performed in a manner analogous to **L2**. Subsequent amine deprotection and reaction with succinic anhydride allowed the incorporation of the carboxylic acid group in **L3**.



Scheme 2. Synthetic procedures for ligands **L3**.

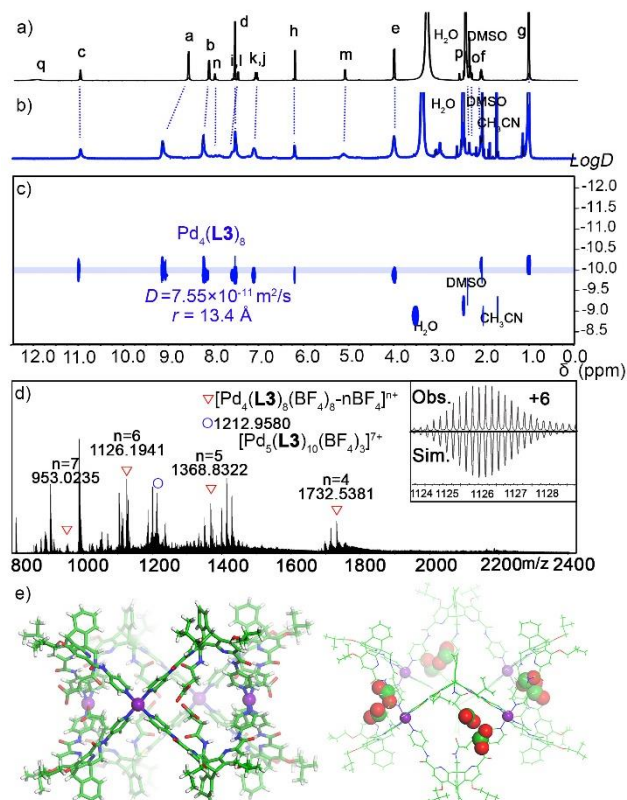


Figure 6. ^1H NMR spectra (500 MHz, DMSO-d_6 , 298 K) of ^1H NMR spectra of a) **L3** and b) its self-assembly product $\text{Pd}_4(\text{L3})_{88+}$ c) the DOSY spectra of $\text{Pd}_4(\text{L3})_{88+}$ d) ESI-TOF-MS for $\text{Pd}_4(\text{L3})_{88+}$ as its BF_4^- salt. Inset shows the comparison of the observed isotopic pattern with the simulated spectrum. e) X-ray crystal structure of $\text{Pd}_4(\text{L3})_{88+}$ with side views (left) and highlighting the 9-position endohedral carboxylic acids (right). Solvent molecules and counterions are omitted for clarity.

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,^[3c, 16] self-assembly with **L3** proceeded without any problems. Upon reaction of **L3** with Pd^{2+} (NO_3^- , BF_4^- , CF_3SO_3^- , or PF_6^- salt), in a 2:1 molar ratio in D_6 -DMSO or D_7 -DMF, similar changes as for self-assembly with **L2**, i.e., a single set of signals shifted relative to the free ligand, are seen by ^1H NMR, Figure 6a-b and Figure S16-S19. Given the similar bend angles expected for **L2** and **L3**, self-assembly with the functionalized ligand should also lead to an M_4L_8 structure. This was supported by DOSY studies ($D = 7.55 \times 10^{-11} \text{ m}^2/\text{s}$; $r = 13.4 \text{ Å}$), which suggested the formation of a complex with a size similar to parent $\text{Pd}_4(\text{L2})_8^{8+}$, Figure 6c. 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 M_5L_{10} structure could also be observed, Figure 6d. The presence of the more bulky group on the 9-position of **L3** relative to **L2** may lead to this minor formation of some of the larger macrocycles.^[14a, 17] 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 $\text{M}_4(\text{L2})_8^{8+}$ structure, Figure 6e. The 9-position substituents are still found pointing into the cavity and oriented towards 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 **L3** and **L2** resulted in statistical mixtures of M_4L_8 species with different ratios of the two ligands, though similar studies using **L3** and **L1** still showed self-sorting into $\text{M}_2(\text{L1})_4^{4+}$ and $\text{M}_4(\text{L3})_8^{8+}$ based on the different bend angles, Figure 7 and Figure S21-S24.

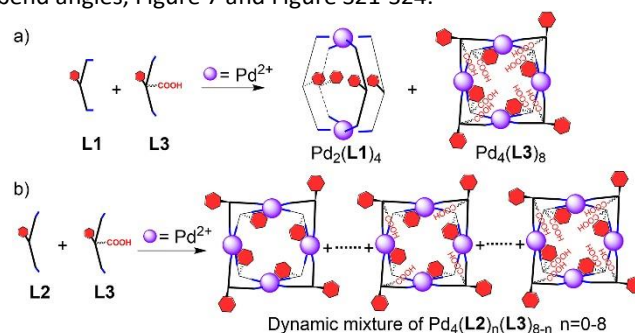


Figure 7. Mixed ligands self-assembly with ligand **L3**, mixed with a) **L1** leads to narcissistic self-sorting of $\text{M}_2(\text{L1})_4^{4+}$ and $\text{M}_4(\text{L3})_8^{8+}$ assemblies and b) **L2** formed non-sorted scrambled dynamic mixtures of $\text{Pd}_4(\text{L2})_n(\text{L3})_{8-n}(\text{BF}_4)_8$, $n=0-8$.

Conclusions

In summary, we have provided an effective strategy for controlling palladium-based self-assembly with flexible and non-planar ligands by combining endohedral non-covalent interactions in aromatic amides with additional shape complementarity brought by a dual curvature in the ligand. Three asymmetric diazatriptycene amide based ligands were synthesized and used for self-assembly with Pd^{2+} . Impressively, the constraints designed into the ligands provide high stereoselectivity for the self-assembly process, leading to only a single M_2L_4 cage (**L1**) or M_4L_8 double-walled metallomacrocyclic (**L2** or **L3**) out of hundreds of possible stereoisomers. Moreover, we show that despite the flexibility around the amide groups in the ligands, the non-covalent 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 $M_4(L)_8$ structures with deep cavities lined with competitive functional groups. These results give 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 diversely functionalized cavities of interest for catalytic applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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Notes and references

- 1 a) C. M. Heckmann, F. Paradisi, *ChemCatChem* **2020**, *12*, 6082-6102; b) R. J. Drouot, L. Robison, O. K. Farha, *Coord. Chem. Rev.* **2019**, *381*, 151-160; c) J. Benkovic Stephen, S. Hammes-Schiffer, *Science* **2003**, *301*, 1196-1202.
- 2 a) Y. Liu, W. Zhao, C. H. Chen, A. H. Flood, *Science* **2019**, *365*, 159-161; b) Z. Liu, S. K. M. Nalluri, J. F. Stoddart, *Chem. Soc. Rev.* **2017**, *46*, 2459-2478; c) D. S. Kim, J. L. Sessler, *Chem. Soc. Rev.* **2015**, *44*, 532-546; d) G. Gil-Ramírez, D. A. Leigh, A. J. Stephens, *Angew. Chem. Int. Ed.* **2015**, *54*, 6110-6150; e) L. F. Lindoy, K.-M. Park, S. S. Lee, *Chem. Soc. Rev.* **2013**, *42*, 1713-1727; f) T. R. Cook, Y.-R. Zheng, P. J. Stang, *Chem. Rev.* **2013**, *113*, 734-777; g) D. V. Kondratuk, L. M. A. Perdigo, M. C. O'Sullivan, S. Svatek, G. Smith, J. N. O'Shea, P. H. Beton, H. L. Anderson, *Angew. Chem. Int. Ed.* **2012**, *51*, 6696-6699; h) T. Tozawa, J. T. A. Jones, S. I. Swamy, S. Jiang, D. J. Adams, S. Shakespeare, R. Clowes, D. Bradshaw, T. Hasell, S. Y. Chong, C. Tang, S. Thompson, J. Parker, A. Trewin, J. Bacsa, A. M. Z. Slawin, A. Steiner, A. I. Cooper, *Nat. Mater.* **2009**, *8*, 973-978; i) L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469-472.
- 3 a) Y.-Q. Zou, D. Zhang, T. K. Ronson, A. Tarzia, Z. Lu, K. E. Jelfs, J. R. Nitschke, *J. Am. Chem. Soc.* **2021**, *143*, 9009-9015; b) E. G. Percástegui, T. K. Ronson, J. R. Nitschke, *Chem. Rev.* **2020**, *120*, 13480-13544; c) A. J. Gosselin, C. A. Rowland, E. D. Bloch, *Chem. Rev.* **2020**, *120*, 8987-9014; d) Y. Sun, C. Chen, P. J. Stang, *Acc. Chem. Res.* **2019**, *52*, 802-817; e) S. Saha, I. Regeni, G. H. Clever, *Coord. Chem. Rev.* **2018**, *374*, 1-14; f) T. R. Cook, P. J. Stang, *Chem. Rev.* **2015**, *115*, 7001-7045.
- 4 a) D. Fujita, Y. Ueda, S. Sato, H. Yokoyama, N. Mizuno, T. Kumasaka, M. Fujita, *Chem* **2016**, *1*, 91-101; b) D. Fujita, Y. Ueda, S. Sato, N. Mizuno, T. Kumasaka, M. Fujita, *Nature* **2016**, *540*, 563-566; c) K. Harris, D. Fujita, M. Fujita, *Chem. Commun.* **2013**, *49*, 6703-6712.
- 5 a) D. Zhang, T. K. Ronson, Y.-Q. Zou, J. R. Nitschke, *Nat. Rev. Chem.* **2021**, *5*, 168-182; b) S. Yadav, P. Kannan, G. Qiu, *Org. Chem. Front.* **2020**, *7*, 2842-2872; c) M. Zhang, M. L. Saha, M. Wang, Z. Zhou, B. Song, C. Lu, X. Yan, X. Li, F. Huang, S. Yin, P. J. Stang, *J. Am. Chem. Soc.* **2017**, *139*, 5067-5074; d) A. Casini, B. Woods, M. Wenzel, *Inorg. Chem.* **2017**, *56*, 14715-14729; e) Q.-Q. Wang, S. Gonell, S. H. A. M. Leenders, M. Dürr, I. Ivanović-Burmazović, J. N. H. Reek, *Nat. Chem.* **2016**, *8*, 225-230; f) C. J. Brown, F. D. Toste, R. G. Bergman, K. N. Raymond, *Chem. Rev.* **2015**, *115*, 3012-3035; g) J. Wang, C. He, P. Wu, J. Wang, C. Duan, *J. Am. Chem. Soc.* **2011**, *133*, 12402-12405; h) P. Mal, B. Breiner, K. Rissanen, J. R. Nitschke, *Science* **2009**, *324*, 1697-1699.
- 6 a) K. A. Dill, J. L. MacCallum, *Science* **2012**, *338*, 1042-1046; b) F. U. Hartl, A. Bracher, M. Hayer-Hartl, *Nature* **2011**, *475*, 324-332.
- 7 S. R. Seidel, P. J. Stang, *Acc. Chem. Res.* **2002**, *35*, 972-983.
- 8 M. Yoshizawa, L. Catti, *Acc. Chem. Res.* **2019**, *52*, 2392-2404.
- 9 J. E. M. Lewis, J. D. Crowley, *ChemPlusChem* **2020**, *85*, 815-827.
- 10 a) J. Tessarolo, H. Lee, E. Sakuda, K. Umakoshi, G. H. Clever, *J. Am. Chem. Soc.* **2021**, *143*, 6339-6344; b) S. Sudan, R.-J. Li, S. M. Jansze, A. Platzek, R. Rudolf, G. H. Clever, F. Fadaei-Tirani, R. Scopelliti, K. Severin, *J. Am. Chem. Soc.* **2021**, *143*, 1773-1778; c) S. Pullen, J. Tessarolo, G. H. Clever, *Chem. Sci.* **2021**, *12*, 7269-7293; d) S. Saha, B. Holzapfel, Y.-T. Chen, K. Terlinden, P. Lill, C. Gatsogiannis, H. Rehage, G. H. Clever, *J. Am. Chem. Soc.* **2018**, *140*, 17384-17388; e) S. Pullen, G. H. Clever, *Acc. Chem. Res.* **2018**, *51*, 3052-3064; f) W. M. Bloch, Y. Abe, J. J. Holstein, C. M. Wandtke, B. Dittrich, G. H. Clever, *J. Am. Chem. Soc.* **2016**, *138*, 13750-13755; g) Y. K. Kryschenko, S. R. Seidel, D. C. Muddiman, A. I. Nepomuceno, P. J. Stang, *J. Am. Chem. Soc.* **2003**, *125*, 9647-9652.
- 11 a) J. E. M. Lewis, *Chem. Eur. J.* **2021**, *27*, 4454-4460; b) S. S. Mishra, S. V. K. Kompella, S. Krishnaswamy, S. Balasubramanian, D. K. Chand, *Inorg. Chem.* **2020**, *59*, 12884-12894; c) L. S. Lisboa, J. A. Findlay, L. J. Wright, C. G. Hartinger, J. D. Crowley, *Angew. Chem. Int. Ed.* **2020**, *59*, 11101-11107; d) J. E. M. Lewis, A. Tarzia, A. J. P. White, K. E. Jelfs, *Chem. Sci.* **2020**, *11*, 677-683; e) B. Chen, S. Horiuchi, J. J. Holstein, J. Tessarolo, G. H. Clever, *Chem. Eur. J.* **2019**, *25*, 14921-14927; f) D. Preston, J. E. Barnsley, K. C. Gordon, J. D. Crowley, *J. Am. Chem. Soc.* **2016**, *138*, 10578-10585; g) S. Löffler, J. Lütben, A. Wuttke, R. A. Mata, M. John, B. Dittrich, G. H. Clever, *Chem. Sci.* **2016**, *7*, 4676-4684; h) S. E. Walker, S. A. Boer, T. Malcomson, M. J. Paterson, K. L. Tuck, D. R. Turner, *Chem. Commun.* **2021**, *57*, 12456-12459.
- 12 C.-L. Liu, E. O. Bobylev, Y. Fu, D. A. Poole Iii, K. Robeyns, C.-A. Fustin, Y. Garcia, J. N. H. Reek, M. L. Singleton, *Chem. Eur. J.* **2020**, *26*, 11960-11965.
- 13 a) F. Kerff, C.-L. Liu, X. Mu, U. Gilbert, L. Smal, L. Meinertzhagen, B. Kauffmann, K. Robeyns, M. L. Singleton, *ChemPlusChem* **2021**, *86*, 1162-1166; b) E. Berni, B. Kauffmann, C. Bao, J. Lefevre, D. M. Bassani, I. Huc, *Chem. Eur. J.* **2007**, *13*, 8463-8469.
- 14 a) S. M. Jansze, G. Cecot, M. D. Wise, K. O. Zhurov, T. K. Ronson, A. M. Castilla, A. Finelli, P. Pattison, E. Solari, R. Scopelliti, G. E. Zelinskii, A. V. Vologzhanina, Y. Z. Voloshin, J. R. Nitschke, K. Severin, *J. Am. Chem. Soc.* **2016**, *138*, 2046-2054; b) A. M. Johnson, C. A. Wiley, M. C. Young, X. Zhang, Y. Lyon, R. R. Julian, R. J. Hooley, *Angew. Chem. Int. Ed.* **2015**, *54*, 5641-5645; c) Q.-F. Sun, J. Iwasa, D. Ogawa, Y. Ishido, S. Sato, T. Ozeki, Y. Sei, K. Yamaguchi, M. Fujita, *Science* **2010**, *328*, 1144-1147.
- 15 M. L. Singleton, N. Castellucci, S. Massip, B. Kauffmann, Y. Ferrand, I. Huc, *J. Org. Chem.* **2014**, *79*, 2115-2122.
- 16 a) Y. Fang, J. A. Powell, E. Li, Q. Wang, Z. Perry, A. Kirchon, X. Yang, Z. Xiao, C. Zhu, L. Zhang, F. Huang, H.-C. Zhou, *Chem.*

- Soc. Rev.* **2019**, *48*, 4707-4730; b) J. Lee, O. K. Farha, J. Roberts, K. A. Scheidt, S. T. Nguyen, J. T. Hupp, *Chem. Soc. Rev.* **2009**, *38*, 1450-1459.
- 17 E. O. Bobylev, D. A. Poole Iii, B. de Bruin, J. N. H. Reek, *Chem. Sci.* **2021**, *12*, 7696-7705.