Balancing Ligand Flexibility versus Rigidity for the Stepwise Self-Assembly of M12L24 via M6L12 Metal–Organic Cages

Liu, C.-L.; Bobylev, E.O.; Fu, Y.; Poole III, D.A.; Robeyns, K.; Fustin, C.-A.; Garcia, Y.; Reek, J.N.H.; Singleton, M.L.

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Balancing Ligand Flexibility versus Rigidity for the Stepwise Self-Assembly of $M_{12}L_{24}$ via $M_6L_{12}$ Metal–Organic Cages


Abstract: Non-covalent interactions are important for directing protein folding across multiple intermediates and can even provide access to multiple stable structures with different properties and functions. Herein, we describe an approach for mimicking this behavior in the self-assembly of metal–organic cages. Two ligands, the bend angles of which are controlled by non-covalent interactions and one ligand lacking the above-mentioned interactions, were synthesized and used for self-assembly with Pd$^{2+}$. As these weak interactions are easily broken, the bend angles have a controlled flexibility giving access to $M_6L_{12}$, $M_6(L_2)_{12}$, and $M_{12}(L_2)_{24}$ cages. By controlling the self-assembly conditions this process can be directed in a stepwise fashion. Additionally, the multiple endohedral hydrogen-bonding sites on the ligand were found to play a role in the binding and discrimination of neutral guests.

The last decades have seen significant advances in the development of molecular systems capable of self-assembling into discrete complex structures. (1) Of the reported approaches, metal–ligand coordination based self-assembly has become one of the most widely used. (2) Numerous nano-sized molecular objects have been reported and found to have interesting applications for sensing, catalysis, drug delivery, storage, and molecular recognition, etc. (3) One of the main tenets in the design of these systems is that the size and shape of the final self-assembled structures can to an extent be predicted based on the shape of the ligands and the coordination preferences of the metal. (4) As an example, the most studied metals for self-assembly, Pd$^{2+}$ and Pt$^{2+}$, form square planar complexes. (5) When combined with rigid, bent, ditopic ligands this leads to metal–organic polyhedra of $M_nL_{2n}$ stoichiometry, where $n$ for the thermodynamically most stable species are generally dependent on the bend angle (angle between donor sites) of the ligand and limited to certain values as a result of geometric constraints. (6) By this strategy, numerous self-assembled $M_nL_{2n}$ cages with $n=2, 4, 6, 8, 9, 12, 24, 30, 48$ have been described. (7) As the number of components involved is generally large, the self-assembly process for even small cages is complex. Multiple factors (examples: counter ion, solvent, etc.) can influence the topology and nuclearity of the self-assembled structures. (8) In the case of $M_{12}L_{24}$ assemblies, studies by the groups of Yoneya, (9) Fujita (10) and Hiraoka (11) have highlighted the diversity of the different possible self-assembly pathways on the potential energy landscape leading to the final most stable structure. Several metastable species, notably $M_6L_{12}$, $M_8L_{16}$, and $M_6L_{18}$, have been identified as kinetic intermediates. However, these species typically exist as mixtures and clean formation of single intermediates in the assembly of larger structures is rare, (12) their stability being limited in part due to tension imparted by the rigid ligands being forced to adapt to narrower bend angles. Though less predictable, flexible ditopic ligands, containing for example aliphatic segments, can lead to the formation of multiple structures, with templates being generally required to shift the equilibrium between them. (13) As such, these provide systems that can evolve, both in terms of structure and function, in response to stimuli. (14) Nevertheless, flexible ditopic ligands generally give smaller self-assembled structures and their use for the formation of larger metal–organic cages is limited. (15)

Interestingly, ditopic ligands that have properties in between flexible and rigid have been less explored (16) but could allow multiple large cages to be selectively obtained from a single combination of metal and ligand. Heteroaromatic amide based ligands, such as in Figure 1, can be an interesting candidate for this purpose. These ligands are flexible in the torsion angles around the amides. However, conjugation across the amide leads to a preferred planar structure and dipole-dipole/hydrogen bonding interactions give strong conformational preferences for the curved structures shown. This motif has been widely used for the development of aromatic oligoamide foldamers with highly predictable and stable structures. (17) For metal based self-assembly, ligands of this type have been used for the formation of small Pd$_4$L$_4$ cages but never been shown to be applicable for larger structures. (18–d) As the above interactions should limit the flexibility of the bend angle, we reasoned that large cages could be accessible. Moreover; as
minor deviations in the torsion angles can lead to an increase in the ligand bend angle, transformation to larger cage structures can potentially be facilitated just by heating; the energetic cost of the less favored conformation being compensated by the additional M–L bonds.

Based on this idea and to study how conformational preferences for the ligand can be used to control self-assembly, we developed ligands L1–L3, Figure 1. L1 and L2 favor the concave structures because of electrostatic/hydrogen bonding interactions, while L3 lacks the above-mentioned N-H-N interactions and is expected to be more flexible. The X-ray structures of L1 and L2 indeed show the expected curved flat structures. To look at the restriction of the torsion angles around the amides and the flexibility of the ligand, molecular dynamics simulations (See Supporting Information) were used to compare the properties of L2 to the analogous structure lacking endocyclic nitrogens, L4. These indeed show that while the latter is wildly flexible, the two pyridyl moieties in L2 prefer the conformation observed in the X-ray structure. Still, a range of bend angles is possible, potentially giving access to multiple stable species. This variability can also be seen in the self-assembly of L1.

Complexation of L1 with Pd^{2+} (NO_3^−, BF_4^−, CF_3SO_3^− or PF_6^− salt) in [D_6]DMSO results in significant shifts of the proton resonances as depicted in the ^1H NMR (Figure 2A,B). The formation of a single species was supported by diffusion-ordered 1H NMR (DOSY), Figure 2C, which shows all new signals having the same diffusion coefficient of D = 7.49 × 10^{-11} m^2 s^{-1}. The diffusion coefficient in hand, a radius of 13.4 Å can be estimated for the formed system using the Stokes-Einstein-Equation. Figure 2D, HRMS analysis suggests formation of a complex with the formula Pd_{L1}4(BF_4)_2 based on a series of isotopic pattern corresponding to the loss of two, three, and four BF_4^− counterions.

The composition was further supported by its solid-state structure, Figure 2E. Each of the palladium ions is found in a square planar N_4 coordination environment comprised of four pyridine units. The N-Pd-N bond angles are all between ~98–99° and the tetrahedral twist is less than 4°, indicating minimal distortion around the metal. The two palladium (II) ions are bridged by four ligands with a metal–metal distance of 13.3 Å. However, the curved structure of the ligands and the isobutoxy side chains result in a larger diameter for the cage. Distances between terminal carbons on the side chains ranged between 22.9–26.7 Å, consistent with the value obtained by 1H DOSY.

Importantly, compared to the crystal of free L1, where the bend angle is ~36°, the average bend angle has increased to ~0° in the Pd_{L1} complex. This difference can be partially attributed to distortions of the C-C-N (113° to 116° in complex) and C-N-C (128° to 124° in complex) angles of the amides. However, the pyridine amides are also twisted away from coplanarity with the central diazaanthracene by ~37–60° further increasing the bend angle. Similar twisting was observed by Gan and co-workers for an analogous complex containing 9-fluorodiazaanthracene units. These changes show that the bend angle of these ligands can adapt to form well-defined self-assembled structures, at the expense of weakening the non-covalent interactions. The balance between flexibility and
the rigidity imparted by these interactions should have important directing effects for the self-assembly of ligands with larger bend angles, such as L2.

To study this, the self-assembly of L2 with Pd2+ (NO3−, BF4−, CF3SO3− or PF6− salt) was followed by 1H NMR. Within ten minutes of mixing L2 with Pd2+ at 75°C in DMSO, the ligand is converted into a single high symmetry species, Figure 3A,B. Once formed, this species can be kept in solution at room temperature with no discernable change observed over the course of at least several days. 1H DOSY experiments (Figure 3D) on this complex indicate a discrete species with $D = 4.21 \times 10^{-11}$ m²s⁻¹, corresponding to a radius of 23.8 Å. This size fits within the calculated dimensions of a Pd₆(L2)₁₂ cage structure (18.8 < $r_{\text{solid}}$ < 29.2 Å), vide infra, and is comparable to sizes for M₁₄L₁₂ structures with similar distances between the N-donor atoms.[74] Further evidence for the Pd₆(L2)₁₂ was obtained by cold-spray ionization mass spectrometry (CSI-MS) on the BF₄− salt of the compound, Figure 3E. A series of isotopic patterns corresponding to [Pd₆(L2)₁₂(BF₄)₈-nBF₄]⁺ (n = 4–9) were observed which match well with the simulated isotopic spectra.

After continued heating for one hour, Pd₆(L2)₁₂ remains the major species in solution by 1H NMR, however a new set of signals starts to appear. These become the major species over the course of four hours giving a spectra with a single set of signals, suggesting the formation of a large symmetric structure, Figure 3C. When this change is followed by CSI-MS, the signals for Pd₆(L2)₁₂ disappear and are replaced by a series of isotopic patterns corresponding to [Pd₆(L2)₁₂(BF₄)₈-nBF₄]⁺ (n = 8–13), Figure 3F. Consistent with this, a single diffusion band ($D = 3.84 \times 10^{-11}$ m²s⁻¹) is seen in the 1H DOSY spectrum indicating an object with a larger radius (26.4 Å) than the M₁₄L₁₂ species, which based on the CSI-MS results is assigned to Pd₆(L2)₂₄.

As the components of the solution are not changed and the self-assembly occurs with a range of counterions, the step-wise process may be rationalized based on the conformational control of the ligand. The para relationship in the amino-pyridine groups in L2 results in an average free ligand bend angle of $\approx 82°$, based on the X-ray structure. This value should favor formation of the observed M₁₄L₁₂ cage.[74] However, a 30° increase, as observed with L1, can permit the formation of the M₁₄L₂₄ cage.[76] While the latter should ultimately be thermodynamically favored,[106] a significant distortion from the preferred conformation of the ligand is needed. By contrast, the narrower angle needed for the former should be more easily accessible and the formed M₁₄L₁₂ structure should further benefit from stronger intraligand non-covalent interactions. For both cages, the control of the ligand conformation by the non-covalent interactions is important. In L3, where the amide proton is replaced by a methyl group, the increased flexibility does not permit the formation of the larger structures. Rather, self-assembly with Pd2+ under all conditions gave the mononuclear Pd(L3), see Supporting Information.

In order to look at changes in the ligands in the M₁₄L₁₂ and M₁₄L₂₄ complexes, theoretical calculations at the semi-empirical PM6 level using Gaussian 09 were employed.[118] The computed structures obtained for L1, L2, and Pd₆(L1) agree well with the structures determined by X-ray diffraction. The geometry-optimized structures proposed for Pd₆(L2)₁₂ and Pd₆(L2)₂₄, Figure 4B,C, show highly symmetric assemblies with radii of 22 and 29 Å respectively, within range of the values determined from the 1H DOSY studies. Relative to the calculated structure of free L2, noticeable distortions are present in both cages. First, the average bend angles have increased to 97° and 120° for Pd₆(L2)₁₂ and Pd₆(L2)₂₄ respectively. Unlike Pd₆(L1)₈, the calculated C-C-N and C-N-C angles show only modest changes between the M₁₄L₁₂ and M₁₄L₂₄ cages (114.8° vs. 115.2° for C-C-N and 125.5° vs. 124.7° for C-N-C). The difference in bend angle appears to result primarily from twisting of the pyridine amides. Average torsion angles between the amides and the central aromatic units for the Pd₆(L2)₁₂ and Pd₆(L2)₂₄ structures are 36° and 55° respectively, versus an angle of nearly 0° in L2. For the free ligand, the observed coplanar conformation results from a combination of conjugation and dipole-dipole interactions. Deviation from this conformation to reach the larger bend angles should thus entail a weakening of these interactions. This can be seen in the intraligand hydrogen bonding, where the longer NH···N distance and smaller NH···N angle calculated for Pd₆(L2)₂₄ (2.67 Å) versus Pd₆(L2)₁₂ (2.48 Å) would be consistent with a weaker interaction. Conversely, the narrower ligand bend angle in Pd₆(L2)₁₂ allows stronger intraligand interactions, which should help stabilize this intermediate during self-assembly.

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![Figure 3](https://example.com/figure3.png)

Figure 3. 1H NMR spectra of A) L2, B) Pd₆(L2)₁₂, and C) Pd₆(L2)₂₄. D) An overlay of the DOSY spectra of L2, Pd₆(L2)₁₂, and Pd₆(L2)₂₄. Corresponding average diffusion coefficients are shown. E) Portion of the UHR CSI-MS for Pd₆(L2)₁₂ and F) Pd₆(L2)₂₄ as their BF₄− salts. Insets show the comparison of the observed isotopic bundles with the simulated spectra.
Of note, during the self-assembly with L2 a decrease in signal intensity was observed in the NMR upon going from M_6L_{12} to M_4L_{24}. Using methylsulfone as an internal standard showed that, while for Pd_4(L1)_4 the ¹H NMR signals represent >90% of the initial ligand concentration, for Pd_4(L2)_{12} and Pd_6(L2)_{24} the signals correspond to 51% and 13% respectively. As no precipitation was observed, this was postulated to be due to aggregation of the complexes, a phenomenon previously observed with some metal organic cages. Indeed, dynamic light scattering (DLS) measurements on solutions of Pd_4(L1)_{12}, Pd_4(L2)_{12} and Pd_6(L2)_{24} indicated the presence of well-defined particles with hydrodynamic radii of 63–85 nm, see the Supporting Information. For Pd_6(L2)_{24} this was further confirmed by SEM analysis which found spherical particles with sizes consistent with radii determined by DLS. For the other two complexes, no particles were observed by SEM. This could be due to the lower concentration of the aggregates as indicated in the NMR. Additionally, the lower value of scattered light intensity (I/I_0) in the DLS studies of Pd_6(L2)_{12} suggest that the aggregates are present in small quantity in this sample. Variable temperature NMR studies suggest that the aggregates are quite stable. Heating a DMSO sample of Pd_6(L2)_{24} gives a minor increase in intensity for the signals corresponding to the cage at 80°C. Nevertheless, this still only accounts for around 21% of the total ligand concentration, indicating only slight disaggregation. Similar results were obtained by variable temperature DLS studies.

In addition to their structural role, the endohedral functionalization by the groups on the ligands can potentially assist in the binding and discrimination of guests. Indeed, the amides appear to interact with the included solvent molecules in the crystal structure of Pd_4(L1)_{12}. While, metal–organic cages have been widely exploited for host-guest chemistry, binding neutral guests in polar solvents is still challenging due to competition with counterions and favorable solvation of the guests. To look at the guest binding ability of the aromatic amides cages, we performed preliminary studies on the interaction of neutral guests pyromellitic diimide (G1) and pyromellitic di-anhydride (G2) with the Pd_4(L1)_{12} cage, Figure 5. Both guests are highly soluble in DMSO. Addition of G1 to a solution of Pd_4(L1)_{12} cage in [D_6]DMSO, resulted in obvious shifts in the proton resonances of the cage, including a noticeable upfield shift for the amide N–H and methyl resonances. NMR titrations for the host-guest binding suggest an affinity of ≈11 M⁻¹ in DMSO. Similar association constants in DMSO were reported for other Pd_4L_4 cages with polar nitrile containing guests. For the interaction between G1 and the cage, aromatic stacking interactions likely play a role given the shielding observed for the majority of the ligand resonances in the presence of the guest. Still, the different binding between G1 and G2 indicates that hydrogen bonding interactions between the guest and the host C–H or N–H groups may also be important. The small downfield shift for the signal at 8.9 ppm suggests an interaction between the guest carbonyls and the 2-position C–H of the pyridines as has been previously observed in other cages.

In summary, we have shown that aromatic amide based ligands are capable of self-assembling with Pd^{2+} to give access...
to multiple $M_{12}L_2$ ($n=2, 6$ and $12$) metal–organic cages. The shape of these ligands is stabilized by non-covalent interactions. This bestows a rigidity that allows access to the larger structures, while at the same time permitting a moderate degree of flexibility so that the bend angle can adapt to both the $M_{12}L_2$ and $M_{12}L_3$ cages. While the self-assembly of ligand L2 eventually gives an $M_{12}L_4$ cage ($\approx 120^\circ$), the narrower bend angle ($\approx 97^\circ$) in the $M_{12}L_2$ structure can allow for stronger intramolecular non-covalent interactions. This can potentially stabilize it as a kinetic intermediate and allow for the unique step-wise self-assembly observed. Preliminary studies with Pd$_2$(L)$_4$ showed the potential for interaction and discrimination of charge-neutral guests in highly polar solvents. This can be potentially interesting for applications in catalysis. Studies aimed at increasing the interaction with guests and fine-tuning the cage environments are underway and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

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