nature portfolio

Peer Review File

Rational design of metal-organic cages to increase the number of components via dihedral angle control

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

Comments to the authors:

The Review article written by Hiraoka and co-workers with the following title “Rational design of metal-organic cages to increase the number of components via dihedral angle control” describes a series of metal organic cages (MOCs) using multitopic ligands such as the exo-tridentate tris-pyridyl-triazine (TPT) and tris-pyridyl-benzene (TPB) ligands and cis-protected square planar Pd(II) ions. The ligands have the same coordination directions but different aromatic core and hence different dihedral angle θ. The output of the research is that using the cis-protected Pd(II) ion and the tridentate ligands with different dihedral angles results in M9L6 and M12L8 cages as kinetic and thermodynamic products if θ = 36° whereas an M12L8 sheet structure is formed when θ = 90. The authors claim that geometric communications among neighboring multitopic ligands through coordination bonds are key for the formation of large assemblies.

The work done by Hiraoka and co-workers is extremely nice as the addressed topic has been done with superb detail and in a meticulous way answering fundamental questions in supramolecular systems made of MOCs. The experimental and theoretical approach used in this work is furnishing structural insights that are very important in the scientific community working in this area. Moreover, the geometrical analysis done can be expanded to many other supramolecular systems involving MOCs, not only isolated MOCs, but for instance in mechanically interlocked MOCs.

The crystallographic data is correct and I did not detect any problem with it. The low completeness is probably due to the weak diffracting at high 2-theta angles in the open icosahedron structure. Both structure are publishable.

After reading the paper, I have some minor comments for the authors that are merely suggestions. The article can be accepted almost as it is, but I feel that some of the comments pointed below should be addressed.

Comments to the authors.

i) In Figure 1, caption, in Scheme 1b, the open octahedron [Pd'624]12+ is formed only in the solution state. Through the article and the SI I could not find any comment about attempts to grow single crystals of the [Pd'624]12+ octahedron. Have the authors tried crystallizing it? I expect some comment on this point that is very important to confirm if such structures are stable in the solid state.

ii) In the SI, there is an energy-minimized structural model (no experimental X-ray data) of [Pd624]12+. I guess no single crystals were obtained also for this M6L4. Here I make the same comment as in the precedent point. How about single crystals? In my opinion, the difficulties in getting single crystals means that maybe the M6L4 using 2 are quite difficult to be formed, and this might be due to the non-planar geometry of the TPB ligand. I mention this because the TPT (ligand 1) forms easily M6L4 single crystals (i.e., Fujita's work).

iii) Regarding the simulated M6L4 structures with 2, it will be good to compare the energy-minimized structures [Pd624]12+ vs [Pd'624]12+. This is optional for the authors if they want to include it or not. At the moment, all the experimental data is sufficient to support their claims.

iv) In page 4, top left column, in the sentence: "Therefore, the large strain caused in the M6L4 open octahedron by increasing θ is the reason why [Pd624]12+ was not formed". Because in Figure 1a, it is shown that using the same ligand 2, but changing the cis-protected Pd(II) group the M6L4 is formed, it means that θ is not the only factor controlling the self-assembly of the octahedron cage. Maybe this sentence should be rephrased accordingly.

v) In Figure 6, caption, it is not clear from which reported structure is the ZnCl2-py (M12L8 cage) geometrical analysis. The authors should indicate in the figure caption the reference from which the structure has been selected to do the analysis.

vi) In page 5, last paragraph in the sentence: "Because the complexation of 2 with ZnCl2 caused immediate precipitation and the resulting solid was not soluble in both polar and apolar solvents, thermodynamic discussion in the solution state was impossible." In this paragraph the authors should indicate the reference 38 (Torresi, S. et al. JACS) that reports also such fast precipitation.

vii) In the Geometric Analysis section, it is emphasized the importance of the dihedral angle θ in the self-assembly outcome, which is calculated to be 36.5 ° according to the energy-minimized structure of 4-pyridylbenzene. I think, it could be good to mention that has been reported

experimentally in a M12L8 nanocage self-assembled of ZnI2 and TPB (ligand 2 in the article) which shows one of the pyridine rings disordered over two positions and the angle formed by the two disordered rings is 35.69 ° that fits very well the calculated by the authors. If the authors find it pertinent, it will be worth quoting this reference: Chem. Eur. J. 2023, 29, e2023020.

Reviewer #2 (Remarks to the Author):

This work discusses the factors influencing dihedral angle control for construction of metal organic cages with large sizes. The authors suggested that the strains in the component rings could be key factors, which could control remote geometric rearrangements among neighboring multitopic ligands through coordination bonds, for large assemblies. The analysis throughout the paper is highly systematic, providing a detailed comparison of the influencing factors on the formation of different metal-organic cage structures, and these analytical approaches are expected to greatly assist subsequent research efforts in the future. However, it should be noted that there already exists a series of prior work on the impact of dihedral angles of metal-organic cages on the assembly of supramolecular structures. Additionally, the topologies of the metal-organic cages discussed in this paper are not new, and they have been reported in previous literatures (J. Am. Chem. Soc. 2008, 130, 35, 11641; J. Am. Chem. Soc. 2019, 141, 12147; Chem. Sci. 2020, 11, 10167.). The authors have not introduced new geometric configurations of cage structures through the aforementioned analysis, thus demonstrating a lack of innovation in structural design. Furthermore, there are some issues identified in the computational analysis process, suggesting a need for major revisions. Therefore, I recommend substantial revisions to address these issues at least.

1.1) The explanation of some structures is based on calculation and comparison of energies. However, doing so on molecular mechanics calculations is quite dangerous. I suggest confirming all these structures by running DFT calculations in order to get more accurate energy differences. This could also allow the authors to better rationalize the geometrical considerations leading to the formation of larger architectures.

2) Similarly, in the paper, particularly in the analysis of certain metal vertices or some simple coordination complex, the authors employed DFT computational simulations. This introduces a lack of uniformity in the computational methods used in the manuscript. Therefore, it is strongly recommended to perform DFT calculations on cage structures and discuss the results accordingly.

2.In the manuscript, authors mentioned: “A large positive entropy change is probably due to the stabilization of the transition state by solvent and/or counter anions.” The solvents used to form [Pd12L8]24+ and [Pd9L6]18+ are also different. Please include necessary discussion and experiments on the effects of solvents to the system.

3.1) Signals of Figure S5. HMQC spectrum is unclear, please expand the aA-aA region.

2) In Figure S10b, there are some sharp signals between 9.2 to 8.6 ppm, please specify these substances.

Reviewer #3 (Remarks to the Author):

In this piece of work, Hiraoka and coworkers revisit Fujita's triazine ligand forming an octahedral cage and show that a slight ligand modification or capping group change can have a big influence on the self-assembly processes. They demonstrate the formation of two new cages of composition M9L6 under kinetic control and a M12L8 species under thermodynamic control. For this, the triazine core in the ligand of Fujita is replaced by a benzene core which is responsible for a notable change in the dihedral angles in the structure resulting in the formation of these higher nuclearity species. An in-depth analysis of structural parameters, strain, and energy differences allows the authors to rationalize their findings. They also show the formation of rings and grids by careful control of dihedral angle and steric hindrance on both ligand and capping group. They eventually demonstrate narcissistic self-sorting when the well-known triazine ligand and the benzene one are mixed in solution.

I think this is an interesting work with a beautiful crystal structure of the Pd12L8 assembly, a very strong theoretical background and overall important new results for the community. The reading experience is rather heavy and I don't know if a broader chemistry community would find the results accessible and well understandable. Maybe some more of the method parts of the mathematical model could be moved into the SI. I would recommend publication but after modification in a way that the manuscript feels a bit "lighter".

I also would like the authors to address the following comments:

- The MS data are of bad quality. The authors used CSI FT-ICR, would it be possible to make use of another method to have cleaner results? Other studies have demonstrated very clean MS spectra for species with even higher nuclearity or mass. Also for most of the isotopic patterns shown in the SI (Fig S3, S11, S26) it is clear that it is not a unique species as the pattern does not show a proper Gaussian shape typical for these types of assemblies. There is therefore overlap of several species (or fragments) from different nuclearities for the same m/z. This is a weak point of the presented data in this study.

- It is a bit confusing that the authors are comparing the formation of the Pd9 and Pd12 species as they are explicitly formed in different solvent mixtures. This also put into question the DOSY data. What viscosity was employed for the CD3NO2/CDCl3/CD3OD mixture to go into the equations? The chosen value will greatly influence the final diameter value given by the authors. Another question is then, can the Pd9 species really be formed in nitromethane only (there is always chloroform)? As seen in figure S9, it looks like heating is more transforming the species than making the signals merge. There is also definitely a side species as seen with the doublet around 8.65 ppm for example. But also an increase of the temperature results in the rise of new signals not present initially. And what is otherwise the influence of the solvent on the formation of the two species? As seen in figure S10, the formation of the Pd12 in the mixture is way less clean and it

seems like side species are present. Can the Pd12 be formed quantitatively in this mixture by directly heating the sample or by heating to even higher temperatures? This is a major question that is not answered here. A solvent influence on kinetic vs thermodynamic processes cannot be overlooked. I would open the same argument for the influence of anions as the authors show that both nitrate and BF4 are present. But why does the formation of these species necessitate TBANO3 and why not using directly a nitrate salt of Palladium?

- For the formation of Pd4(4)2, what is the final extra ligand coordinated to the outer Palladium cations? This is not given anywhere in the text or SI.

- The analysis in this paper focuses on additive strain contributions on the organic building blocks. I am missing, however, a mentioning (including proper references) of other possible factors that may influence assembly formation, such as the role/degree of dispersive through-space attractions between building blocks, solvation effects (concerning polarity, trapped solvents inside the cages), counter anion accessibility to the cationic metal sites and overall dipole moment of the assembly (even if such factors were not considered in the here employed model).

Responses to Reviewers' comments on NCOMMS-24-11077-T

Reviewer 1's comments and our responses

The Review article written by Hiraoka and co-workers with the following title "Rational design of metal-organic cages to increase the number of components via dihedral angle control" describes a series of metal organic cages (MOCs) using multitopic ligands such as the *exo*-tridentate tris-pyridyl-triazine (TPT) and tris-pyridyl-benzene (TPB) ligands and cis-protected square planar Pd(II) ions. The ligands have the same coordination directions but different aromatic core and hence different dihedral angle θ. The output of the research is that using the cis-protected Pd(II) ion and the tridentate ligands with different dihedral angles results in M_9L_6 and $M_{12}L_8$ cages as kinetic and thermodynamic products if $\theta = 36°$ whereas an $M_{12}L_8$ sheet structure is formed when $\theta = 90$. The authors claim that geometric communications among neighboring multitopic ligands through coordination bonds are key for the formation of large assemblies.

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After reading the paper, I have some minor comments for the authors that are merely suggestions. The article can be accepted almost as it is, but I feel that some of the comments pointed below should be addressed.

Comments to the authors

i) In Figure 1, caption, in Scheme 1b, the open octahedron $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ is formed only in the solution state. Through the article and the SI I could not find any comment about attempts to grow single crystals of the $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ octahedron. Have the authors tried crystallizing it? I expect some comment on this point that is very important to confirm if such structures are stable in the solid state.

Our response

We attempted to prepare single crystals of $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ truncated tetrahedron several times, but suitable crystals were not grown. This result has been added to the main text of the revised manuscript.

ii) In the SI, there is an energy-minimized structural model (no experimental X-ray data) of $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$. I guess no single crystals were obtained also for this M_6L_4. Here I make the same comment as in the precedent point. How about single crystals? In my opinion, the difficulties in getting single crystals means that maybe the M_6L_4 using **2** are quite difficult to be formed, and this might be due to the non-planar geometry of the TPB ligand. I mention this because the TPT (ligand **1**) forms easily M_6L_4 single crystals (i.e., Fujita's work).

Our response

As the reviewer surmised, we have not obtained single crystals of $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$. As mentioned in the original manuscript, single crystallization of a solution of $[\boldsymbol{Pd}_9\mathbf{2}_6]^{18+}$ in the presence of NO_3^- afforded single crystals of $[\boldsymbol{Pd}_{12}\mathbf{2}_8]^{24+}$. This result implies that the conversion of $[\boldsymbol{Pd}_9\mathbf{2}_6]^{18+}$ to $[\boldsymbol{Pd}_{12}\mathbf{2}_8]^{24+}$ occurs during crystallization. This is partly because of the high thermodynamic stability of $[\boldsymbol{Pd}_{12}\mathbf{2}_8]^{24+}$ and probably because of the packing effect of the assemblies. Because we found that $[\boldsymbol{Pd}_9\mathbf{2}_6]^{18+}$ can be obtained without NO_3^- in the revision of the manuscript, crystallization of $[\boldsymbol{Pd}_9\mathbf{2}_6]^{18+}$ was tested. Although single crystals that are different from those of $[\boldsymbol{Pd}_{12}\mathbf{2}_8]^{24+}$ were obtained, their poor quality prevented its structural determination.

Because solution studies of the complexation of $\boldsymbol{Pd}^{2+}$ and **2** do not indicate the formation of $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$, we could not attempt crystallization from a solution of $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$. As the reviewer suggested, the difficulty in obtaining single crystals of $[M_6\mathbf{2}_4]^{12+}$ truncated tetrahedron may be due to the nonplanarity of tritopic ligand **2**. However, because we did not have sufficient experimental results to support this hypothesis, although it is highly anticipated, we decided not to discuss this point in our manuscript.

iii) Regarding the simulated M_6L_4 structures with **2**, it will be good to compare the energy-minimized structures $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ vs. $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$. This is optional for the authors if they want to include it or not. At the moment, all the experimental data is sufficient to support their claims.

Our response

Thank you for this reviewer's suggestion of comparing the energy-minimized structures $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ and $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$. According to our DFT calculation (Figure 3a), when the *cis*-protecting group is ethylenediamine (en), φ can adopt wider range than in the case of TEMDA away from ideal φ value of 90°. Indeed, DFT-optimized structures of $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ and $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ indicate that they have similar average θ values of 22.6±1.9° (for $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$) and 27.5±1.5° (for $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$). In contrast, the φ values in $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ and $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ show a larger difference; 70.9±7.2° for $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ and 82.0±2.8° for $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$, indicating that φ in $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ is largely deviated from the ideal 90°. The small φ values in $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ relieve the strain in subcomponent rings of $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ caused by the dihedral angle θ being about 30°. This discussion has been added in the revised manuscript as follows:

"In other words, in the case of en, variable φ values cancel the effect of θ, diminishing the geometric communication among the tritopic ligands. This idea was confirmed by comparing the DFT-optimized structures of the $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ and $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ open octahedrons. Both cage structures have similar average θ values; 22.6±1.9° for $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ and 27.5±1.5° for $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$. In contrast, the φ values in $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ and $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ show a larger difference; 82.0±2.8 for $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ and 70.9±7.2° for $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ (Supplementary Fig. 16d), indicating that φ in $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ is largely deviated from the ideal 90°. The small φ values in $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ relieve the strain in subcomponent rings of $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ caused by the dihedral angle θ being about 30°."

iv) In page 4, top left column, in the sentence: "Therefore, the large strain caused in the M_6L_4 open octahedron by increasing θ is the reason why $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ was not formed". Because in Figure 1a, it is shown that using the same ligand **2**, but changing the *cis*-protected Pd(II) group the M_6L_4 is formed, it means that θ is not the only factor controlling the self-assembly of the octahedron cage. Maybe this sentence should be rephrased accordingly.

Our response

As the reviewer pointed out, θ is not the only factor to realize the self-assembly of large $[\boldsymbol{Pd}_9L_6]^{18+}$ and $[\boldsymbol{Pd}_{12}L_8]^{24+}$, and fixed φ value is the other key factor. This sentence is revised as follows:
"Therefore, the large strain caused in the M_6L_4 open octahedron by increasing θ under the fixed φ value is the reason why $[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$ was not formed."

v) In Figure 6, caption, it is not clear from which reported structure is the $ZnCl_2$-py ($M_{12}L_8$ cage) geometrical analysis. The authors should indicate in the figure caption the reference from which the structure has been selected to do the analysis.

Our response

Thank you for this reviewer's kind comment. The original crystal structure adopted for the analysis was reported in Ref. 38 in the manuscript. This reference is cited from the revised caption in Figure 6.

vi) In page 5, last paragraph in the sentence: "Because the complexation of **2** with $ZnCl_2$ caused immediate precipitation and the resulting solid was not soluble in both polar and apolar solvents, thermodynamic discussion in the solution state was impossible." In this paragraph the authors should indicate the reference 38 (Torresi, S. et al. JACS) that reports also such fast precipitation.

Our response

According to this reviewer's suggestion, Ref. 38 is cited properly in the revised manuscript.

vii) In the Geometric Analysis section, it is emphasized the importance of the dihedral angle θ in the self-assembly outcome, which is calculated to be 36.5° according to the energy-minimized structure of 4-pyridylbenzene. I think, it could be good to mention that has been reported experimentally in a $M_{12}L_8$ nanocage self-assembled of ZnI_2 and TPB (ligand **2** in the article) which shows one of the pyridine rings disordered over two positions and the angle formed by the two disordered rings is 35.69 ° that fits very well the calculated by the authors. If the authors find it pertinent, it will be worth quoting this reference: Chem. Eur. J. 2023, 29, e2023020.

Our response

Thank you for this kind comment. We agree with the reviewer's suggestion that the optimal θ value for the tritopic ligand **2** and 4-pyridylbenzene is observed in the crystal structures of $M_{12}\mathbf{2}_8$ cage structures (M = ZnX_2). Unfortunately, we could not find the reference suggested by the reviewer (*Chem. Eur. J.* **2023**, *29*, e2023020.). Instead, the reference that reports the crystal structure of $M_{12}\mathbf{2}_8$ cage structures (M = ZnI_2) (*Sci. Rep*. **2023**, *13*, 5605) is cited in the revised manuscript (Ref. 40).

Reviewer 2's comments and our responses

This work discusses the factors influencing dihedral angle control for construction of metal organic cages with large sizes. The authors suggested that the strains in the component rings could be key factors, which could control remote geometric rearrangements among neighboring multitopic ligands through coordination bonds, for large assemblies. The analysis throughout the paper is highly systematic, providing a detailed comparison of the influencing factors on the formation of different metal-organic cage structures, and these analytical approaches are expected to greatly assist subsequent research efforts in the future. However, it should be noted that ①there already exists a series of prior work on the impact of dihedral angles of metal-organic cages on the assembly of supramolecular structures. Additionally, the topologies of the metal-organic cages discussed in this paper are not new, and they have been reported in previous literatures (*J. Am. Chem. Soc*. **2008**, *130*, 35, 11641; *J. Am. Chem. Soc.* **2019**, *141*, 12147; *Chem. Sci.* **2020**, *11*, 10167.). The authors have not introduced new geometric configurations of cage structures through the aforementioned analysis, thus demonstrating a lack of innovation in structural design. Furthermore, there are some issues identified in the computational analysis process, suggesting a need for major revisions. Therefore, I recommend substantial revisions to address these issues at least.

Our response

Comment ①: As mentioned by this reviewer, our research does not provide new geometric configurations for constructing new structures. On the contrary, this is the point of this research that is different from previous contributions to the metal–organic cages. We supramolecular chemists believe that metal–organic cages can be designed by geometric complementarity among the building blocks based on the coordination directions (coordination vectors) of the multitopic ligand and the metal center. Therefore, we expect that self-assembly of the building blocks with the same coordination vectors such as tritopic ligands **1** and **2** would provide the same geometry. In this study, we observed the self-assembly of $[\boldsymbol{Pd}_9\mathbf{2}_6]^{18+}$ and $[\boldsymbol{Pd}_{12}\mathbf{2}_8]^{24+}$cages from **2** and $\boldsymbol{Pd}^{2+}$, which enabled us to deepen our understanding of the molecular design of building blocks and finally elucidated the importance of the remote geometric communication of building blocks. This was described in the conclusion section of our original manuscript as follows:

"The results obtained from a simple self-assembly system suggest that *remote geometric communications* among building blocks are a hidden important factor enabling giant assemblies in nature. Such a new perspective would allow us to rationally design large self-assemblies based on a higher level of geometric communication among the building blocks beyond the mere design of the shape of the building block itself."

Unlike usual research on metal–organic cages, this research does not provide perfectly new geometric types of assemblies, but finding an insight into the deterministic factors of the assembled structures is also worth evaluating in supramolecular chemistry.

The literature cited by this reviewer for M_9L_6 open triaugmented triangular prism has been added to the references in the revised manuscript (Ref. 37).

1.1) The explanation of some structures is based on calculation and comparison of energies. However, doing so on molecular mechanics calculations is quite dangerous. I suggest confirming all these structures by running DFT calculations in order to get more accurate energy differences. This could also allow the authors to better rationalize the geometrical considerations leading to the formation of larger architectures.

2) Similarly, in the paper, particularly in the analysis of certain metal vertices or some simple coordination complex, the authors employed DFT computational simulations. This introduces a lack of uniformity in the computational methods used in the manuscript. Therefore, it is strongly recommended to perform DFT calculations on cage structures and discuss the results accordingly.

Our response

According to this reviewer's suggestion, we performed DFT calculations of three types of assembled

structures composed of tritopic ligand **2** and $\boldsymbol{Pd}^{2+}$ ($[\boldsymbol{Pd}_6\mathbf{2}_4]^{12+}$, $[\boldsymbol{Pd}_9\mathbf{2}_6]^{18+}$, and $[\boldsymbol{Pd}_{12}\mathbf{2}_8]^{24+}$). The results have been added to the revised Supplementary Fig. 15 and Supplementary Table 1.

According to Reviewer 1's comment, the DFT-optimized structure of $[\boldsymbol{Pd'}_6\mathbf{2}_4]^{12+}$ was also obtained to discuss the effect of *cis*-protecting groups on the assembled structures. The structure has been added to the revised Supplementary Fig. 16d.

Optimized structures of $[\boldsymbol{Pd}\mathbf{1}_2]^{2+}$ and $[\boldsymbol{Pd}\mathbf{2}_2]^{2+}$ were also obtained by DFT calculations.

2. In the manuscript, authors mentioned: "A large positive entropy change is probably due to the stabilization of the transition state by solvent and/or counter anions." The solvents used to form $[\boldsymbol{Pd}_{12}L_8]^{24+}$ and $[\boldsymbol{Pd}_9L_6]^{18+}$ are also different. Please include necessary discussion and experiments on the effects of solvents to the system.

Our response

The sentence quoted by this reviewer is in the discussion on the dynamic motion in $[\boldsymbol{Pd}_{12}\mathbf{2}_8]^{12+}$ based on experimentally obtained $\Delta S^{\ddagger}$ determined by the Eyring plot. Thus, this value has nothing to do with the $[\boldsymbol{Pd}_9L_6]^{18+}$ structure. Regarding the solvent used for the formation of $[\boldsymbol{Pd}_9\mathbf{2}_6]^{18+}$ and $[\boldsymbol{Pd}_{12}\mathbf{2}_8]^{24+}$ cages, in our previous experiments, we used a mixed solvent ($CD_3NO_2/CDCl_3/CD_3OD$ = 7/3/2 (*v*/*v*/*v*)) because the tritopic ligand **2** is not solved in either CD_3NO_2 or CD_3OD. Because both $[\boldsymbol{Pd}_9\mathbf{2}_6]^{18+}$ and $[\boldsymbol{Pd}_{12}\mathbf{2}_8]^{24+}$ cages are soluble in CD_3NO_2, we performed the self-assembly of **2** and $\boldsymbol{Pd}(BF_4)_2$ in CD_3NO_2 and found that both cages can be generated in CD_3NO_2 only by heating in high yield. Thus, all NMR spectra for the characterization of the cages were recorded in CD_3NO_2, and these data are shown in the revised manuscript and SI.

3.1) Signals of Figure S5. HMQC spectrum is unclear, please expand the a^A–a^A region.

Our response

According to the reviewer's suggestion, Supplementary Figure 5 (Figure S5) has been revised to clearly show the correlation between the a^A–a^A region.

Reviewer 3's comments and our responses

In this piece of work, Hiraoka and coworkers revisit Fujita's triazine ligand forming an octahedral cage and show that a slight ligand modification or capping group change can have a big influence on the self-assembly processes. They demonstrate the formation of two new cages of composition M_9L_6 under kinetic control and a $M_{12}L_8$ species under thermodynamic control. For this, the triazine core in the ligand of Fujita is replaced by a benzene core which is responsible for a notable change in the dihedral angles in the structure resulting in the formation of these higher nuclearity species. An in-depth analysis of structural parameters, strain, and energy differences allows the authors to rationalize their findings. They also show the formation of rings and grids by careful control of dihedral angle and steric hindrance on both ligand and capping group. They eventually demonstrate narcissistic self-sorting when the well-known triazine ligand and the benzene one are mixed in solution.

I think this is an interesting work with a beautiful crystal structure of the $\boldsymbol{Pd}_{12}L_8$ assembly, a very strong theoretical background and overall important new results for the community. ①The reading experience is rather heavy and I don't know if a broader chemistry community would find the results accessible and well understandable. Maybe some more of the method parts of the mathematical model could be moved into the SI. I would recommend publication but after modification in a way that the manuscript feels a bit "lighter".

Our response

Comment ①: As mentioned by the reviewer, the description of geometric analysis in the Methods section is lengthy and not familiar to chemists. However, this analysis is one of the main points supporting the conclusion of this manuscript, and it is expected that this analysis can be applied to other systems to purely abstract the strain arising from geometric inconsistency. Therefore, after careful consideration, we decided to keep this section in Methods in the revised manuscript.

I also would like the authors to address the following comments:

(1) The MS data are of bad quality. The authors used CSI FT-ICR, would it be possible to make use of another method to have cleaner results? Other studies have demonstrated very clean MS spectra for species with even higher nuclearity or mass. Also for most of the isotopic patterns shown in the SI (Fig S3, S11, S26) it is clear that it is not a unique species as the pattern does not show a proper Gaussian shape typical for these types of assemblies. There is therefore overlap of several species (or fragments) from different nuclearities for the same *m/z*. This is a weak point of the presented data in this study.

Our response

As to the isotopic patterns of some signals for the cages, as pointed out by the reviewer, signals of other species, which would be assemblies composed of fewer components with smaller charge number, is(are) overlapped. In this research, we used three different mass spectrometers for the characterization of the assemblies (two types of ESI-TOF mass spectrometers and cold spray FT-ICR mass spectrometer) and found that FT-ICR mass is the best to detect the cages. For the revision of our manuscript, we again measured FT-ICR mass spectrometry for the cages under different conditions. Because $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ was obtained in the absence of NO_3^-, mass measurement of a solution of $[\boldsymbol{Pd}_9\boldsymbol{2}_6](BF_4)_{18}$ without NO_3^- was tested. It was found that the signals of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ were not found, indicating that the presence of NO_3^- is essential for the detection of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$. Solvent effect was also investigated for the measurements of the $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ cages. However, any improvement was not found.

(2) It is a bit confusing that the authors are ②comparing the formation of the Pd9 and Pd12 species as they are explicitly formed in different solvent mixtures. ③This also put into question the DOSY data. What viscosity was employed for the $CD_3NO_2/CDCl_3/CD_3OD$ mixture to go into the equations? The chosen value will greatly influence the final diameter value given by the authors.

Our response

Comment ②: In our previous experiments, a mixed solvent was used for the self-assembly of **2** and $\boldsymbol{Pd}(BF_4)_2$ because **2** is not soluble in CD_3NO_2. However, because the $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ cages are soluble in CD_3NO_2, we attempted self-assembly in CD_3NO_2 and found that $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ was selectively obtained in high yield by heating and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ was also selectively formed by heating in the presence of NO_3^-. NO_3^- accelerates the ligand exchanges to reach equilibration. Thus, all NMR spectral data are reported for CD_3NO_2 in the revised manuscript and SI.

Comment ③ : As to the question of the reviewer "*What viscosity was employed for the $CD_3NO_2/CDCl_3/CD_3OD$ mixture to go into the equations?*", the ^{1}H DOSY spectrum of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ cages were recorded in CD_3NO_2 after the solvent exchange; therefore, the viscosity of CH_3NO_2 was used for the calculation of the hydrodynamic radii of the cages.

(3) ④Another question is then, can the Pd9 species really be formed in nitromethane only (there is always chloroform)? ⑤As seen in figure S9, it looks like heating is more transforming the species than making the signals merge. There is also definitely a side species as seen with the doublet around 8.65 ppm for example. ⑥But also an increase of the temperature results in the rise of new signals not present initially.

Our response

Comment ④: Yes. As mentioned above, our additional experiment indicates that the $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ cage is selectively produced in CD_3NO_2 only.

Comment ⑤: The signal around 9.3 ppm is assigned to the $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ cage and the one at 8.65 is to the free **2**. Assignment of these signals has been added to the revised Supplementary Fig. 9 (Fig S9).

Comment ⑥: The appearance of the new signals and increase in the signal intensity of these signals by increasing the measurement temperature would be due to the transformation of the metastable $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ cage. For the revision of this manuscript, VT ^{1}H NMR measurements were performed in CD_3NO_2 only and we found that the minor signals found in the previous VT ^{1}H NMR measurement did not appear, and clean ^{1}H NMR spectra are shown in the revised Supplementary Fig. 9. This result indicates that the thermal stability of the $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ cage is higher in CD_3NO_2 only.

(4) ⑦And what is otherwise the influence of the solvent on the formation of the two species? As seen in figure S10, the formation of the Pd12 in the mixture is way less clean and it seems like side species are present. ⑧Can the Pd12 be formed quantitatively in this mixture by directly heating the sample or by heating to even higher temperatures? This is a major question that is not answered here. A solvent influence on kinetic vs thermodynamic processes cannot be overlooked.

Our response

Comment ⑦: In our previous attempt, the self-assembly of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ was performed in a mixed solvent at

298 K because tritopic ligand **2** is not soluble in CD_3NO_2. To this reviewer's point we tested the self-assembly of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ in CD_3NO_2 only and found that $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ is also produced in CD_3NO_2 by heating at 343 K in 96% yield. Thus, both $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ are formed in CD_3NO_2. It was also found that NO_3^- is necessary for the formation of $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ and that clean conversion was realized in CD_3NO_2, suggesting that heating at high temperature for a long time in the presence of $CDCl_3$ and CD_3OD initiates the decomposition of the assemblies. The new results obtained using CD_3NO_2 only as the solvent have been added to the revised Supplementary Fig. 10 (Fig. S10).

Comment ⑧: $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ was formed in 84% yield by heating a solution of $\boldsymbol{Pd}^{2+}$, **2**, and NO_3^- in a 3:2:1 ratio in CD_3NO_2 at 343 K for 51 h followed by 363 K for 94 h. The $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ cage was also generated first and then converted into $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$.

(5) I would open the same argument for the influence of anions as the authors show that both nitrate and BF_4^- are present. ⑨But why does the formation of these species necessitate $TBANO_3$ and ⑩why not using directly a nitrate salt of Palladium?

Our response

Comment ⑨: As mentioned above, it was found that $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ is produced without NO_3^- in 96% yield by heating 343 K in CD_3NO_2 and that NO_3^- is necessary for the efficient formation of $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ and the conversion of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ into $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$. Encapsulation of NO_3^- anions and strong interaction between NO_3^- and the $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ structure are not found in the crystal structure, indicating that the template effect of NO_3^- for the formation of $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ is very weak. Thus, the main role of NO_3^- is acceleration of ligand exchanges.

Comment ⑩: As mentioned above, NO_3^- promotes the conversion of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ into $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$, thus NO_3^- is not a suitable anion for the assembly of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$. In our previous attempt to form $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$, $\boldsymbol{Pd}^{2+}$, **2**, and NO_3^- were mixed in a 3:2:1 ratio at 298 K. When $\boldsymbol{Pd}(NO_3)_2$ is used as the metal source, NO_3^- presents in a higher concentration ($[\boldsymbol{Pd}^{2+}]_0$, $[\boldsymbol{2}]_0$, and $[NO_3^-]_0$ = 3:2:6), which is six times higher than that under our experimental conditions. Thus, as far as the self-assembly of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ is concerned, $\boldsymbol{Pd}(NO_3)_2$ is not a suitable metal source.

For the formation of $\boldsymbol{Pd}_4\boldsymbol{4}_2$, what is the final extra ligand coordinated to the outer Palladium cations? This is not given anywhere in the text or SI.

Our response

It is unclear what ligand coordinates to the outer $\boldsymbol{Pd}^{2+}$ units in $[\boldsymbol{Pd}_4\boldsymbol{4}_4]^{8+}$. There are no ^1H NMR signals for the candidate ligand coordinating to $\boldsymbol{Pd}^{2+}$ in $[\boldsymbol{Pd}_4\boldsymbol{4}_4]^{8+}$, except for the 4-pyridyl groups in **4**. The chemical shift of CH_3CN (used as the leaving ligand of the metal source) is the same as that of free CH_3CN. Because the same ^1H NMR spectrum of $[\boldsymbol{Pd}_4\boldsymbol{4}_4]^{8+}$ was obtained without NO_3^-, the coordination of NO_3^- to the Pd(II) center was excluded. Thus, residual H_2O in the solvent, CH_3CN, or BF_4^- would coordinate to the outer Pd(II) centers under faster exchange than the NMR time scale. This discussion has been added to the revised caption of Supplementary Fig. 19.

(6) The analysis in this paper focuses on additive strain contributions on the organic building blocks. I am missing, however, a mentioning (including proper references) of other possible factors that may influence assembly formation, such as the role/degree of dispersive through-space attractions between building blocks, solvation effects (concerning polarity, trapped solvents inside the cages), counter anion accessibility to the cationic metal sites and overall dipole moment of the assembly (even if such factors were not considered in the here employed model).

Our response

Thank you for this kind comment on the possibility of contributions from intermolecular interactions to the selection of the assembled structures. As the reviewer pointed out, the free energy differences among the assemblies in solution (higher thermodynamic stability of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ compared with $[\boldsymbol{Pd}_6\boldsymbol{2}_4]^{12+}$ in this research) are affected by various factors.

With regard to the dispersion interactions among the building blocks in the assemblies ($[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$, $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$, and $[\boldsymbol{Pd}_6\boldsymbol{2}_4]^{12+}$), there is no close contact among the tritopic ligands **2** in these structures, indicating that the dispersion interactions among the building blocks are negligibly small.

With regard to the solvation effects (concerning polarity, trapped solvents inside the cages), we could not

find solvents that alter the distribution of $[\boldsymbol{Pd}_6\boldsymbol{2}_4]^{12+}$, $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$, and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ under kinetic and thermodynamic controls, suggesting that the solvent effect would be small.

As for the counter anion accessibility to the cationic metal sites, as mentioned above, the $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ cages were produced without NO_3^-, although the yield of $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ in the absence of NO_3^- is not high, and the ^{1}H NMR spectra of the two cages were not affected by NO_3^-, indicating that the effect of relatively stronger coordination of NO_3^- to the Pd(II) centers in these cages was ruled out. ^{19}F NMR spectra of $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ cages showed only a signal of free BF_4^-, indicating weak interaction of BF_4^-. Considering that the local structures around Pd(II) centers in the $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$ cages are similar and that the cavities of these cages are larger than the size of NO_3^- and BF_4^-, the effect of these small anions appears to be small.

As to the overall dipole moment of the assembly, because of the relatively high symmetry of the assemblies ($[\boldsymbol{Pd}_6\boldsymbol{2}_4]^{12+}$, $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$, and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$) and of intramolecular dynamic motion as seen in $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{12+}$, causing further symmetrization, these assemblies would behave like a spherical molecule, although the symmetry of the $[\boldsymbol{Pd}_9\boldsymbol{2}_6]^{18+}$ cannot be reduced compared to $[\boldsymbol{Pd}_6\boldsymbol{2}_4]^{12+}$ and $[\boldsymbol{Pd}_{12}\boldsymbol{2}_8]^{24+}$.
Therefore, as a first approximation, the energy differences among the assemblies can be dictated as the strain in the assemblies. Such a simplified artificial system enabled us to abstract the importance of remote geometric communications between the building blocks to discriminate the assemblies composed of different numbers of building blocks.

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

I reviewed the revised article written by Hiraoka and co-workers with the following title “Rational design of metal-organic cages to increase the number of components via dihedral angle control” describes a series of metal organic cages (MOCs) using multitopic ligands such as the exo-tridentate tris-pyridyl-triazine (TPT) and tris-pyridyl-benzene (TPB) ligands and cis-protected square planar Pd(II) ions.

Hiraoka and co-workers have responded to the comments raised by the referees with great detail and justified their findings in their response. The manuscript has been modified accordingly, and two new authors have been added.

After reading the reply to the comments raised by the referees and the revised manuscript and Supporting Information, I feel that the article can be accepted for publication in Nature Communications without additional corrections from my side.

The article is very important as it describes new insights into the “remote geometric communication of building blocks” for the self-assembling of multi-component metal organic cages. This structural analysis is unique in the field of supramolecular metal organic cages.

Reviewer #2 (Remarks to the Author):

This work discusses the factors influencing dihedral angle control for construction of metal organic cages with large sizes. The authors suggested that the strains in the component rings could be key factors, which could control remote geometric rearrangements among neighboring multitopic ligands through coordination bonds, for large assemblies. The analysis throughout the paper is highly systematic, providing a detailed comparison of the influencing factors on the formation of different metal-organic cage structures, and these analytical approaches are expected to greatly assist subsequent research efforts in the future. The authors have already revised the manuscript accordingly. The revised manuscript currently also meets the high standard of Nat. Commun. and I recommend it for publication in Nat. Commun. without change.

Reviewer #3 (Remarks to the Author):

In the revised version of manuscript NCOMMS-24-11077-T, Hiraoka and coworkers have addressed all the comments raised by the reviewers. In particular, they have commented on the situation concerning the lack of Xray data, provided new DFT data for comparing isomeric structures, and clarified the discussion concerning crucial parts of the manuscript. Also, a reasonable set of additional references was added. Concerning the criticism of reviewer 2, novelty in terms of providing new structural motifs is not the focus and thus not required for this more mechanistic study. Also, the citations provided by reviewer 2 do not refer to the same class of Pd-based assemblies as is described herein. Concerning the points raised by reviewer 3, meaningful additional data has been provided and discussions updated accordingly. Overall the quality of the manuscript has improved and it can be accepted in the current form.

Response to referees' comments on NCOMMS-24-11077A

Reviewer #1:

I reviewed the revised article written by Hiraoka and co-workers with the following title "Rational design of metal-organic cages to increase the number of components via dihedral angle control" describes a series of metal organic cages (MOCs) using multitopic ligands such as the exo-tridentate tris-pyridyl-triazine (TPT) and tris-pyridyl-benzene (TPB) ligands and cis-protected square planar Pd(II) ions.

Hiraoka and co-workers have responded to the comments raised by the referees with great detail and justified their findings in their response. The manuscript has been modified accordingly, and two new authors have been added.

After reading the reply to the comments raised by the referees and the revised manuscript and Supporting Information, I feel that the article can be accepted for publication in Nature Communications without additional corrections from my side.

The article is very important as it describes new insights into the "remote geometric communication of building blocks" for the self-assembling of multi-component metal organic cages. This structural analysis is unique in the field of supramolecular metal organic cages.

Our response:

Thank you very much for this reviewer's kind review of our manuscript and providing valuable comments, which enriched the discussions in this paper and enhanced the value of this study.

Reviewer #2:

This work discusses the factors influencing dihedral angle control for construction of metal organic cages with large sizes. The authors suggested that the strains in the component rings could be key factors, which could control remote geometric rearrangements among neighboring multitopic ligands through coordination bonds, for large assemblies. The analysis throughout the paper is highly systematic, providing a detailed comparison of the influencing factors on the formation of different metal-organic cage structures, and these analytical approaches are expected to greatly assist subsequent research efforts in the future. The authors have already revised the manuscript accordingly. The revised manuscript currently also meets the high standard of Nat. Commun. and I recommend it for publication in Nat. Commun. without change.

Our response:

Thank you very much for this reviewer's kind review of our manuscript and providing valuable comments, especially to put us forward to conducting the DFT calculations of assemblies that contain 9 and 12 heavy metal ions. We are delighted to receive positive comments on our revised manuscript from the reviewer.

Reviewer #3:

In the revised version of manuscript NCOMMS-24-11077-T, Hiraoka and coworkers have addressed all the comments raised by the reviewers. In particular, they have commented on the situation concerning the lack of Xray data, provided new DFT data for comparing isomeric structures, and clarified the discussion concerning crucial parts of the manuscript. Also, a reasonable set of additional references was added. Concerning the criticism of reviewer 2, novelty in terms of providing new structural motifs is not the focus and thus not required for this more mechanistic study. Also, the citations provided by reviewer 2 do not refer to the same class of Pd-based assemblies as is described herein. Concerning the points raised by reviewer 3, meaningful additional data has been provided and discussions updated accordingly. Overall the quality of the manuscript has improved and it can be accepted in the current form.

Our response:

Thank you very much for your kind review of our manuscript and valuable comments. In particular, we had a great opportunity to consider possibilities for stabilizing the $Pd_{12}L_8$ cage other than the geometric reason we proposed in this paper, as pointed out by this reviewer, which allowed us to enjoy considering possible factors and prepare our responses to this reviewer in the previous revision. Although we eventually concluded that geometric factors mainly determined the high stability of $Pd_{12}L_8$, we could attain a deeper understanding of this phenomenon. Thank you again for your kind support of this paper.