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Citation for published version:

Digital Object Identifier (DOI):
10.1021/jacs.9b07779

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Journal of the American Chemical Society

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Navigated Self-Assembly of a Pd$_2$L$_4$ Cage by Modulation of an Energy Landscape under Kinetic Control

Tomoki Tateishi, Satoshi Takahashi, Atsushi Okazawa, Vicente Martí-Centelles, Jianzhu Wang, Tatsuo Kojima, Paul J. Lusby,* Hirofumi Sato, and Shuichi Hiraoka

1Department of Basic Science, Graduate School of Arts and Sciences, The University of Tokyo, 3-8-1 Komaba, Meguro-ku, Tokyo 153-8902, Japan
2EaStCHEM School of Chemistry, University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh, Scotland EH9 3FJ, UK
3Department of Molecular Engineering, Kyoto University, Kyoto 615-8510, Japan
4Elements Strategy Initiative for Catalysts and Batteries, Kyoto University, Kyoto 615-8510, Japan
5Fukui Institute for Fundamental Chemistry, Kyoto University, Kyoto 606-8103, Japan

ABSTRACT: Kinetic control of molecular self-assembly remains difficult because of insufficient understanding of molecular self-assembly mechanism. Here we report the formation of a metastable [Pd$_2$L$_4$]$_{2+}$ cage structure composed of naphthalene-based ditopic ligands (L) and Pd(II) ions in very high yield (99%) under kinetic control by modulating the energy landscape. The guest anion trapped in the cage and the solvent with very weak coordination ability prefer the formation of suitable intermediates and prevent the conversion of the metastable cage into the thermodynamically most stable decomposed state. The cage formation pathways under kinetic control and the effect of the anions encapsulated on the self-assembly processes were investigated by QASAP (quantitative analysis of self-assembly process) and NASAP (numerical analysis of self-assembly process). It was found that the self-assembly with a preferred guest (BF$_4^-$) proceeds through intermediates composed of no more components than the cage ([Pd$_n$L$_m$X]$_{2+}$ (a $\leq$ 2, b $\leq$ 4, X indicates a leaving ligand)) and that the final intramolecular cage-closure step is the rate-determining step. In contrast, a weaker guest (OTf$^-$) causes the transient formation of intermediates composed of more components than the cage ([Pd$_n$L$_m$X]$_{2+}$ (a $>$ 2, b $>$ 4)), which are finally converted into the cage.

INTRODUCTION

Controlling molecular self-assembly to bias the production of a desired assembled structure depends on nature of the product. If the desired structure is thermodynamically most stable, the reaction conditions should be selected so that the self-assembly can easily reach equilibration. If the desired structure is not thermodynamically most stable, isolating the product depends on modulating the reaction conditions to select a given reaction pathway on the energy landscape so as to avoid the thermodynamic sink and efficiently produce the metastable state. In many cases, molecular self-assemblies proceed under thermodynamic control based on reversible chemical bonds connecting the building blocks, so self-assembly pathways have tended to be disregarded. However, an understanding of molecular self-assembly processes enables selected metastable species to be produced under kinetic control along a well-defined pathway, which is created by modulating the energy landscape.

Here we report an example of kinetically controlled molecular self-assembly found in a Pd$_2$L$_4$ cage system. The self-assembly from ditopic ligands I and Pd(II) ions in the absence of a guest molecule leads to a complex mixture containing 40-nm-sized large species as major species, because the [Pd$_2$I$_4$]$^{2+}$ cage is likely to be destabilized by electrostatic repulsion between the two Pd(II) ions with a short separation (Figure 1). In the presence of a guest anion (Y$^-$), however, the self-assembly smoothly proceeds at 298 K to produce a (Y$^-$)@[Pd$_2$I$_4$]$^{2+}$ cage, where the guest anion (Y$^-$) is encapsulated in the cavity of the [Pd$_2$I$_4$]$^{2+}$ cage. The cage is not thermodynamically most stable but metastable at 298 K because heating of a solution of the cage causes its decomposition. Thus, the self-assembly of the (Y$^-$)@[Pd$_2$I$_4$]$^{2+}$ cage is disadvantageous in such solvents that promote ligand exchanges by their coordination to the Pd(II) centers. Consequently, the metastable (Y$^-$)@[Pd$_2$I$_4$]$^{2+}$ cage was obtained in very high yield (99%) under optimized reaction conditions (in the presence of BF$_4^-$ in weak coordinative solvent CD$_3$NO$_2$). The self-assembly process was analyzed experimentally (QASAP; quantitative analysis of self-assembly process) and numerically (NASAP; numerical analysis of self-assembly process) to reveal the effect of guest anions on the energy landscape. QASAP indicates that a good guest anion (BF$_4^-$) promotes the formation of a partial cage structure, (Y$^-$)@[Pd$_2$I$_4$X]$^{4+}$ (X indicates a leaving ligand). The conversion of the partial cage structure to the cage is the rate-determining step, which was supported by NASAP. With OTf$^-$ counter anion, which is encapsulated more weakly than BF$_4^-$, the cage is formed through intermediates consisting of more components than the cage, [Pd$_2$I$_4$X]$_{2+}$ (a $>$ 2, b $>$ 4). The metastable (Y$^-$)@[Pd$_2$I$_4$]$^{2+}$ cages, which cannot be obtained under usual
conditions of Pd(II)-linked coordination self-assemblies (in coordinative solvent at high temperature), are produced almost quantitatively by modulation of the energy landscape.

Figure 1. Navigated self-assembly of the (BF₄⁻)₄[Pd₁₁L₄]⁺⁺⁺ cage from ditopic ligands 1 and [PdX₂]Y₂ (X = CH₂CN or Py*, Y = BF₄ or BArF). The chemical structures of 1 and Py* are shown in Figure 3. In the absence of guest anions, the self-assembly gave a complex mixture containing 40-nm-sized large species and the [Pd₁₁L₄]⁺⁺⁺ cage (24% at most), while the (BF₄⁻)₄[Pd₁₁L₄]⁺⁺⁺ cage was obtained in very high yield in the presence of a guest anion with high binding affinity, which modulates the energy landscape of the self-assembly so that suitable intermediates for the cage are efficiently generated during the self-assembly. When the self-assembly was carried out at high temperature (343 K) in solvent with coordination ability (CDCl₃ or DMSO-d₆), the coordination bonds in the cage were recombined to result in the thermodynamically most stable decomposed state.

RESULTS AND DISCUSSION

Ditopic ligand 1 (Figure 2), where two 3-pyridyl rings are introduced in a naphthalene ring, was designed to give a Pd₁₁L₄ host for small, organic ditopic guests, building on the encapsulation methodology developed by the Lusby group.⁷ A molecular modeling study of the [Pd₁₁L₄]⁺⁺⁺ cage shows that there is not significant structural distortion in the ditopic ligands and around the Pd(II) centers of the cage, suggesting that this cage seems to be enthalpically stable enough to be produced under usual conditions adopted in coordination self-assembly. Besides, since this ligand is relatively rigid, the entropic loss for the formation of the [Pd₁₁L₄]⁺⁺⁺ cage would be small, which is also advantageous to produce the cage under thermodynamic control. However, the self-assembly from 1 and [Pd(CH₂CN)₂]Y₂ (Y = BF₄ or OTf) in CDCl₃ and CD₂Cl₂ (4:1, v/v) at 343 K for 12 h gave the cage in lower yields than expected: 51% (Y = BF₄) and 60% (Y = OTf), which were determined by ¹H NMR spectroscopy using an internal standard. CD₂Cl₂ was added because of slightly low solubility of 1 in polar solvent. If kinetically trapped species are produced during the self-assembly, these species would be converted into the cage in more coordinating solvents, which promote ligand exchanges to correct “wrong” connections.⁸ Thus, the self-assembly from 1 and [Pd(CH₂CN)₂]Y₂ was carried out in DMSO-d₆ and CD₂Cl₂ (4:1, v/v) at 343 K for 12 h but surprisingly the cage was not obtained at all. Then, the self-assembly in DMSO-d₆ and CD₂Cl₂ (4:1, v/v) was monitored by ¹H NMR spectroscopy. It was found that the yield of the cage reached 86% at 30 min, after which the yield decreased with time to finally reached 0% at 12 h (Figure S1a). This result suggests that the [Pd₁₁L₄]⁺⁺⁺ cage is not thermodynamically most stable, yet metastable. The self-assembly of the cage in CDCl₃ and CD₂Cl₂ (4:1, v/v) at 343 K was also monitored by ¹H NMR spectroscopy. As observed in DMSO-d₆, most of the cages were decomposed by heating in CDCl₃, though the decomposition in CD₂Cl₂ is slower than in DMSO-d₆ (Figure S1b and c). Heating the reaction mixture in CDCl₃ gave a precipitate, suggesting the formation of insoluble polymeric structures. The precipitate was not found by heating in DMSO-d₆, probably because the polymeric, or oligomeric, structures are soluble in more polar solvent DMSO-d₆. These results suggest that more coordinative solvent promotes the decomposition of the cage faster by the initiating the rearrangement of the Pd(II)–N coordination bonds in the cage to
lead to thermodynamically more stable species than the cage. Prominent signals for the thermodynamic product(s) were not observed by $^1$H NMR spectroscopy after the decomposition of the cage, and ESI-TOF mass spectrometry of the reaction mixture did not show any species larger than the cage (Figure S1d).

Since coordinating solvents tended to decompose the cage, Cd(NO$_2$)$_2$, whose coordination ability is much weaker than either Cd(CN) or DMSO-d$_6$, was used as the major solvent. When the self-assembly of the cage was carried out from I and [Pd(CH$_3$CN)$_2$](OTf)$_2$ in Cd(NO$_2$) and CdCl$_2$ (4:1, v/v) at 343 K, the yield of the cage was 62%, which is almost the same as the yield obtained in Cd(CN) (60%). However, the decomposition of the cage was largely suppressed in Cd(NO$_2$). Surprisingly, the self-assembly from I and [Pd(CH$_3$CN)$_2$](OTf)$_2$ at 343 K gave the cage in 99% yield. This result suggests that the self-assembly of the [Pd$_2$]$_2^{4+}$ cage is strongly affected not only by solvents but also by counter anions.

The encapsulation of the counter anions (BF$_x$ or OTf$^-$) in the cavity of the cage was confirmed by $^{19}$F NMR spectroscopy (Figure S2). Two $^{19}$F NMR signals for the encapsulated and free anions were observed, indicating the exchange of the free and bound anions is slower than the NMR timescale. Their integrations indicate that one counter anion is encapsulated in the [Pd$_2$]$_2^{4+}$ cage. The inclusion complexes, (Y)]=[Pd$_2$]$_2^{4+}$ (Y = BF$_x$ and OTf$^-$), were further characterized by $^1$H- and $^{19}$F-NOESY and $^1$H and $^{19}$F-DOSY spectroscopies. The correlation between the $^{19}$F NMR signal of the encapsulated BF$_x$ and the $^1$H NMR signals for the hydrogen atoms inside the cavity (H$^+$ and H$^+$) was observed (Figure S3). The diffusion coefficient of the $^{19}$F NMR signal of the encapsulated OTf$^-$, 6.51 × 10$^{-10}$ m$^2$ s$^{-1}$, is similar to that of the $^1$H NMR signals of the cage, 6.49 × 10$^{-10}$ m$^2$ s$^{-1}$ (Figures S4 and S5). The encapsulation of BF$_x$ in the cage was also confirmed in the same way (Figures S3 and S5).

Finally, the structure of the (BF$_x$)=[Pd$_2$]$_2^{4+}$ cage was revealed by single-crystal X-ray analysis. Single crystals of the cage were obtained by diffusion of benzene in a solution of the cage in CH$_2$NO$_2$ at 298 K for 7 weeks. Four ditopic ligands, I, are connected by two Pd(II) ions with a square-planar coordination geometry to form an 1-nm-sized cage structure, where the ditopic ligands I are slightly distorted (Figures 2 and S6). There are two crystallographically independent cage in the unit cell, and the intramolecular distances between the two Pd(II) ions are 9.789 and 9.808 Å. One BF$_x$ anion is encapsulated in the cavity of the cage, being placed in a disordered manner at the inversion center of site symmetry between the two Pd(II) ions. Some short F···H$^+$ and F···H$^+$ contacts are found between the guest BF$_x$ and I of the host cage, where the respective shortest distances of 2.627 and 2.587 Å are apparently shorter than the sum of their van der Waals radii (2.670 Å, H$^+$: 2.691 Å), suggesting a strong host–guest interaction. The average value of the shortest distances between each fluorine atom and H$^+$ is 2.643 Å (H$^+$: 2.691 Å), which implies that the BF$_x$ anion just fits into the cavity. These results are consistent with the solution structure of the (BF$_x$)=[Pd$_2$]$_2^{4+}$ cage.

The relative binding affinity between OTf$^-$ and BF$_x$ for the cage was investigated by competition experiments. Upon addition of n-Bu$_2$NBF$_x$ to a solution of (OTf$^-$)=[Pd$_2$]$_2^{4+}$, most of the OTf$^-$ anions in the cage were exchanged with BF$_x$ to give the (BF$_x$)=[Pd$_2$]$_2^{4+}$ cage, while nothing happened by addition of n-Bu$_2$NBF$_x$ to a solution of (BF$_x$)=[Pd$_2$]$_2^{4+}$ (Figure S7). These results indicate that BF$_x$ is a stronger guest for the [Pd$_2$]$_2^{4+}$ cage. As the yield of the cage from [Pd(CH$_3$CN)$_2$](BF$_x$)$_2$, 99%, is much higher than that from [Pd(CH$_3$CN)$_2$](OTf)$_2$, 62%, the guest with higher binding affinity (BF$_x$) assists the self-assembly of the cage more efficiently.

![Figure 2](image-url)  
**Figure 2.** Crystal structure of the (BF$_x$)=[Pd$_2$]$_2^{4+}$ cage. (a) A side view. (b) A top view. The [Pd$_2$]$_2^{4+}$ cage is shown as a stick model, while the encapsulated BF$_x$ is shown as a CPK model. One configuration is shown for the disordered BF$_x$ anion. Color labels: grey, C; white, H; yellow, Pd; blue, N; pink, B; green, F.

![Figure 3](image-url)  
**Figure 3.** $^1$H NMR spectra (500 MHz, aromatic region, 298 K) of [PdPy*$_x$]$_2$Y$_2$ and Py* in Cd(NO$_2$) and I and the reaction mixture for the self-assembly of the (Y)=[Pd$_2$]$_2^{4+}$ cage from [PdPy*$_x$]$_2$Y$_2$ in Cd(NO$_2$) and CdCl$_2$ (4:1, v/v) at 298 K. (a) The self-assembly from [PdPy*$_x$](BF$_x$)$_2$ ([Pd] = 0.95 mM) and I ([I] = 1.9 mM). (b) The self-assembly from [PdPy*$_x$](OTf)$_2$ ([Pd] = 0.90 mM) and I ([I] = 1.8 mM). The signals colored in blue, green, magenta, and brown indicate the (Y)=[Pd$_2$]$_2^{4+}$ cage, Py*, I, and [PdPy*$_x$]Y$_2$, respectively. The signal at 7.78 ppm in (a) was not colored because
The H⁺ signal of Py* and the H⁺ signal of the (BF₄)⁻[Pd₁:1⁺]⁺ cage are overlapped. The signal marked with the black solid triangle at 7.52 ppm indicates CHCl₃, which was used during the preparation of the reaction mixture.

The effect of counter anions on the self-assembly process of the cage was investigated by QASAP. QASAP is a method to find transiently produced intermediates, most of which cannot be observed by spectroscopy, by quantifying all the substrates and the products. In the case of the self-assembly of the (Y⁻⁻)⁺[Pd₁:1⁺]⁺ cage from I and [PdX₄]²⁻ (X and Y indicate a leaving ligand and counter anion, respectively), any intermediate in this self-assembly can be expressed as [Pd₁:1.X]⁺(1−c)·c−X (a−c indicate the number of components). From the amount of the substrates (I and [PdX₄]²⁻), the yields (Yc) assembly processes are more clearly observed by ¹H NMR spectroscopy (Figures S10a). The first (a) value indicates the average number of Pd(II) ions trapped in a single ditopic ligand I, while the (k) value the stoichiometric ratio of the Pd(II) ions to I in [PdₙO₁₀X₀]³⁺(Y⁻⁻). Three signals assigned to H NMR signals of the H⁺ proton in the ditopic ligand I were found after the convergence of the reaction. The integration of these signals based on the internal standard indicates that the cage structure was in 97% (Y = BF₄) and 76% (Y = OTF) yields, which are similar to those found in the self-assembly carried out from I and [Pd(CH₃CN)₄]²⁻[Pd₁:1]⁺ at 343 K (99% (Y = BF₄) and 62% (Y = OTF)). On the other hand, when a larger counter anion than the size of the cavity of the [Pd₁:1]⁺ cage, Barf (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate), was used as the counter anion, a complicated NMR spectrum was obtained (Figure S10a). Three signals assigned to H⁺ proton in the ditopic ligand I were found after the convergence of the reaction. The integration of these signals based on the internal standard indicates that the cage structure was in 97% (Y = BF₄) and 76% (Y = OTF). The (a) value started from around (1.7, 0.6) at 5 min, with the decrease of the (k) value, finally reaching around (1.75, 0.5) at 20 min. The (a), (k) value remained around there until 1 h (Figure 4c). Then the (a) value slightly decreased, while the (k) value was constant. This result suggests that the ditopic ligand I was incorporated in intermediates from 5 to 20 min to form the partial cage structure, (BF₄)⁻[Pd₁:1.Py*]⁺, whose (n, k) value is (1.75, 0.5). From 20 to 60 min, the (n, k) value remained around (1.75, 0.5), so (BF₄)⁻[Pd₁:1.Py*]⁺ was converted to the (BF₄)⁻[Pd₁:1]⁺ cage slowly (the rate-determining step) in the self-assembly process (Figure S10a). This is because the intermediate and the transition state produced during the ligand exchange in the final step, where one of the two Pd(II) ions adopts five-coordinate geometry, are destabilized by the structural rigidity of ditopic ligand I and the guest anion further rigidifies the structure of the partial cage.

Addition of n-BuNBF₄ to a reaction mixture of I and [PdPy*₄][BArF₄]₂ after the convergence (1 day) led to the (BF₄)⁻[Pd₁:1]⁺ cage at 298 K in 3 h (Figure S10b). These results indicate that the self-assembly pathway largely depends on the counter anion. The counter anion effect on the conversion into the cage was investigated by addition of several anions (Y = OTF, ClO₂⁻, NO₃⁻, and PF₆⁻) (Table I and Figure S10c). The highest yield (92%) was obtained when ClO₂⁻ was added. The yield of the cage increased with increasing size of the anions, indicating that the size of the guest anion affects the efficiency of the conversion of large species to the cage.

### Table 1. The yields of the cage by the addition of n-BuNPF₆ in the reaction mixture from [PdPy*₄][BArF₄]; and I after 1 day.

<table>
<thead>
<tr>
<th>Anion (Y⁻⁻)</th>
<th>volume / Å³</th>
<th>Symmetry</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₃⁻</td>
<td>42.2</td>
<td>Dₕ</td>
<td>85</td>
</tr>
<tr>
<td>BF₄⁻</td>
<td>50.6</td>
<td>Tₐ</td>
<td>83</td>
</tr>
<tr>
<td>ClO₂⁻</td>
<td>59.2</td>
<td>Tₐ</td>
<td>92</td>
</tr>
<tr>
<td>PF₆⁻</td>
<td>76.7</td>
<td>Oₙ</td>
<td>88</td>
</tr>
<tr>
<td>OTF</td>
<td>89.8</td>
<td>Cᵥ</td>
<td>62</td>
</tr>
</tbody>
</table>

The self-assembly processes of the cages with different counter anions (BF₄⁻ or OTF⁻) were investigated. The changes in the stoichiometry of the cages in the self-assembly of the (Y⁻⁻)⁺[Pd₁:1]⁺ cations from I and [PdPy*₄][Y₂] (Y = BF₄ or OTF) are shown in Figure 4a and b. The cage formation from [PdPy*₄][BF₄]₂ occurred much faster than from [PdPy*₄][OTF]₂, suggesting that the guest anion strongly trapped in the cage (BF₄⁻) does not only increase the yield of the cage (thermodynamic effect) but also accelerates the self-assembly (kinetic effect). The self-assembly processes in both cases were investigated by the n-k analysis (Figure 4c and d). During the self-assembly from [PdPy*₄][BF₄]₂, the (n, k) value started from around (1.7, 0.6) at 5 min, with the decrease of the (k) value, finally reaching around (1.75, 0.5) at 20 min. The (n, k) value remained around there until 1 h (Figure 4c). Then the (n) value slightly decreased, while the (k) value was constant. This result suggests that the ditopic ligand I was incorporated in intermediates from 5 to 20 min to form the partial cage structure, (BF₄⁻)[Pd₁:1.Py*]⁺, whose (n, k) value is (1.75, 0.5). From 20 to 60 min, the (n, k) value remained around (1.75, 0.5), so (BF₄⁻)[Pd₁:1.Py*]⁺ was converted to the (BF₄⁻)[Pd₁:1]⁺ cage slowly (the rate-determining step) in the self-assembly process (Figure 1). This is because the intermediate and the transition state produced during the ligand exchange in the final step, where one of the two Pd(II) ions adopts five-coordinate geometry, are destabilized by the structural rigidity of ditopic ligand I and the guest anion further rigidifies the structure of the partial cage.
is dissociated from the Pd(II) center under the ionization condition, so (BF$_4$)$^-$-[Pd$_2$I$_4$Py*]$^{4+}$ would also be detected as the cage by the loss of Py* in the mass spectrometer.$^{5,6}$

Figure 4. QASAP data for the self-assembly of the (Y - [Pd$_2$I$_4$])$^{4+}$ cage from [PdPy*]$_2$Y$_2$ (Y = BF$_4$ or OTf) and 1 in CD$_3$NO$_2$ and CD$_2$Cl$_2$ (4:1, v/v) at 298 K. (a) and (b) Existence ratios of the substrates and the products for the self-assembly from [PdPy*]$_2$Y$_2$ (Y = BF$_4$ or OTf) and 1 (c) and (d) $n$-$k$ plots for the self-assembly from [PdPy*]$_2$Y$_2$ (Y = BF$_4$ or OTf) and 1.

To get more detailed information about the self-assembly process on the navigated pathway, NASAP (numerical analysis of self-assembly process)$^{2a,b}$ was carried out. In NASAP, the rate constants of the reactions in the reaction network where the possible intermediates that contain no more components than the final assembly (Y - [Pd$_2$I$_4$])$^{4+}$ in this case are considered (Figure S23) and are numerically determined so that the calculated existence ratios and the $(\langle n \rangle, \langle k \rangle)$ values well reproduce the corresponding experimental values. QASAP for the self-assembly of the (BF$_4$)$^-$-[Pd$_2$I$_4$Py*]$^{4+}$ cage suggested that most of the intermediates should contain no more components than the cage, [Pd$_2$I$_4$Py*]$^{4+}$, after 4 h. The large increase in the $(\langle n \rangle)$ value with slight decrease in the $(\langle k \rangle)$ value from 5 to 20 min indicates the growth of intermediates through intra- and intermolecular ligand exchanges during this period to lead to large intermediates. In the case where the [Pd$_2$I$_4$]$^{4+}$ cage is produced by intramolecular ligand exchanges in [Pd$_2$I$_4$Py*]$^{4+}$, the $(\langle n \rangle)$ value always decreases. As the (OTf)$^-$-[Pd$_2$I$_4$]$^{4+}$ cage was produced with the release of Py* until 4 h, the cage would be formed from the (OTf)$^-$$^{4+}$ partial cage and from the large intermediates in different pathways.

The self-assembly of the (OTf)$^-$$^{4+}$ cage was monitored by ESI-TOF mass spectrometry (Figures S18–22 and Table S14). Several dinuclear species with 1–5 ditopic ligands were detected during the self-assembly. All the species are considered to be possible intermediates for the cage. However, as all the species appeared during the self-assembly, detailed information about the cage formation process was not gained from the time-dependent mass spectrometry.

The self-assembly process of the (OTf)$^-$$^{4+}$ cage was investigated by QASAP in the same way. A significant feature of the self-assembly of the (OTf)$^-$$^{4+}$ cage from [PdPy*]$_2$(OTf)$_2$ and 1 is that the (OTf)$^-$$^{4+}$ cage (54%) was produced without release of Py* after 4 h (Figure 4b). Considering that at least one Py* should be released for the production of one cage from an intermediate composed of no more components than the cage, [Pd$_2$I$_4$Py*]$^{4+}$ ($a \leq 2, b \leq 4, c \geq 1$), the (OTf)$^-$$^{4+}$ cage should be produced from intermediates composed of more components than the cage, [Pd$_2$I$_4$Py*]$^{4+}$ ($a > 2, b > 4$) after 4 h. The large increase in the $(\langle n \rangle)$ value with slight decrease in the $(\langle k \rangle)$ value from 5 to 20 min indicates the growth of intermediates through intra- and intermolecular ligand exchanges during this period to lead to large intermediates. In the case where the (BF$_4$)$^-$-[Pd$_2$I$_4$Py*]$^{4+}$ cage suggested that most of the intermediates should contain no more components than the cage, [Pd$_2$I$_4$Py*]$^{4+}$, after 4 h, and that the final step of the self-assembly ((BF$_4$)$^-$$^{4+}$-[Pd$_2$I$_4$Py*]$^{4+}$ → (BF$_4$)$^-$$^{4+}$-[Pd$_2$I$_4$Py*]$^{4+}$ + Py*) is the rate-determining step, so the reaction network where the 25 possible intermediates that are produced by tracking back from the final cage was prepared and total 68 reactions in the network are classified into five types shown in Figure 5a. As QASAP for the (BF$_4$)$^-$$^{4+}$-[Pd$_2$I$_4$Py*]$^{4+}$ cage suggested that the rigidity of dinuclear intermediates would affect the rate of the intramolecular ligand exchanges, the intramolecular reactions are treated separately based on the number of cross-links (Types III–V). A set of rate constants that well reproduces the experimental data (the existence ratios and the $(\langle n \rangle, \langle k \rangle)$ value with time) was found by master equation approach.

The data set of the rate constants obtained by NASAP (Figure 5e) well reproduces the change in the existence ratios of the substrates and the products (Figure 5b) and captures the trend of the changes in the $(\langle n \rangle, \langle k \rangle)$ values with time (Figure 5c and d). All the rate constants for backward reaction except for $k_4$ are much smaller than those of the corresponding forward reactions.
Considering that the self-assembly was carried out at mM concentration, the rate for the backward reactions for Type IV is slower than that for the intramolecular forward reactions, even though $k_4$ is larger than $k_3$. Thus, the backward reactions in the self-assembly of the (BF$_4$)$^-$⊂[Pd$_2$L$_4$]$_{4+}$ cage are negligibly slow under this condition (in less coordinative solvent at 298 K). When the rate constants for the intramolecular reactions ($k_3$, $k_4$, and $k_5$) are compared, $k_3$ (10$^{-1.9}$ min$^{-1}$) is about one order magnitude smaller than $k_4$ (10$^{-0.6}$ min$^{-1}$) and $k_5$ (10$^{-0.5}$ min$^{-1}$), which is explained by more rigid structure of the (BF$_4$)$^-$⊂[Pd$_2$L$_4$]$_{4+}$ partial cage, where one of the Pd(II) ions is hard to adopt five-coordination geometry in the transition state of the ligand exchange. The time-course of the main species during the self-assembly suggests the predominant self-assembly pathways (Figure 5e). [Pd$^{+}$Py$^{*}$)$_2$]$_{2+}$, which is indicated as (1,1,3), is mainly produced and then dinuclear open-chain species ((2,1,6), (2,2,5), (2,3,4), and (2,4,3)) are generated in 1 min. These open structures are cyclized to afford cyclic structures ((2,2,4), (2,3,3), and (2,4,2)) from 1 to 10 min. The second cross-linking (Type IV in Figure 5a) in the cyclic structures yields partial cage structures ((2,3,2) and (2,4,1)) and finally (2,4,1) becomes the dominant intermediate.

**Figure 5.** Numerical analysis of self-assembly process (NASAP) of the (BF$_4$)$^-$⊂[Pd$_2$L$_4$]$_{4+}$ cage from [PdPy$^{*}$]$_4$(BF$_4$)$_2$ and 1 in CD$_3$NO$_2$ and CD$_2$Cl$_2$ (4:1, v/v) at 298 K. (a) The five reaction types in the self-assembly of the cage considered in NASAP. Typical examples are shown. The guest anion that would be trapped in between the two Pd(II) ions in the intermediates is omitted. (b) The experimental and numerical data of the existence ratios of the substrates (1 and [PdPy$^{*}$]$_4$(BF$_4$)$_2$) and the products ((BF$_4$)$^-$⊂[Pd$_2$L$_4$]$_{4+}$ and Py$^*$). (c) The experimental and numerical $n$-$k$ plots. (d) The changes in the experimental and numerical $n$ and $k$ values with time. (e) The time-variation of mainly produced species and a set of the rate constants determined by NASAP.

It was found that the guest anions affect the self-assembly pathway. A good guest anion (BF$_4$)$^-$, whose binding affinity for the cage is higher than that of OTf$^-$ (confirmed by competition experiments), led the self-assembly along the pathways where...
the intermediates are composed of no more components than the cage, while OTf could not prevent the transient production of large species because of its weaker template effect. The effect of guest anion found in this study is different from previous examples of template effect in coordination self-assembly. As the (Y’ )= [Pd2I4]6- host-guest complex is not energetically most stable, the yield of the cage cannot be improved by simply increasing the thermodynamic stability by encapsulating a good guest anion. A very high yield of the (BF4)’ = [Pd2I4]6- cage (99%) was attained due to kinetic effects, wherein the complementary guest anion promotes selective navigation of the self-assembly pathway thus avoiding the formation of large species. Furthermore, the kinetic stability of the host-guest complex prevents the conversion of the cage to the thermodynamically most stable decomposed state.

CONCLUSIONS
A metastable (Y’ )= [Pd2I4]6- cage composed of rigid ditopic ligands I and Pd(II) ions was synthesized in very high yield along proper self-assembly pathways navigated by a preferred guest anion (BF4)’ and little coordinating solvent under kinetic control. The short distance between the two Pd(II) ions in the [Pd2I4]6- cage electrostatically destabilizes the cage without the encapsulated anion, so uncharacterized species, which would be divergent polymeric structures, are produced in the absence of the guest anion. QASAP for the self-assembly of the (BF4)’ = [Pd2I4]6- cage indicates that the intramolecular cross linking in the (BF4)’ = [Pd2I4Py*]6+ partial cage is the rate-determining step, which is supported by NASAP, while intermediates composed of more components than the cage, [Pd2I4Py*]2+ (a > 2, b > 4), were transiently produced during the self-assembly of the (OTf)’ = [Pd2I4]6- cage. Without guest anions (Y’ = BArF’), the self-assembly did not afford the [Pd2I4]6- cage at all and instead produced uncharacterized species, which however can be quickly transferred into the cage by the guest anion (BF4)’ . Considering that these metastable (Y’ )= [Pd2I4]6- cages cannot be obtained under usual self-assembly conditions for Pd(II)-linked assemblies (heating in coordinating solvents), the understanding of the self-assembly processes and the knowledge about how to modulate the energy landscape will enable the synthesis of metastable self-assemblies under kinetic control in a rational way.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.

Synthetic and analytical procedures, analytical data, and NMR spectra (PDF)
Crystallographic data of the (BF4)’ = [Pd2I4]6- cage, CCDC 1940829 (CIF)

AUTHOR INFORMATION
Corresponding Authors
*Paul.Lusby@ed.ac.uk
*chiraoka@mail.ecc.u-tokyo.ac.jp

ORCID
Tomoki Tateishi: 0000-0003-0842-6033
Satoshi Takahashi: 0000-0002-0889-5449
Atsushi Okazawa: 0000-0001-8760-041X
Vicente Marti-Centelles: 0000-0002-9142-9392

Tatsuo Kojima: 0000-0001-7799-8153
Paul J. Lusby: 0000-0001-8418-5687
Hirofumi Sato: 0000-0001-6266-9058
Shuichi Hiraoka: 0000-0002-9262-4747

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS
This work was supported by JSPS KAKENHI Grant Numbers 19H02731, 19K22196, and 19K15531 and The Asahi Glass Foundation and the Leverhulme Trust (V.M.C.; RPG-2015-232).

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Heteroleptic Pills Binding One or Two Fullerenes.


