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Self-assembly process of a quadruply interlocked palladium cage

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A supramolecular approach is effective to construct topologically complicated molecules with the aid of reversible bond formation. Although topologically complicated molecules have been synthesized for the past three decades, their formation mechanisms have rarely been discussed. Here we report the formation process of a tetranuclear interlocked palladium cage composed of two binuclear cages, which are quadruply interlocked with each other. In the main pathway, the binuclear cages are produced with binuclear partial cages. The ditopic ligand that does not bridge the two palladium(II) ions in the binuclear partial cage then threads into the binuclear cage to afford a tetranuclear partially interlocked cage, with partial conversion of the binuclear cage into the binuclear partial cage. The tetranuclear partially interlocked cage interlocks intramolecularly through repetitive cleavage and formation of Pd(II)–N coordination bonds mediated by a free pyridyl group, finally leading to the tetranuclear interlocked cage.

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Interlocked molecules are nanoscale miniature artworks composed of intertwined molecules that are not connected by covalent bonds but cannot apart from each other without breaking chemical bonds^{1–7}. Nowadays, such mechanically connected molecules have been recognized as a class of structural motifs for molecular machines beyond simple synthetic targets^{8–14}. Molecular self-assembly is the best way to efficiently synthesize interlocked molecules. Molecular building blocks spontaneously assemble into a well-organized interlocked structure in high yield as long as the interlocked structure is thermodynamically most stable. The advantage of molecular self-assembly in the formation of interlocked structures is that if the building blocks are incorrectly connected, the reversible chemical bonds employed in molecular self-assembly enable the building blocks to rearrange so that improper species are converted into the final product. A variety of structurally complicated interlocked molecules have been reported by molecular self-assembly for the past three decades^{15–25}. However, how molecular building blocks assemble into such complicated interlocked structures has rarely been discussed²⁶ mainly because the observation of transiently produced intermediates, whose stability is lower than the final product, is quite difficult. Recent progress in the investigation of coordination self-assembly processes by a method that can provide information about intermediates by quantifying all substrates and products instead of intermediates (QASAP: quantitative analysis of self-assembly process) has gradually unveiled ordering processes of supramolecular self-assemblies at the molecular level^{27–30}.

Here we report the self-assembly process of a Pd₄L₈ interlocked cage (IC)^{31–39}, where two molecules of Pd₂L₄ cages are quadruply interlocked. This is an attempt to understand the formation mechanism of an interlocked coordination assembly. In the self-assembly of the Pd₄L₈ IC, the Pd₂L₄ cage is firstly produced with the concomitant formation of a Pd₂L₄X partial cage (PC) (X: leaving ligand). A ditopic ligand (L) with a free coordination site in PC threads into the Pd₂L₄ cage or another PC to afford a Pd₄L₈X partially interlocked cage (PIC). Subsequent intramolecular interlocking in PIC promoted by the coordination of a free ligand (free coordination sites in PC, PIC or Py*) finally gives the thermodynamically most stable Pd₄L₈ IC.

Results

Monitoring the self-assembly by ¹H NMR. The self-assembly process of the Pd₄L₈ IC from ditopic ligand **1** (Fig. 1)³⁹, which possesses two 3-picolyl groups connected to a benzophenone by ether linkages, and PdPy*₄(BF₄)₂ (Py*: 3-chloropyridine) in CD₃NO₂ at 298 K was monitored by ¹H NMR spectroscopy (Fig. 2 and Supplementary Fig. 1). Right after the self-assembly started, many ¹H NMR signals appeared (5 min), which is due to the formation of primitive intermediates. These signals soon disappeared and the signals for the Pd₂L₄ cage (signals coloured in red) were observed. The ¹H NMR signals of the Pd₄L₈ IC (signals coloured in blue) appeared at 5 h with concomitant decrease in the intensity of the signals for the Pd₂L₄ cage. The self-assembly finally reached the convergent sample containing 69% of the Pd₄L₈ IC and 31% of kinetically trapped species (calculated based on the ditopic ligand **1** by using an internal standard), which could not be converted into the IC even by heating.

A very similar result was obtained when the self-assembly was carried out with Pd(CH₃CN)₄(BF₄)₂ as a metal source instead of PdPy*₄(BF₄)₂ (Supplementary Figs. 2 and 3); the only difference between the two self-assemblies is that <6% of free ditopic ligand **1** remained until the end in the case of the self-assembly from **1** and Pd(CH₃CN)₄(BF₄)₂. In the previous report³⁹, the Pd₄L₈

IC was synthesized from **1** and Pd(CH₃CN)₄(BF₄)₂ in polar coordinative solvent, DMSO, at a higher temperature of 333 K. Thus, it was found that the Pd₄L₈ IC can be assembled in less coordinative solvent at 298 K whether CH₃CN or Py* is used as the leaving ligand.

PdPy*₄(BF₄)₂ was used as the Pd(II) ion source so that we could quantify both metal ion source (PdPy*₄) and the leaving ligand (Py*) by ¹H NMR measurement. During the self-assembly of the Pd₄L₈ IC, ¹H NMR signals for the Pd₂L₄ cage, which is a transient intermediate, were observed, while any other intermediates except for the small signals in the beginning of the self-assembly were not detected by ¹H NMR spectroscopy. Thus, the ditopic ligand **1**, the Pd₄L₈ IC and the Pd₂L₄ cage were quantified, from which the existence ratio of the species that cannot be observed by ¹H NMR (**Int**) was determined (gray lines in Fig. 3a, b). In the beginning of the self-assembly, **Int** was produced in about 80% yield (based on the ditopic ligand **1**) and gradually decreased with time. Therefore, the characterization of **Int** is necessary to understand the self-assembly process of the Pd₄L₈ IC. However, none of the signals of **Int** were observed by ¹H NMR spectroscopy, which is the reason for the difficulty in the investigation of self-assembly processes. To solve this problem, in QASAP the average composition of **Int** (Pd_(a)L_(b)Py*_(c), ⟨a⟩, ⟨b⟩ and ⟨c⟩ indicate composition ratios) was determined by the existence ratios of all the substrates, products and the Pd₂L₄ cage. The time variation of Pd_(a)L_(b)Py*_(c) enables us to discuss the self-assembly process of the Pd₄L₈ IC.

Quantitative analysis of the self-assembly process. The changes in the existence ratios of the substrates (**1** and PdPy*₄), the products (the Pd₄L₈ IC and Py*), the Pd₂L₄ cage and all the intermediates except for the Pd₂L₄ cage (**Int**) with time are shown in Fig. 3a, b. The yield of the Pd₂L₄ cage reached the maximum (52%) at 5 h and then decreased. The Pd₄L₈ IC started to produce at 5 h. Interestingly, after the decrease in the yield of the Pd₂L₄ cage, the existence ratio of **Int** turned to increase for some time and decreased again after 1 day. Slight decrease in the existence ratio of Py* (1.6%) observed during the period when **Int** increased (5 h to 1 day) indicates that the reverse reaction from the Pd₂L₄ cage and Py* to Pd₂L₄Py* took place (Pd₂L₄ + Py* → Pd₂L₄Py*). As the amount of Py* consumed is very small (only 1.6%), the formation of Pd₂L₄Py* would be most probable. All the Pd₂L₄ cages at 5 h (52%) were finally converted into the Pd₄L₈ IC in 69% yield, indicating that at least 75% of the Pd₄L₈ IC was derived from the Pd₂L₄ cage.

In order to investigate the intermediates for the Pd₂L₄ cage and for the Pd₄L₈ IC, *n*–*k* analysis^{27–30} was carried out. In QASAP, two parameters (⟨*n*⟩ and ⟨*k*⟩) indicating the nature of **Int** (whose average composition is indicated as Pd_(a)L_(b)Py*_(c)) are defined and used for the characterization of the intermediates. The ⟨*n*⟩ value, which is defined as ⟨*n*⟩ = (4⟨a⟩ – ⟨c⟩)/⟨b⟩, indicates the average number of Pd(II) ions binding to a single ditopic ligand, while the ⟨*k*⟩ value (⟨*k*⟩ = ⟨a⟩/⟨b⟩) indicates the ratio between the Pd(II) ions and the ditopic ligands in **Int**. The change in the (⟨*n*⟩, ⟨*k*⟩) value with time is shown in Fig. 3c. From 5 to 30 min, the ⟨*n*⟩ value increased with time, while the ⟨*k*⟩ value decreased, which reflects the incorporation of free ditopic ligands **1** into **Int** (Fig. 3a). The (⟨*n*⟩, ⟨*k*⟩) value finally reached (1.85, 0.50) and stayed around there until almost the end of the self-assembly. The Pd₂L₄ cage was predominantly produced during the first 5 h, while the Pd₄L₈ IC was produced after 5 h. With this in mind, the result that the (⟨*n*⟩, ⟨*k*⟩) value observed at 15 min (1.76 ± 0.09, 0.52 ± 0.01), is very near to the (*n*, *k*) value of a Pd₂L₄Py* partial cage (PC), (1.75, 0.5), suggests that the Pd₂L₄Py* PC is the long-lived intermediate of the Pd₂L₄ cage. The ⟨*n*⟩ value at 35 min

Fig. 1 Self-assembly process of the interlocked cage. The self-assembly of the Pd_4I_8 interlocked cage (**IC**) takes place through reaction steps (1)–(6): (1) formation of the $\text{Pd}_2\text{I}_4\text{Py}^*$ partial cage (**PC**) from $\text{PdPy}^*_4(\text{BF}_4)_2$ and the ditopic ligand **1** by ligand exchanges between Py^* (3-chloropyridine) and the pyridyl groups of **1**. As the coordination ability of Py^* is slightly weaker than that of the pyridyl groups in **1**, the reaction takes place towards the formation of $\text{Pd}(\text{II})$ –**1** coordination bonds. (2) Intramolecular ligand exchange(s) in the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC** to lead to the Pd_2I_4 cage. (3) Conversion of the Pd_2I_4 cage to the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC**. (4) Threading of a partially free ditopic ligand in the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC** into the Pd_2I_4 cage to lead to a $\text{Pd}_4\text{I}_8\text{Py}^*$ partially interlocked cage (**PIC**). (5) Threading of a partially free ditopic ligand in the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC** into another $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC** followed by the intramolecular ligand exchange to lead to a $\text{Pd}_4\text{I}_8\text{Py}^*$ **PIC**. (6) One of the possible pathways of interlocking in $\text{Pd}_4\text{I}_8\text{Py}^*$ **PIC** through repetitive cleavage and formation of $\text{Pd}(\text{II})$ –**1** coordination bonds to form the Pd_4I_8 **IC**.

(1.84) is much larger than the n value of the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC** (1.75) but smaller than that of $\text{Pd}_4\text{I}_8\text{Py}^*$ (1.875). This suggests that the intermediates for the Pd_2I_4 cage (mainly the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC**) and for the Pd_4I_8 **IC** (mainly the $\text{Pd}_4\text{I}_8\text{Py}^*$ **PIC**) have already been produced much earlier than when the Pd_4I_8 **IC** begins to produce (5 h). The $(\langle n \rangle, \langle k \rangle)$ value reached (1.88, 0.5) at 3 days, which indicates that the $\text{Pd}_4\text{I}_8\text{Py}^*$ **PIC**, whose (n, k) value is (1.875, 0.5), is the main intermediate of the Pd_4I_8 **IC**.

The self-assembly of the Pd_4I_8 **IC** under the same condition was monitored by ESI-TOF mass spectrometry (Supplementary Fig. 4). The species mainly observed are listed in Table 1. The signals for the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC** could not be found. This is due to the removal of the Py^* molecule, whose coordination ability is weaker than **1**, during the ionization. Similar results have often been obtained in other $\text{Pd}(\text{II})$ –linked coordination self-assemblies^{40–42}. The result that the signals for Pd_4I_8 were observed instead of that for $\text{Pd}_4\text{I}_8\text{Py}^*$ can be interpreted in the same way. Interestingly, the signals for Pd_4I_8 ($m/z = 526.40$ for $[\text{Pd}_4\text{I}_8(\text{BF}_4)]^{7+}$ and 771.60 for $[\text{Pd}_4\text{I}_8(\text{BF}_4)_3]^{5+}$) appeared at 30 min, which is much faster than when the ^1H NMR signals for the Pd_4I_8 **IC** started to appear (5 h). This result indicates that these mass signals should arise from the $\text{Pd}_4\text{I}_8\text{Py}^*$ **PIC** by the removal of the Py^* molecule

during the ionization. Thus, the $\text{Pd}_4\text{I}_8\text{Py}^*$ **PIC** have already been produced by 30 min as the intermediates of the Pd_4I_8 **IC**, which is well consistent with the result that the $(\langle n \rangle, \langle k \rangle)$ value at 35 min, (1.84, 0.5), is between those of the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC** (1.75, 0.5) and the $\text{Pd}_4\text{I}_8\text{Py}^*$ **PIC** (1.875, 0.5) (Fig. 3c).

Transformation mechanism of the Pd_2I_4 cage to the Pd_4I_8 **IC**.

QASAP for the self-assembly of the Pd_4I_8 **IC** from **1** and $\text{PdPy}^*_4(\text{BF}_4)_2$ revealed that all the Pd_2I_4 cages (52% yield at 5 h determined based on **1**) were transformed into the Pd_4I_8 **IC** in 69% yield (based on **1**) after the convergence (Fig. 3b). This indicates that the Pd_4I_8 **IC** is mainly produced through the Pd_2I_4 cage. Thus, the conversion mechanism from the Pd_2I_4 cage to the Pd_4I_8 **IC** was investigated. The Pd_2I_4 cage can be isolated from a reaction mixture of **1** ($[\text{1}]_0 = 77.5$ mM) and $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ in CH_3CN at 343 K as a precipitate³⁹, but once the Pd_2I_4 cage is precipitated, the cage is not soluble in any solvent except DMSO ³⁹. After several attempts, we found that the reaction of **1** and $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ in CD_3NO_2 in a 4:2.2 ratio at 343 K, where slightly excess amount of $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ was added, resulted in the selective formation of the Pd_2I_4 cage in 70% yield

Fig. 2 ^1H NMR spectra of the self-assembly of the interlocked cage. ^1H NMR spectra (500 MHz, CD_3NO_2 , 298 K) of $\text{PdPy}^*_4(\text{BF}_4)_2$, the ditopic ligand **1**, Py^* and the reaction mixture for the self-assembly of the Pd_4I_8 interlocked cage (**IC**) from $\text{PdPy}^*_4(\text{BF}_4)_2$ ($[\text{Pd}]_0 = 1.0$ mM) and the ditopic ligand **1** ($[\text{1}]_0 = 2.0$ mM) in CD_3NO_2 at 298 K. The signals coloured in blue, red, green, magenta and brown indicate the Pd_4I_8 **IC**, the Pd_2I_4 cage, Py^* , the ditopic ligand **1** and $\text{PdPy}^*_4(\text{BF}_4)_2$, respectively

(based on **1**) without the formation of the Pd_4I_8 **IC** (Fig. 3e and Supplementary Fig. 5). Although the isolation of the Pd_2I_4 cage from this reaction mixture failed, the conversion of the species that remained after the convergence of the self-assembly into the Pd_4I_8 **IC** is negligible because the Pd_4I_8 **IC** was not produced by standing this solution mainly containing the Pd_2I_4 cage at 343 K for 4 days. As breaking of $\text{Pd}(\text{II})$ coordination bonds does not take place without coordination of a certain ligand to the $\text{Pd}(\text{II})$ center to form five-coordinate intermediates and the transition structure through associative mechanism^{43,44}, the transformation of the Pd_2I_4 cage to the Pd_4I_8 **IC** should be promoted by Py^* or free ditopic ligand **1**.

Upon the addition of Py^* (11.4 equiv. against the Pd_2I_4 cage, which is equal to 2.0 equiv. against the initial amount of **1**) to the above CD_3NO_2 solution containing the Pd_2I_4 cage (70% yield), 2.0 equiv. of Py^* molecules against the Pd_2I_4 cage were consumed in 1 day (blue solid circles in Fig. 3f). (The ^1H NMR spectra and the existence ratios are shown in Supplementary Figs 6 and 7, respectively.) The production of the Pd_4I_8 **IC** started at 3 h after the addition of Py^* (blue open circles in inset of Fig. 3f). The Pd_4I_8 **IC** was formed in 64% yield (based on **1**) at 12 days, so most of the Pd_2I_4 cages (91%) were converted into the Pd_4I_8 **IC**. It is worth noting that after the convergence of the conversion, 1.5 equiv. of Py^* were still consumed, suggesting that a part of Py^* molecules should be incorporated into the uncharacterized species. This is reasonable because a part of the $\text{Pd}(\text{II})$ centers in the uncharacterized species should be occupied with CH_3CN molecules, whose coordination ability is weaker than that of Py^* . Therefore, only the difference between the maximum consumption (2.0 equiv.) and the consumption after the convergence (1.5 equiv.), 0.5 equiv. of Py^* , is the amount of Py^* molecules used in the transformation. This suggests that the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC** and the $\text{Pd}_4\text{I}_8\text{Py}^*$ **PIC** were produced as the dominant intermediates, which is consistent with the $\langle n \rangle$ value of about 1.85 after 20 min in the self-assembly of the Pd_4I_8 **IC** from **1** and PdPy^*_4 (Fig. 3c). During the time-lag between the

addition of Py^* and the formation of **IC** (2 h), formation of the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC**, threading the **PC** into the Pd_2I_4 cage to lead to the $\text{Pd}_4\text{I}_8\text{Py}^*$ **PIC** and intramolecular interlocking in the **PIC** should take place (Fig. 1). The rate of formation of the Pd_4I_8 **IC** from the Pd_2I_4 cage in the presence of Py^* is slower than that from **1** and PdPy^*_4 (Fig. 3f). This is because the $\text{Pd}_2\text{I}_4\text{Py}^*$ **PC** has already been produced as a part of **Int** in the self-assembly from **1** and PdPy^*_4 .

The conversion of the Pd_2I_4 cage into the Pd_4I_8 **IC** also took place by the addition of 0.57 equiv. of free ditopic ligand **1** against the Pd_2I_4 cage (red solid and open circles in Fig. 3f). (The ^1H NMR spectra and the existence ratios are shown in Supplementary Figs. 8 and 9, respectively.) As the yield of the Pd_4I_8 **IC** is 70% after the convergence (red open circles in Fig. 3f), all the Pd_2I_4 cages were efficiently converted into the Pd_4I_8 **IC**. As observed in the conversion of the Pd_2I_4 cage in the presence of Py^* , 0.23 equiv. of the added ditopic ligand **1** were consumed after the convergence (red solid circles in Fig. 3f), indicating that a part of ditopic ligands **1** were incorporated into the uncharacterized species. Compared with the addition of Py^* instead of **1**, the time-lag between the addition of **1** and the formation of **IC** (1 h) is shorter and the formation of the Pd_4I_8 **IC** took place faster even though the amount of **1** added is much fewer than the amount of Py^* added (inset in Fig. 3f). This is probably because the coordination ability of **1** is stronger than that of Py^* . The mass signal of (2,5,0) observed during the self-assembly of the Pd_4I_8 **IC** from **1** and PdPy^*_4 (Table 1) suggests that a part of the Pd_4I_8 **IC** molecules is produced mediated by the Pd_2I_5 **PC**. As mentioned above, 6% of free ditopic ligand **1** remained until the end of the self-assembly of the Pd_4I_8 **IC** from $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ and **1**, while the Pd_4I_8 **IC** could not be obtained at all when slightly excess amount of $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ was used. These results indicate that free ditopic ligand **1** plays a role as the catalyst for the conversion of the Pd_2I_4 cage into the Pd_4I_8 **IC** in the self-assembly of **IC** from $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ and **1**. As a consequence, species with sufficiently strong coordination

Fig. 3 Kinetic data for the self-assembly of the interlocked cage. **a** The existence ratios of the substrates (**1** and $\text{PdPy}^*_4(\text{BF}_4)_2$), the products (the $\text{Pd}_4\mathbf{1}_8$ IC and Py^*) and the $\text{Pd}_2\mathbf{1}_4$ cage in the beginning of the self-assembly of the $\text{Pd}_4\mathbf{1}_8$ IC from **1** and $\text{PdPy}^*_4(\text{BF}_4)_2$. **b** The existence ratios of the substrates (**1** and $\text{PdPy}^*_4(\text{BF}_4)_2$), the products ($\text{Pd}_4\mathbf{1}_8$ IC and Py^*) and the $\text{Pd}_2\mathbf{1}_4$ cage from the beginning till the end of the self-assembly of the $\text{Pd}_4\mathbf{1}_8$ IC from **1** and $\text{PdPy}^*_4(\text{BF}_4)_2$. **c** The change in the $\langle n \rangle$, $\langle k \rangle$ value with time for the self-assembly of the $\text{Pd}_4\mathbf{1}_8$ IC from **1** and $\text{PdPy}^*_4(\text{BF}_4)_2$. Blue crosshairs indicate the (n, k) value of the species, $\text{Pd}_a\mathbf{1}_b\text{Py}^*_c$, which is indicated as (a, b, c) . **d** The change in the $\langle n \rangle$ value with time for the self-assembly of the $\text{Pd}_4\mathbf{1}_8$ IC from **1** and $\text{PdPy}^*_4(\text{BF}_4)_2$. Error bars indicate the standard errors of the means of the existence ratios (**a** and **b**) and the $\langle n \rangle$, $\langle k \rangle$ values (**c** and **d**). **e** The formation of the $\text{Pd}_4\mathbf{1}_8$ IC from the $\text{Pd}_2\mathbf{1}_4$ cage in the presence of Py^* or **1**. **f** The existence ratios of the $\text{Pd}_4\mathbf{1}_8$ IC, Py^* and the free ditopic ligand **1** for the formation of the $\text{Pd}_4\mathbf{1}_8$ IC from the $\text{Pd}_2\mathbf{1}_4$ cage (70% based on **1** initially used) in the presence of Py^* or **1**. 11.4 equiv. of Py^* against the $\text{Pd}_2\mathbf{1}_4$ cage was added, while 0.57 equiv. of **1** against the $\text{Pd}_2\mathbf{1}_4$ cage was added. The existence ratios of Py^* and **1** are indicated based on Py^* and **1** added at $t = 0$. The inset is a magnified plot of the initial change of the existence ratio of the $\text{Pd}_4\mathbf{1}_8$ IC.

ability (free ditopic ligand **1**, Py^* and the free pyridyl groups in the $\text{Pd}_2\mathbf{1}_4\text{Py}^*$ PC and the $\text{Pd}_4\mathbf{1}_8\text{Py}^*$ PIC) can promote the formation of the $\text{Pd}_4\mathbf{1}_8\text{Py}^*$ PIC and the intramolecular treading in the PIC.

Effect of BF_4^- anions on the self-assembly process. As seen in every $\text{Pd}_4\mathbf{1}_8$ IC reported so far, the trapping of three counter anions in between the Pd(II) ions in the $\text{Pd}_4\mathbf{1}_8$ ICs is essential for

their formation as templates (Fig. 1)^{31–39}, so the effect of the counter anions on the self-assembly process of the $\text{Pd}_4\mathbf{1}_8$ IC from **1** and $\text{PdPy}^*_4(\text{BF}_4)_2$ was investigated by ^{19}F NMR spectroscopy (Fig. 4). The signals for the two kinds of BF_4^- anions trapped in the $\text{Pd}_4\mathbf{1}_8$ IC were observed at -144.0 ppm (inner) and -142.6 ppm (outer), respectively (Fig. 4a), whose assignment is the same as was reported previously³⁹. These ^{19}F NMR signals for the encapsulated BF_4^- anions appeared at almost the same

Table 1 List of species detected by ESI-TOF mass spectrometry during the self-assembly.^a

5 min	30 min	3 h	6 h	12 h
(2, 4, 0) ^b	(2, 4, 0)	(2, 4, 0)	(2, 4, 0)	(2, 4, 0)
(2, 5, 0)	(2, 5, 0)	(2, 5, 0)↑	(2, 5, 0)	(2, 5, 0)
(3, 6, 0)	(3, 6, 0)	(3, 6, 0)↓		
	(4, 8, 0)↑ ^c	(4, 8, 0)↑	(4, 8, 0)↑	(4, 8, 0)↑

^aTime variation of the species detected by ESI-TOF mass spectrometry for the self-assembly of the Pd₄1₈ IC from PdPy*₄(BF₄)₂ ([Pd]₀ = 0.95 mM) and **1** ([**1**]₀ = 1.9 mM) in CD₃NO₂ at 298 K was monitored

^b(a, b, c) indicates species Pd_a1_bPy*_c

^cUp and down arrows, ↑ and ↓, indicate increase and decrease in the intensity of the signal compared to the previous measurement, respectively

time when the ¹H NMR signals of the Pd₄1₈ IC appeared. Only one signal of BF₄[−] was observed at −152.3 ppm before the formation of the Pd₄1₈ IC. This signal is near to the signal of free BF₄[−] (−153.0 ppm) but slightly shifted to downfield. This signal was gradually shifted to upfield with time and finally only the signals for the free and encapsulated BF₄[−] anions in the Pd₄1₈ IC were observed. The diffusion coefficient of the BF₄[−] signal at −152.3 ppm determined by ¹⁹F DOSY spectroscopy (Supplementary Fig. 10), $1.01 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$, is larger than that bound in the Pd₄1₈ IC (−142.6 and −144.0 ppm), $2.39 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ (Supplementary Fig. 11), and smaller than that of free BF₄[−], $1.36 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ (Supplementary Fig. 12). These results indicate that there exist BF₄[−] anions chemically different from the free BF₄[−] and the encapsulated ones in the Pd₄1₈ IC, which should

Fig. 4 ¹⁹F NMR spectra of the self-assembly of the interlocked cage. ¹⁹F NMR spectra (470 MHz, CD₃NO₂) of the reaction mixture for the self-assembly of the Pd₄1₈ interlocked cage (IC) from PdPy*₄(BF₄)₂ ([Pd]₀ = 1.0 mM) and the ditopic ligand **1** ([**1**]₀ = 2.0 mM) in CD₃NO₂ at 298 K. **a** Time variation of the ¹⁹F NMR spectra of the reaction mixture measured at 298 K. Signals coloured in blue indicate two kinds of chemically different (inner and outer) BF₄[−] anions trapped in the Pd₄1₈ IC. The ¹⁹F NMR spectrum of the Pd₂1₄ cage is shown as a comparison. **b** A magnified view of the ¹⁹F NMR spectra observed in upfield region for the reaction mixture at 6 h and 7 days with the ¹⁹F NMR spectrum of the Pd₂1₄ cage measured at 298 K. **c** A magnified view of the ¹⁹F NMR spectra observed in upfield region for the reaction mixture at 6 h and 7 days with the ¹⁹F NMR spectrum of the Pd₂1₄ cage measured at 253 K

be the BF_4^- anions that interact with the Pd_2I_4 cage and/or the intermediates of the Pd_4I_8 IC, and that the exchange between these and the free BF_4^- anions is faster than the NMR time scale at 298 K. In order to characterize these BF_4^- anions, ^{19}F NMR measurements were carried out at 253 K (9 K higher than the melting point of CD_3NO_2). Upon decreasing the temperature of the reaction mixture at 6 h to 253 K, the ^{19}F NMR signal at -152.3 ppm observed at 298 K was not divided, indicating that the exchange between the chemically different BF_4^- anions is still faster than the NMR time scale. Similar ^{19}F NMR spectra showing only one signal at -152.3 and -152.3 ppm at 298 and 253 K, respectively, were observed (Fig 4b, c). The interaction between BF_4^- anions and the inner space of the Pd_2I_4 cage was previously confirmed by ^1H NMR titration experiment³⁹. Considering the fact that the Pd_2I_4 cage and the intermediates (mainly $\text{Pd}_2\text{I}_4\text{Py}^*$ PC and $\text{Pd}_4\text{I}_8\text{Py}^*$ PIC) coexist in the reaction mixture at 6 h, the BF_4^- anions should interact not only with the Pd_2I_4 cage but also with the intermediates. As a consequence, BF_4^- anions participate in the self-assembly process of the Pd_4I_8 IC but are not bound to the intermediates as strongly as to the Pd_4I_8 IC.

Discussion

In conclusion, the self-assembly process of the Pd_4I_8 IC was investigated by QASAP. Although the production of the Pd_4I_8 IC was observed by time-dependent ^1H NMR spectroscopy and ESI-TOF mass spectrometry, the signals for the intermediates except the Pd_2I_4 cage could not be observed due to their lower symmetry and lower stability than the Pd_2I_4 and Pd_4I_8 cages. Nevertheless, valuable information to discuss the self-assembly process was obtained by QASAP. The self-assembly of the Pd_4I_8 IC takes place in three steps. Initially, the $\text{Pd}_2\text{I}_4\text{Py}^*$ partial cages (PC) were produced, about half of which were converted into the Pd_2I_4 cage. Then, threading the $\text{Pd}_2\text{I}_4\text{Py}^*$ PC into the Pd_2I_4 cage leads to the $\text{Pd}_4\text{I}_8\text{Py}^*$ PICs. Finally, the Pd_4I_8 IC is produced by the intramolecular interlocking through repetitive cleavage and formation of $\text{Pd(II)}-\text{N}$ coordination bonds in the PIC with the aid of free pyridyl ligands (Py^* or free pyridyl group in the $\text{Pd}_2\text{I}_4\text{Py}^*$ PC and the $\text{Pd}_4\text{I}_8\text{Py}^*$ PIC). Although the $\text{Pd}_4\text{I}_8\text{Py}^*$ PIC would be produced from two molecules of $\text{Pd}_2\text{I}_4\text{Py}^*$ PCs, the result that at least 75% of the Pd_4I_8 IC is derived from the Pd_2I_4 cage indicates that this route is a minor pathway. Considering the fact that the Pd_4I_8 IC is a topologically complicated structure where two Pd_2I_4 cages are quadruply interlocked, it is expected that many undesired species in which several $\text{Pd(II)}-\text{pyridyl}$ coordination bonds are mistakenly formed are produced under mild condition (at 298 K), where kinetically controlled products tend to be formed. Contrary to this intuition, the Pd_4I_8 IC was assembled in a straightforward way in high yield mainly through the Pd_2I_4 cage and the $\text{Pd}_2\text{I}_4\text{Py}^*$ PC as primary intermediates. ESI-TOF mass spectrometry and $n-k$ analysis suggest that the formation of the $\text{Pd}_4\text{I}_8\text{Py}^*$ PIC started quickly (at 30 min). On the other hand, ^1H NMR measurements indicate that the Pd_4I_8 IC appeared after 5 h. During this time-lag, the intramolecular interlocking in the $\text{Pd}_4\text{I}_8\text{Py}^*$ PIC should take place. Similarly, it takes 3 h to start to produce the Pd_4I_8 IC from the Pd_2I_4 cage in the presence of Py^* . Thus, the intramolecular interlocking in the $\text{Pd}_4\text{I}_8\text{Py}^*$ PIC is the rate-determining steps of the self-assembly of the Pd_4I_8 IC. The Pd_4I_8 IC binds three BF_4^- anions in between the four Pd(II) ions, which stabilize the Pd_4I_8 IC. ^{19}F NMR spectroscopy of the reaction mixture indicates that BF_4^- anions interact with the Pd_2I_4 cage and the $\text{Pd}_4\text{I}_8\text{Py}^*$ PIC, yet the binding of the BF_4^- anions in these species is as weak as the exchange of the BF_4^- anions with free BF_4^- is faster than the NMR time scale. Therefore, the effect of the counter anion on the self-assembly process

of the IC is to shift the equilibrium towards the IC by the selective stabilization of the IC.

Methods

General information. ^1H and ^{19}F NMR spectra were recorded using a Bruker AV-500 (500 MHz) spectrometer. All ^1H NMR spectra were referenced using a residual solvent peak, CD_3NO_2 (δ 4.33), and all ^{19}F NMR spectra were referenced using a peak of $n\text{-Bu}_4\text{NBF}_4$ (δ -153.0) in CD_3NO_2 at 298 K. Electrospray ionization time-of-flight (ESI-TOF) mass spectra were obtained using a Waters Xevo G2-S ToF mass spectrometer.

Materials. Unless otherwise noted, all solvents and reagents were obtained from commercial suppliers (TCI Co., Ltd., WAKO Pure Chemical Industries Ltd., KANTO Chemical Co., Inc. and Sigma-Aldrich Co.) and were used as received. CD_3NO_2 was purchased from Acros Organics and used after dehydration with molecular sieves 4 Å. Ditopic ligand **1**³¹ and $\text{PdPy}^*_4(\text{BF}_4)_2$ ⁴⁵ were prepared according to the literature.

Monitoring the self-assembly of the $\text{Pd}_4\text{I}_8(\text{BF}_4)_8$ IC by ^1H and ^{19}F NMR. A 2.4 mM solution of [2.2]paracyclophane in CHCl_3 (125 μL), which was used as an internal standard, was added to two NMR tubes (tubes I and II) and the solvent was removed in vacuo. A solution of $\text{PdPy}^*_4(\text{BF}_4)_2$ (12 mM) in CD_3NO_2 was prepared (solution A). Solution A (50 μL) and CD_3NO_2 (450 μL) were added to tube I. The exact concentration of $\text{PdPy}^*_4(\text{BF}_4)_2$ in solution A was determined through the comparison of the signal intensity with [2.2]paracyclophane by ^1H NMR. A solution of ditopic ligand **1**, (12 mM) in CHCl_3 (100 μL) was added to tube II and the solvent was removed in vacuo. Then CD_3NO_2 (500 μL) for **1** was added to tube II and the exact amount of **1** in tube II was determined through the comparison of the signal intensity with [2.2]paracyclophane by ^1H NMR. 0.50 equiv. (against the amount of ligand **1** in tube II) of solution A (ca. 50 μL ; the exact amount was determined based on the exact concentration of solution A and of ligand in tube II) were added to tube II at 263 K. The self-assembly of the $\text{Pd}_4\text{I}_8(\text{BF}_4)_8$ IC was monitored at 298 K by ^1H and ^{19}F NMR spectroscopy. Examples of the ^1H NMR spectra are shown in Fig. 2 and Supplementary Fig. 1 and those of the ^{19}F NMR spectra are shown in Fig. 4a, b. The exact ratio of **1** and $\text{PdPy}^*_4(\text{BF}_4)_2$ was unambiguously determined by the comparison of the integral value of each ^1H signal of [2.2]paracyclophane. The amounts of **1**, $\text{PdPy}^*_4(\text{BF}_4)_2$, the $\text{Pd}_2\text{I}_4(\text{BF}_4)_4$ cage, the $\text{Pd}_4\text{I}_8(\text{BF}_4)_8$ IC and Py^* were quantified by the integral value of each ^1H signal against the signal of the internal standard ([2.2]paracyclophane). In order to confirm the reproducibility, the same experiment was carried out three times (runs 1–3). These data, the average values of the existence ratios and the $\langle n \rangle$, $\langle k \rangle$ values are listed in Supplementary Tables 1–5.

Determination of the existence ratio of each species. The relative integral value of each ^1H NMR signal against the internal standard [2.2]paracyclophane is used as the integral value in this description. We define the integral values of the signal for the substrates (**1** and PdPy^*_4), the products (the Pd_4I_8 IC and Py^*) and the Pd_2I_4 cage at each time t as follows; $I_L(t)$: 1/2 of the integral value of the a proton in free ligand **1**; $I_M(t)$: the integral value of the i proton of Py^* in $[\text{PdPy}^*_4]^{2+}$; $I_{\text{cage}}(t)$: 1/2 of the integral value of the a proton in the Pd_2I_4 cage; $I_{\text{IC}}(t)$: the integral value of the a_i proton in the Pd_4I_8 IC; $I_{\text{Py}^*}(t)$: the integral value of the i proton of free Py^* . (The assignment of signals for the Pd_4I_8 IC is shown in Fig. 2 and Supplementary Fig. 1.)

$I_M(0)$ was determined based on the exact concentration of solution A determined by ^1H NMR and the exact volume of solution A added into tube II.

$I_L(0)$ was determined by ^1H NMR measurement before the addition of solution A into tube II.

Existence ratio of $[\text{PdPy}^*_4]^{2+}$: As the total amount of $[\text{PdPy}^*_4]^{2+}$ corresponds to $I_M(0)$, the existence ratio of $[\text{PdPy}^*_4]^{2+}$ at t is expressed by $I_M(t)/I_M(0)$.

Existence ratio of **1**: As the total amount of free ligand **1** corresponds to $I_L(0)$, the existence ratio of **1** at t is expressed by $I_L(t)/I_L(0)$.

Existence ratio of Py^* : As the total amount of Py^* corresponds to $I_M(0)$, the existence ratio of Py^* at t is expressed by $I_{\text{Py}^*}(t)/I_M(0)$.

Existence ratio of the Pd_2I_4 cage: As the Pd_2I_4 cage is quantified based on **1**, the existence ratio of the Pd_2I_4 cage at t is expressed by $I_{\text{cage}}(t)/I_L(0)$.

Existence ratio of the Pd_4I_8 IC: As the Pd_4I_8 IC is quantified based on **1**, the existence ratio of the Pd_4I_8 IC at t is expressed by $I_{\text{IC}}(t)/I_L(0)$.

Existence ratio of the total intermediates not observed by ^1H NMR (**Int**): The existence ratio of the total intermediates not observed by ^1H NMR (**Int**) is determined based on the amount of ligand **1** in the intermediates. Thus, the existence ratio of **Int** is calculated by subtracting the other species containing **1** (free **1**, the cage and IC) from the total amount of **1** ($I_L(0)$). The existence ratio of **Int** at t is expressed by $(I_L(0) - I_L(t) - I_{\text{cage}}(t) - I_{\text{IC}}(t))/I_L(0)$.

(a): The total amount of Pd(II) ions corresponds to $I_M(0)/4$. The amount of Pd(II) ions in $[\text{PdPy}^*_4]^{2+}$ at t corresponds to $I_M(t)/4$. The amount of Pd(II) ions in the cage and IC at t corresponds to $I_{\text{cage}}(t)/2$ and $I_{\text{IC}}(t)/2$, respectively. The amount of Pd(II) ions in **Int** at t is thus expressed by $I_M(0)/4 - I_M(t)/4 - I_{\text{cage}}(t)/2 - I_{\text{IC}}(t)/2$.

(b): The total amount of ligand **1** corresponds to $I_L(0)$. The amount of free ligand **1** at t corresponds to $I_L(t)$. The amounts of ligand **1** in the cage and IC at

t corresponds to $I_{\text{cage}}(t)$ and $I_{\text{IC}}(t)$, respectively. The amount of ligand **1** in **Int** at t is thus expressed by $I_{\text{L}}(0) - I_{\text{L}}(t) - I_{\text{cage}}(t) - I_{\text{IC}}(t)$.

(c): The total amount of Py^* corresponds to $I_{\text{M}}(0)$. The amount of free Py^* at t corresponds to $I_{\text{Py}^*}(t)$. The amount of Py^* in $[\text{PdPy}^*_4]^{2+}$ at t corresponds to $I_{\text{M}}(t)$. The amount of Py^* in **Int** at t is thus expressed by $I_{\text{M}}(0) - I_{\text{Py}^*}(t) - I_{\text{M}}(t)$.

The $\langle n \rangle$ and $\langle k \rangle$ values are determined with these $\langle a \rangle$, $\langle b \rangle$ and $\langle c \rangle$ values as follows:

$$n = \frac{4\langle a \rangle - \langle c \rangle}{\langle b \rangle} \quad (1)$$

$$k = \frac{\langle a \rangle}{\langle b \rangle} \quad (2)$$

Quantitative analysis of the self-assembly process. In QASAP, all the substrates (**1** and $\text{PdPy}^*_4(\text{BF}_4)_2$), the products (the $\text{Pd}_4\text{I}_8(\text{BF}_4)_8$ **IC** and Py^*) and the $\text{Pd}_2\text{I}_4(\text{BF}_4)_4$ cage were quantified by ^1H NMR spectroscopy during the self-assembly of the cage and then the amount of the intermediates not observed by ^1H NMR (**Int**) and the average composition of the unobservable intermediates, $\text{Pd}_{(a)}\text{I}_{(b)}\text{Py}^*_{(c)}$, were obtained. The existence ratios of the substrates, the products, the $\text{Pd}_2\text{I}_4(\text{BF}_4)_4$ cage and **Int** and $\langle a \rangle$, $\langle b \rangle$, $\langle c \rangle$, $\langle n \rangle$ and $\langle k \rangle$ with time are listed in Supplementary Tables 1–5 and plotted in Fig. 3.

Self-assembly of the $\text{Pd}_4\text{I}_8(\text{BF}_4)_8$ **IC from $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ and **1**.** The self-assembly of the $\text{Pd}_4\text{I}_8(\text{BF}_4)_8$ **IC** from $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ ($[\text{Pd}]_0 = 1.0$ mM) and **1** ($[\text{I}]_0 = 2.0$ mM) was monitored by ^1H NMR spectroscopy. The experiment was conducted in the same way as was described in the section “Monitoring the self-assembly of the $\text{Pd}_4\text{I}_8(\text{BF}_4)_8$ **IC** by ^1H and ^{19}F NMR” with the difference that $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ was used instead of $\text{PdPy}^*_4(\text{BF}_4)_2$. Because of the difficulty in the quantification of $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ and CH_3CN by ^1H NMR, only the consumption of **1** and the formation of the Pd_2I_4 cage and the Pd_4I_8 **IC** were monitored by ^1H NMR at 298 K. ^1H NMR spectra are provided in Supplementary Fig. 2 and the existence ratios of the substrates (**1** and $\text{PdPy}^*_4(\text{BF}_4)_2$), the products (the Pd_4I_8 **IC** and Py^*), the Pd_2I_4 cage and **Int** are plotted in Supplementary Fig. 3.

Mass spectrometry. A solution of $\text{PdPy}^*_4(\text{BF}_4)_2$ ($[\text{Pd}]_0 = 0.95$ mM) and **1** ($[\text{I}]_0 = 1.9$ mM) were mixed in CD_3NO_2 (550 μL). At each time point, 25 μL of the reaction mixture was taken, diluted with CH_3NO_2 (500 μL), filtered through a membrane filter (pore size: 0.20 μm) and injected in the mass spectrometer (measurement condition: capillary/1.5 kV; sampling cone/30 V; source offset/80 V; source/80 $^\circ\text{C}$; desolvation/150 $^\circ\text{C}$; cone gas/50 L h^{-1} ; desolvation gas/800 L h^{-1}) with 5.0 $\mu\text{L min}^{-1}$ flow rate to obtain ESI-TOF mass spectra (Supplementary Fig. 4). A list of predominantly observed species is shown in Table 1.

Preparation of the $\text{Pd}_2\text{I}_4(\text{BF}_4)_4$ cage. The exact amount of **1** in an NMR tube was determined through the comparison of the signal intensity with [2.2]paracyclophane by ^1H NMR. Then the self-assembly of the $\text{Pd}_2\text{I}_4(\text{BF}_4)_4$ cage was carried out from $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ ($[\text{Pd}]_0 = 1.1$ mM) and **1** ($[\text{I}]_0 = 2.0$ mM) in CD_3NO_2 (550 μL) at 343 K in the same way as was described in the section “Monitoring the self-assembly of the $\text{Pd}_4\text{I}_8(\text{BF}_4)_8$ **IC** by ^1H and ^{19}F NMR”. After 12 h, the $\text{Pd}_2\text{I}_4(\text{BF}_4)_4$ cage was obtained in 70% yield (determined by ^1H NMR based on the internal standard ([2.2]paracyclophane)). ^1H NMR spectra are provided in Supplementary Fig. 5.

Formation of the Pd_4I_8 **IC from the Pd_2I_4 cage in the presence of Py^* .** The $\text{Pd}_2\text{I}_4(\text{BF}_4)_4$ cage was prepared in the same way as described in the section “Preparation of the $\text{Pd}_2\text{I}_4(\text{BF}_4)_4$ cage” in 70% yield (determined by ^1H NMR based on the internal standard ([2.2]paracyclophane)). Then 2.0 equiv. of Py^* (2.0 μmol) against the initial amount of **1** (1.0 μmol) was added into the reaction mixture and then the reaction of the Pd_2I_4 cage and Py^* was monitored by ^1H NMR at 298 K. ^1H NMR spectra are provided in Supplementary Fig. 6 and the existence ratios of the substrates (the Pd_2I_4 cage and Py^*), the products (the Pd_4I_8 **IC**) and **Int** are plotted in Supplementary Fig. 7.

Formation of the Pd_4I_8 **IC from the Pd_2I_4 cage in the presence of **1**.** The $\text{Pd}_2\text{I}_4(\text{BF}_4)_4$ cage was prepared in the same way as described in the section “Preparation of the $\text{Pd}_2\text{I}_4(\text{BF}_4)_4$ cage” in 70% yield (determined by ^1H NMR based on the internal standard ([2.2]paracyclophane)). Then 0.1 equiv. of **1** (0.10 μmol) against the initial amount of **1** (1.0 μmol) was added into the reaction mixture and then the reaction of the Pd_2I_4 cage and **1** was monitored by ^1H NMR at 298 K. ^1H NMR spectra are provided in Supplementary Fig. 8 and the existence ratios of the substrates (the Pd_2I_4 cage and **1**), the products (the Pd_4I_8 **IC**) and **Int** are plotted in Supplementary Fig. 9.

^{19}F DOSY NMR measurements. ^{19}F DOSY NMR spectra of the reaction mixture for the self-assembly from $\text{PdPy}^*_4(\text{BF}_4)_2$ ($[\text{Pd}]_0 = 1.0$ mM) and **1** ($[\text{I}]_0 = 2.0$ mM)

in CD_3NO_2 recorded at 6 h and at 7 days and of a solution of $n\text{-Bu}_4\text{NBF}_4$ in CD_3NO_2 are shown in Supplementary Figs. 10–12, respectively. The diffusion coefficients and the hydrodynamic radii of the observed species are summarized in Supplementary Table 6. The hydrodynamic radii, r , were determined by the Stokes–Einstein equation (3), where D is a diffusion coefficient obtained from ^{19}F DOSY NMR spectroscopy, k_B is Boltzmann constant, T is the measurement temperature, which was applied to be 298 K, and η is the viscosity of solvent, which was applied to be 0.61 mPa s (CH_3NO_2).

$$D = \frac{k_B T}{6\pi\eta r} \quad (3)$$

Data availability

The authors declare that all the other data supporting the findings of this study are available within the article and its supplementary information files and from the corresponding author upon request.

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References

1. Bruns, C. J. & Stoddart, J. F. *The Nature of the Mechanical Bond: from Molecules to Machines* (John Wiley & Sons, Inc., New York, 2016).
2. Amabilino, D. B. & Stoddart, J. F. Interlocked and intertwined structures and superstructures. *Chem. Rev.* **95**, 2725–2828 (1995).
3. Du, S. M., Stollar, B. D. & Seeman, N. C. A synthetic DNA molecule in three knotted topologies. *J. Am. Chem. Soc.* **117**, 1194–1200 (1995).
4. Mao, C., Sun, W. & Seeman, N. C. Assembly of borromean rings from DNA. *Nature* **386**, 137–138 (1997).
5. Raymo, F. M. & Stoddart, J. F. Interlocked macromolecules. *Chem. Rev.* **99**, 1643–1664 (1999).
6. Amabilino, D. B. & Pérez-García, L. Topology in molecules inspired, seen and represented. *Chem. Soc. Rev.* **38**, 1562–1571 (2009).
7. Liu, Y., O’Keeffe, M., Treacy, M. M. J. & Yaghi, O. M. The geometry of periodic knots, polycatenanes and weaving from a chemical perspective: a library for reticular chemistry. *Chem. Soc. Rev.* **47**, 4642–4664 (2018).
8. Pease, A. R. et al. Switching devices based on interlocked molecules. *Acc. Chem. Res.* **34**, 433–444 (2001).
9. Leigh, D. A., Wong, J. K. Y., Dehez, F. & Zerbetto, F. Unidirectional rotation in a mechanically interlocked molecular rotor. *Nature* **424**, 174–179 (2003).
10. Balzani, V., Credi, A., Silvi, S. & Venturi, M. Artificial nanomachines based on interlocked molecular species: recent advances. *Chem. Soc. Rev.* **35**, 1135–11149 (2006).
11. Champin, B., Mobian, P. & Sauvage, J.-P. Transition metal complexes as molecular machine prototypes. *Chem. Soc. Rev.* **36**, 358–366 (2007).
12. van Dongen, S. F. M., Cantekin, S., Elemans, J. A. A. W., Rowan, A. E. & Nolte, R. J. M. Functional interlocked systems. *Chem. Soc. Rev.* **43**, 99–122 (2014).
13. Jester, S.-S. & Famulok, M. Mechanically interlocked DNA nanostructures for functional devices. *Acc. Chem. Res.* **47**, 1700–1709 (2014).
14. Chang, J.-C. et al. Mechanically interlocked daisy-chain-like structures as multidimensional molecular muscles. *Nat. Chem.* **9**, 128–134 (2017).
15. Dietrich-Buchecker, C. O. & Sauvage, J.-P. A synthetic molecular trefoil knot. *Angew. Chem. Int. Ed. Engl.* **28**, 189–192 (1989).
16. Hasenknopf, B., Lehn, J.-M., Kneisel, B. O., Baum, G. & Fenske, D. Self-assembly of a circular double helicate. *Angew. Chem. Int. Ed. Engl.* **35**, 1838–1840 (1996).
17. Fujita, M. Self-assembly of [2]catenanes containing metals in their backbones. *Acc. Chem. Res.* **32**, 53–61 (1999).
18. Chichak, K. S. et al. Molecular borromean rings. *Science* **304**, 1308–1312 (2004).
19. Guo, J., Mayers, P. C., Breault, G. A. & Hunter, C. A. Synthesis of a molecular trefoil knot by folding and closing on an octahedral coordination template. *Nat. Chem.* **2**, 218–222 (2010).
20. Forgan, R. S., Sauvage, J.-P. & Stoddart, J. F. Chemical topology: complex molecular knots, links, and entanglements. *Chem. Rev.* **111**, 5434–5464 (2011).
21. Leong, W. L. & Vittal, J. J. One-dimensional coordination polymers: complexity and diversity in structures, properties, and applications. *Chem. Rev.* **111**, 688–764 (2011).
22. Chambron, J.-C. & Sauvage, J.-P. Topologically complex molecules obtained by transition metal templation: it is the presentation that determines the synthesis strategy. *New J. Chem.* **37**, 49–57 (2013).

23. Lewis, J. E. M., Beer, P. D., Loeb, S. J. & Goldup, S. M. Metal ions in the synthesis of interlocked molecules and materials. *Chem. Soc. Rev.* **46**, 2577–2591 (2017).
24. Sawada, T., Yamagami, M., Ohara, K., Yamaguchi, K. & Fujita, M. Peptide [4] catenane by folding and assembly. *Angew. Chem. Int. Ed.* **55**, 4519–4522 (2016).
25. Zhang, L. et al. Stereoselective synthesis of a composite knot with nine crossings. *Nat. Chem.* **10**, 1083–1088 (2018).
26. Ponnuswamy, N., Cougnon, F. B. L., Clough, J. M., Pantos, G. D. & Sanders, J. K. M. Discovery of an organic trefoil knot. *Science* **338**, 783–785 (2012).
27. Tsujimoto, Y., Kojima, T. & Hiraoka, S. Rate-determining step in the self-assembly process of supramolecular coordination capsules. *Chem. Sci.* **5**, 4167–4172 (2014).
28. Hiraoka, S. What do we learn from the molecular self-assembly process? *Chem. Rec.* **15**, 1144–1147 (2015).
29. Hiraoka, S. Unresolved issues that remain in molecular self-assembly. *Bull. Chem. Soc. Jpn.* **91**, 957–978 (2018).
30. Hiraoka, S. Self-assembly processes of Pd(II)- and Pt(II)-linked discrete self-assemblies revealed by QASAP. *Isr. J. Chem.* <https://doi.org/10.1002/jch.201800073> In the press (2018).
31. Fukuda, M., Sekiya, R. & Kuroda, R. A quadruply stranded metallohelicate and its spontaneous dimerization into an interlocked metallohelicate. *Angew. Chem. Int. Ed.* **47**, 706–710 (2008).
32. Freye, S. et al. Allosteric binding of halide anions by a new dimeric interpenetrated coordination cage. *Angew. Chem. Int. Ed.* **51**, 2191–2194 (2012).
33. Freye, S. et al. Template control over dimerization and guest selectivity of interpenetrated coordination cages. *J. Am. Chem. Soc.* **135**, 8476–8479 (2013).
34. Frank, M. et al. Assembly and stepwise oxidation of interpenetrated coordination cages based on phenothiazine. *Angew. Chem. Int. Ed.* **52**, 10102–10106 (2013).
35. Löffler, S. et al. Triggered exchange of anionic for neutral guests inside a cationic coordination cage. *J. Am. Chem. Soc.* **137**, 1060–1063 (2015).
36. Zhu, R., Lübken, J., Dittrich, B. & Clever, G. H. Stepwise halide-triggered double and triple catenation of self-assembled coordination cages. *Angew. Chem. Int. Ed.* **54**, 2796–2800 (2015).
37. Sekiya, R., Fukuda, M. & Kuroda, R. Site-selective anion recognition of an interlocked dimer. *Org. Biomol. Chem.* **15**, 4328–4335 (2017).
38. Clever, G. H. & Punt, P. Cation–anion arrangement patterns in self-assembled Pd₂L₄ and Pd₄L₈ coordination cages. *Acc. Chem. Res.* **50**, 2233–2243 (2017).
39. Sekiya, R., Fukuda, M. & Kuroda, R. Anion-directed formation and degradation of an interlocked metallohelicate. *J. Am. Chem. Soc.* **134**, 10987–10997 (2012).
40. Kai, S. et al. The effect of solvent and coordination environment of metal source on the self-assembly pathway of a Pd(II)-mediated coordination capsule. *Inorg. Chem.* **56**, 12652–12663 (2017).
41. Kai, S. et al. Self-assembly process of a Pd₂L₄ capsule: steric interactions between neighboring components favor the formation of large intermediates. *Chem. Eur. J.* **24**, 3965–3969 (2018).
42. Tateishi, T., Kojima, T. & Hiraoka, S. Chiral self-sorting process in the self-assembly of homochiral coordination cages from axially chiral ligands. *Commun. Chem.* **1**, 20 (2018).
43. Tobe, M. L. & Burgess, J. *Inorganic Reaction Mechanisms* (Longman: London, U.K., 1999).
44. Cooper, J. & Ziegler, T. A density functional study of S_N2 substitution at square-planar platinum complexes. *Inorg. Chem.* **41**, 6614–6622 (2002).
45. Tateishi, T. et al. Self-assembly of a Pd₄L₈ double-walled square partly takes place through the formation of kinetically trapped species. *Eur. J. Inorg. Chem.* 1192–1197 (2018).

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Author contributions

T.T., Y.Y., T.K., S.T. and S.H. conceived the project. S.H. prepared the manuscript and all the authors discussed the results and commented on the manuscript. T.T. and Y.Y. synthesized the ditopic ligands **1**. T.T. carried out all the NMR and ESI-TOF mass measurements. T.T., T.K. and S.H. analyzed the experimental data.

Additional information

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