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Direct and Quantitative Characterization of Dynamic Ligand Exchange between Coordination-Driven Self-Assembled Supramolecular Polygons

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During the last two decades, coordination-driven self-assembly has become a well-established methodology in supramolecular chemistry for constructing ensembles of varying structural motifs, as witnessed by the development of diverse metallosupramolecular helicates, polygons, and polyhedra.[1] While most investigations have largely focused on the structural features of these supramolecules, reports about the dynamic characteristics of such structures are limited.[2] Nevertheless, the dynamic nature of self-assembly is widely recognized as a significant feature of the supramolecular assemblies.[3] Detailed mechanistic studies are not only important for understanding of the self-assembly processes but also crucial for the use of supramolecular assemblies in applications such as construction of constitutional dynamic libraries,[4] self-assembly of supramolecular polymers,[5] and control of supramolecular transformations.[6]

One of the most fundamental features of the dynamic nature of coordination-driven (and indeed all) supramolecular self-assembly is dynamic component exchange: the mutual exchange of molecular components between the supramolecular assemblies under thermodynamic control.[3b,c] Although such constitutional dynamic features have routinely been used in explaining experimental results and developing theoretical understandings of supramolecular self-assembly,[7] very few examples that directly and quantitatively characterize such exchanges in self-assembled supramolecules have been reported.[8] Very recently, Rebek and co-workers[8] demonstrated an innovative way to characterize such dynamic features of supramolecular capsules using the fluorescent resonance energy transfer (FRET) technique, but these studies have so far been limited to hydrogen-bonding-driven self-assembly. Such reports are rare[2f] for coordination-driven self-assembly, likely because of the lack of a suitable characterization method.

Isotope labeling is an appropriate tool for characterizing dynamic exchange in metallosupramolecular assemblies. Indeed, isotope labeling has been widely used in biological studies such as proteomics, where it is used in the quantitative study of proteins based on mass spectral characterization.[9] Herein, we demonstrate an isotope-labeling-based method capable of direct and quantitative characterization of the constitutional dynamic features of coordination-driven self-assembly using electrospray ionization mass spectrometry (ESI-MS). This method allows for a thorough study of the poorly understood dynamic nature of Pt−N coordination-driven self-assembly.[1b,e,10] With this technique, the dynamic ligand exchange process as well as the subsequent equilibration under thermodynamic control can be directly characterized. Moreover, on the basis of quantitative mass spectral results, the kinetics of the exchange process has also been investigated.

We have employed the $^{1}H/^{2}D$ isotope-labeled pyridyl ligands **1** and **2** (Figure 1) and ESI-MS to observe and characterize the dynamic ligand exchange of supramolecular polygons **5**[11] and **6**[12] assembled by Pt−N coordination bonding interactions. Combining **1** or **2** with organoplatinum acceptor **3** or **4** results in the self-assembly of isotopically pure supramolecular polygons **5a**, **5b**, **6a**, or **6b**. As Scheme 1 shows, mixing homoisotopic rectangles (**5a** or **5b**) and/or homoisotopic triangles (**6a** or **6b**) leads, as a result of ligand exchange, to heteroisotopic polygons **5c** or **6c** and **6d**, which can be easily distinguished by mass spectral analysis. More importantly, the relative distribution of these isotopically varying supramolecular entities in the mixture can be quantitatively calculated using the different intensities of their corresponding spectral signals.

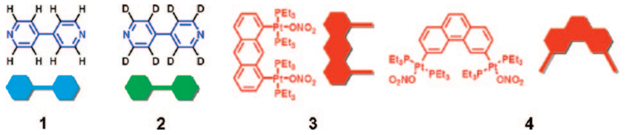
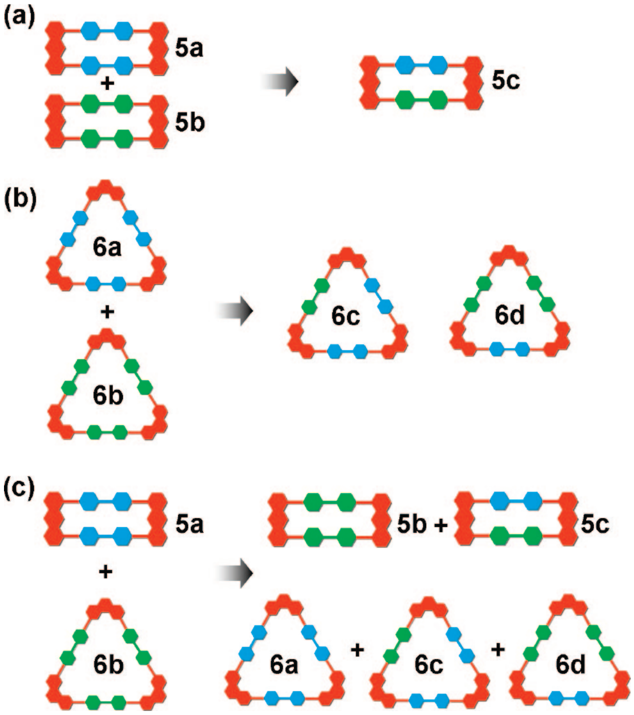


Figure 1. Schematic and molecular structures of the linear dipyridyl donors **1** and **2** as well as the 0 and 60° organoplatinum acceptors **3** and **4**, respectively.

Scheme 1. Representation of Dynamic Ligand Exchange between (a, b) the Same and (c) Different Types of Supramolecular Polygons (Rectangles, **5a** and **5b**; Triangles, **6a** and **6b**) with $^{1}H/^{2}D$ Isotope Labels



In order to explore the dynamic ligand exchange between supramolecular polygons sharing the same motif, individually prepared **5a**/**5b** or **6a**/**6b** were mixed in a 1:1 ratio and heated to 64 ± 1 °C in a 1:1 (v/v) aqueous acetone solution (Scheme 1a,b).

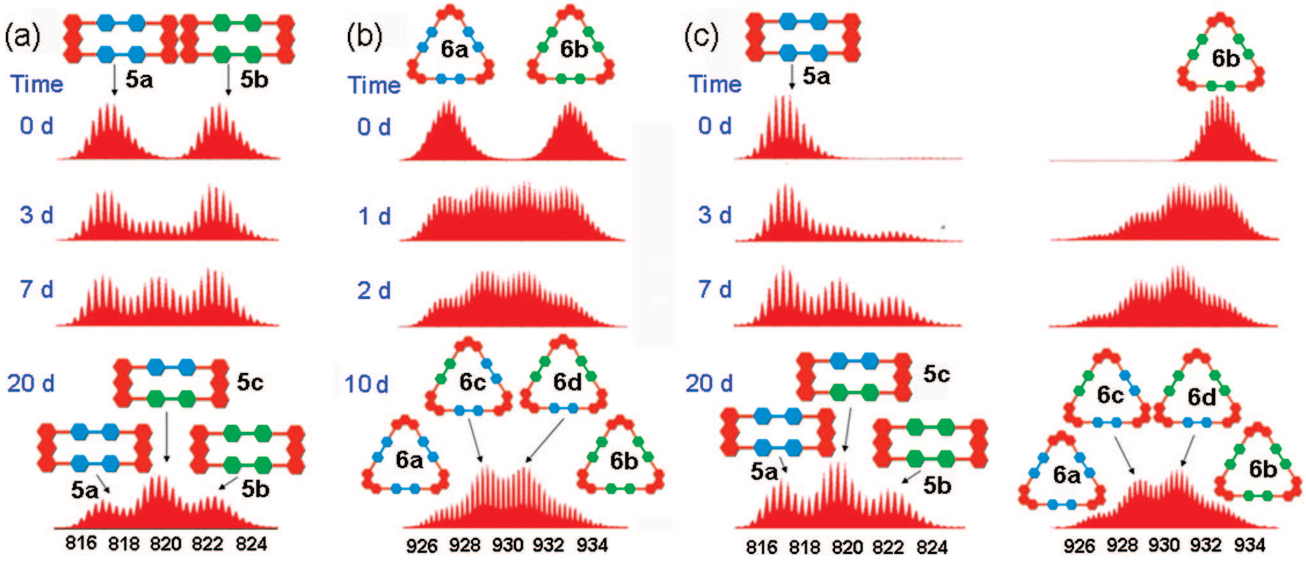


Figure 2. ESI-MS spectra of dynamic ligand exchange between (a) supramolecular rectangles (**5a** and **5b**), (b) supramolecular triangles (**6a** and **6b**), and (c) rectangle **5a** and triangle **6b**, recorded at different time intervals (d = day).

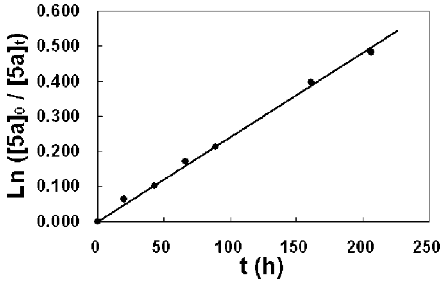


Figure 3. Plot of ESI-MS data obtained over 240 h, displaying the first-order exchange kinetics for supramolecular rectangles **5a** and **5b**.

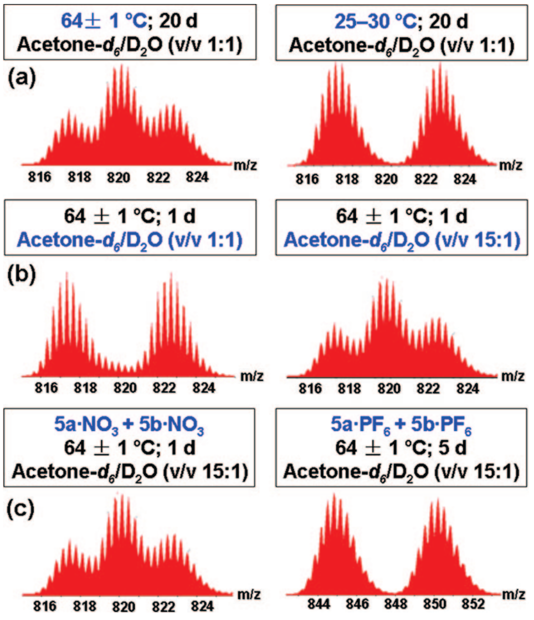


Figure 4. ESI-MS spectra of ligand exchange between **5a** and **5b** influenced by differences in (a) temperature, (b) solvent, and (c) counteranion.

ESI-MS was used to monitor ligand exchange over a period of days (Figure 2a,b and Figures S1 and S2 in the Supporting Information). Initially, in each mixture, only those signals corresponding to homoisotopic polygons (**5a**, 817.3; **5b**, 822.7; **6a**, 927.3; **6b**, 933.3) were observed, with similar intensities. When the mixture was heated at 64 ± 1 °C, signals corresponding to polygons **5c** (820.0), **6c** (929.3), and **6d** (931.3) could be resolved, clearly indicating dynamic ligand exchange between the supramolecules. After 10−20 days, the dynamic ligand exchange processes reached equilibrium, as indicated by the unchanging ESI-MS signals. The resulting equilibrium mixtures in each case (Figures S1 and S2) represented statistical product distributions: for the rectangles, **5a**/**5c**/**5b** = 0.518:1.00:0.580 (theoretical value 1:2:1); for the triangles, **6a**/**6c**/**6d**/**6b** = 0.334:1.00:0.962:0.326 (theoretical value 1:3:3:1).[13]

Similar mass spectral studies were also carried out in a system containing supramolecular polygons **5a** and **6b** in different motifs capable of self-sorting.[10a] Dynamic ligand exchange between these different polygons was observed, as indicated by the increases in the mass spectral signals corresponding to **5b**, **5c**, **6a**, **6c**, and **6d** (Figure 2c and Figure S3) next to the peaks for **5a** and **6b** upon heating the mixture at 64 ± 1 °C in a 1:1 (v/v) aqueous acetone solution for 20 days.

In addition to the mass spectral characterization, supportive NMR spectral studies were also employed to follow these exchange processes. For ligand exchange between structures in the same motif (**5a**/**5b** or **6a**/**6b**), as expected, no significant changes could be found in either the $^{31}P\{^1H\}$ or ^1H NMR spectra during the exchange (Figures S4 and S5). Dynamic ligand exchange between **5a** and **6b** causes increases in the signals at 8.52, 8.71, and 9.18 ppm and decreases in the signals at 8.32 and 9.08 ppm in the ^1H NMR spectra (Figure S6) but no change in the $^{31}P\{^1H\}$ NMR spectra as the result of the formation of triangles (**6a**, **6c**, and **6d**) and rectangles (**5b** and **5c**). These results indicate that only component exchange between discrete supramolecules occurred, without generation of any disordered byproduct.

These combined ESI-MS and NMR results not only unambiguously support the dynamic ligand exchange of these metallosupramolecular polygons but also directly demonstrate the subsequent equilibration under thermodynamic control. For example, for the exchange reaction of rectangles (**5a** + **5b** ⇄ 2 **5c**), constitutional dynamic exchange between these rectangles allows for the redistribution of the isotopically different **5a**, **5b**, and **5c** from the initial input ratio of 1:1:0 toward the equilibrium value of 1:1:2, which agrees well with the thermodynamic equilibrium constant $K = 4$

based on statistical factors.[14] Because of the similar intrinsic stabilities of **5a**, **5b**, and **5c**, such a dynamic redistribution process is mainly entropy-driven.

Furthermore, quantitative mass spectral results acquired over time allow for the kinetics of supramolecular dynamic ligand exchange to be determined. Analysis of the data (Figure S7 and Table S1 in the Supporting Information) indicates that the dynamic ligand exchange between **5a** and **5b** is a first-order kinetic process with rate constant $k = 0.0024\ \mathrm{h}^{-1}$, as shown in Figure 3 ($R^2 = 0.99$). Presumably, the first-order exchange kinetics corresponds to the ring-opening of the rectangular supramolecules upon nucleophilic attack on the Pt−N coordination bond by a nitrate anion as the rate-determining step. Nitrate anions and the cationic rectangle are likely to form an ion pair in acetone solution,[15] and the ring-opening step could consequently be considered as an intramolecular process of the ion pair, whereby the first-order kinetics can be established.

We also explored the influence of temperature, solvent, and counteranion on the ligand exchange process between **5a** and **5b**. As may be expected, decreasing the temperature significantly slows the exchange process. At 25−30 °C, the exchange was no longer observed (Figure 4a), even after 20 days. Interestingly, as Figure 4b shows, decreasing the percentage of water in the solution can significantly accelerate the rate of the exchange process. At 64 ± 1 °C in a 15:1 (v/v) aqueous acetone solution, the exchange process reached equilibrium within 1 day. Additionally, changing the counteranion from nitrate (NO_3^-) to hexafluorophosphate (PF_6^-) anions resulted in no exchange as observed by ESI-MS spectra (Figure 4c). The influence of solvent and counteranion further substantiates the role of the nitrate anions in the rate-determining step of the ligand exchange process: nitrate anions are more nucleophilic when fewer water molecules are present, and when the counteranion was changed from NO_3^- to PF_6^-, the dynamic exchange did not proceed because PF_6^- is a less nucleophilic anion.

In conclusion, we have directly demonstrated the constitutional dynamic exchange of Pt−N coordination-driven self-assembled supramolecular polygons (triangles and rectangles) using stable ^{1}H/^{2}D isotope labeling of the pyridyl donors and ESI-MS combined with NMR spectroscopy. Both the thermodynamic and kinetic aspects of such exchange processes have been established on the basis of quantitative mass spectral results. Further investigation showed that, as expected, the exchange is highly dependent on experimental conditions such as temperature, solvent, and the counteranions. The isotope-labeling-based mass spectral technique described here represents a new method for the direct and quantitative study of supramolecular dynamics.

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Supporting Information Available: Experimental details, ESI-MS trace spectra and NMR spectra of the dynamic exchange process, and details of the kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Stang, P. J.; Olenyuk, B. *Acc. Chem. Res.* **1997**, *30*, 502. (b) Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem. Rev.* **2000**, *100*, 853. (c) Holliday, B. J.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2022. (d) Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, N.; Kusukawa, T.; Biradha, K. *Chem. Commun.* **2001**, 509. (e) Seidel, S. R.; Stang, P. J. *Acc. Chem. Res.* **2002**, *35*, 972. (f) Ruben, M.; Rojo, J.; Romero-Salguero, F. J.; Uppadine, L. H.; Lehn, J.-M. *Angew. Chem., Int. Ed.* **2004**, *43*, 3644. (g) Fiedler, D.; Leung, D. H.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2005**, *38*, 351. (h) Fujita, M.; Tominaga, M.; Hori, A.; Therrien, B. *Acc. Chem. Res.* **2005**, *38*, 369. (i) Lukin, O.; Voegtle, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1456. (j) Severin, K. *Chem. Commun.* **2006**, 3859. (k) Nitschke, J. R. *Acc. Chem. Res.* **2007**, *40*, 103. (l) Pitt, M. A.; Johnson, D. W. *Chem. Soc. Rev.* **2007**, *36*, 1441. (m) Northrop, B. H.; Yang, H.-B.; Stang, P. J. *Chem. Commun.* **2008**, 5896. (n) Schmittel, M.; Mahata, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 5284.

(2) (a) Hori, A.; Akasaka, A.; Biradha, K.; Sakamoto, S.; Yamaguchi, K.; Fujita, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3269. (b) Yamamoto, T.; Arif, A. M.; Stang, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12309. (c) Davis, A. V.; Raymond, K. N. *J. Am. Chem. Soc.* **2005**, *127*, 7912. (d) Davis, A. V.; Fiedler, D.; Seeber, G.; Zahl, A.; Van Eldik, R.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 1324. (e) Pluth, M. D.; Raymond, K. N. *Chem. Soc. Rev.* **2007**, *36*, 161. (f) Claessens, C. G.; Vicente-Arana, M. J.; Torres, T. *Chem. Commun.* **2008**, 6378. (g) Levin, M. D.; Stang, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 7428.

(3) (a) Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4763. (b) Davis, A. V.; Yeh, R. M.; Raymond, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4793. (c) Lehn, J.-M. *Chem. Soc. Rev.* **2007**, *36*, 151.

(4) (a) Wheaton, C. A.; Jennings, M. C.; Puddephatt, R. J. *J. Am. Chem. Soc.* **2006**, *128*, 15370. (b) Chow, C.-F.; Fujii, S.; Lehn, J.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5007. (c) Friese, V. A.; Kurth, D. G. *Coord. Chem. Rev.* **2008**, *252*, 199.

(5) (a) Barboiu, M.; Vaughan, G.; Graff, R.; Lehn, J.-M. *J. Am. Chem. Soc.* **2003**, *125*, 10257. (b) Giuseppone, N.; Schmitt, J.-L.; Lehn, J.-M. *J. Am. Chem. Soc.* **2006**, *128*, 16748.

(6) (a) Heo, J.; Jeon, Y.-M.; Mirkin, C. A. *J. Am. Chem. Soc.* **2007**, *129*, 7712. (b) Hiraoka, S.; Sakata, Y.; Shionoya, M. *J. Am. Chem. Soc.* **2008**, *130*, 10058. (c) Zhao, L.; Northrop, B. H.; Stang, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 11886.

(7) (a) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901. (b) Ercolani, G. *J. Phys. Chem. B* **1998**, *102*, 5699. (c) Ercolani, G. *J. Phys. Chem. B* **2003**, *107*, 5052. (d) Ercolani, G. *J. Am. Chem. Soc.* **2003**, *125*, 16097.

(8) (a) Barrett, E. S.; Dale, T. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 3818. (b) Barrett, E. S.; Dale, T. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 8818. (c) Barrett, E. S.; Dale, T. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 2344.

(9) (a) Ong, S.-E.; Foster, L. J.; Mann, M. *Methods* **2003**, *29*, 124, and references therein. (b) Ong, S.-E.; Mann, M. *Nat. Chem. Biol.* **2005**, *1*, 252, and references therein.

(10) (a) Addicott, C.; Das, N.; Stang, P. J. *Inorg. Chem.* **2004**, *43*, 5335. (b) Yang, H.-B.; Ghosh, K.; Northrop, B. H.; Stang, P. J. *Org. Lett.* **2007**, *9*, 1561. (c) Zheng, Y.-R.; Yang, H.-B.; Northrop, B. H.; Ghosh, K.; Stang, P. J. *Inorg. Chem.* **2008**, *47*, 4706. (d) Northrop, B. H.; Yang, H.-B.; Stang, P. J. *Inorg. Chem.* **2008**, *47*, 11257.

(11) Kuehl, C. J.; Huang, S. D.; Stang, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9634.

(12) Kryschenko, Y. K.; Seidel, S. R.; Arif, A. M.; Stang, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 5193.

(13) We thank a reviewer for pointing out that the exchange ratio should be 1:3:3:1 and not 1:2:2:1, considering the symmetry-number method in ref 14. For the equilibrium $^2/_3$ **6a** + $^1/_3$ **6b** $\leftrightarrows$ **6c**, the symmetry numbers of **6a** and **6b** are both equal to 6 (C_3 and C_2 axis) and that of **6c** is equal to 2 (C_2 axis); the statistical equilibrium constant is thus given by $6^{2/3}6^{1/3}/2 = 3$. Accordingly, if the equilibrium concentrations of **6a** and **6b** are taken as equal to 1, the equilibrium concentration of **6c** would be 3. The same consideration holds for the equilibrium $^1/_3$ **6a** + $^2/_3$ **6b** $\leftrightarrows$ **6d**. Thus, a theoretical distribution of **6a/6c/6d/6b** = 1:3:3:1 is established.

(14) Ercolani, G.; Piguet, C.; Borkovec, M.; Hamacek, J. *J. Phys. Chem. B* **2007**, *111*, 12195.

(15) Vacek, J.; Caskey, D. C.; Horinek, D.; Shoemaker, R. K.; Stang, P. J.; Michl, J. *J. Am. Chem. Soc.* **2008**, *130*, 7629.

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