Supramolecular Chemistry

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Ultramacrocyclization through Reversible Catenation**

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Dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Whereas the cyclization of small (five- or six-membered) rings is a facile and high-yielding process in synthetic chemistry, that of larger rings becomes increasingly difficult with increasing number of ring members (n).[1–3] Macrocyclization with $n \approx 10$–30 is a difficult task, but is often achieved under high-dilution conditions. However, ultramacrocyclization[4] with $n > 100$ has scarcely been described because the entropy cost is too high in bringing the ends of a long acyclic compound together for cyclization to proceed (Figure 1 a). However, if the reaction sites are sufficiently large, the probability of the association of the both ends prior to cyclization should significantly increase and ultramacrocyclization should proceed efficiently. Such an idea prompted us to examine the reversible catenation[5,6] of coordination rings for ultramacrocyclization (Figure 1 b). Palladium(II)-clipped macrocycle **1** has a nanometer-sized framework and easily transforms into its catenated dimer in polar media through π–π aromatic interactions between the two rings.[7] In expectation of ultramacrocyclization through catenation, we designed the long acyclic compound **2**, which comprises Pd^{II}-clipped macrocyclic units at both ends. Accordingly, we found that compound **2** selectively catenates into ultramacrocyclic dimer **3**, which contains over 200 non-hydrogen atoms in its backbone.

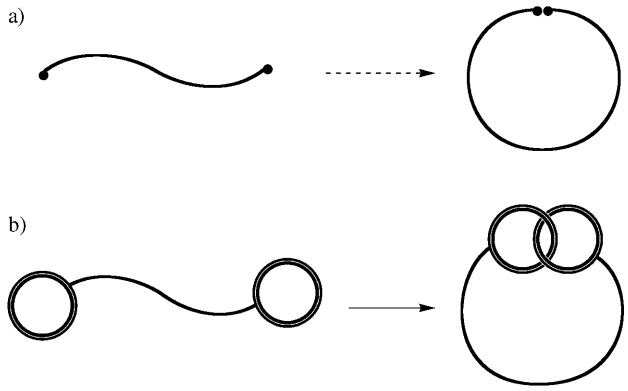

Figure 1. Cartoon representation for macrocyclization through a) the formation of a chemical bond and b) reversible catenation.

Double-loop compound **2a** was obtained by treating ligand **4** with bimetallic linker **5**[8] in dimethyl sulfoxide (DMSO; Scheme 1). Typically, ligand **4** (7.1 mg, 10 μmol) was treated with **5** (4.6 mg, 5.0 μmol) in DMSO (0.50 mL) for a few minutes at ambient temperature. The formation of **2a** as a single product was confirmed by ^{1}H NMR spectroscopy (Figure 2 a) and cold-spray ionization mass spectrometry (CSI-MS[9]).[10] Subsequently, we examined the catenation of **2a** at both loops by adding water to the solution in DMSO.[7] As revealed by ^{1}H NMR spectroscopy (Figure 2 b–g), peaks for the protons of the monomer **2a** decreased with increasing water content. Instead, significantly highfield-shifted aromatic protons appeared around $\delta = 8.20$–6.75 ppm, characteristic of the catenation of the Pd^{II}-clipped rings. CSI-MS clearly indicated that the newly formed product was cyclic dimer **3**, which contains two catenated frameworks. The spectrum from a solution in *N*,*N*-dimethylformamide (DMF) and H_2O (1:2) showed a series of peaks for $[\mathbf{3}-(NO_3)_n + (dmf)_m]^{n+}$: for example, $m/z = 669.7$ corresponds to $[\mathbf{3}-(NO_3)_7 + (dmf)_7]^{7+}$;

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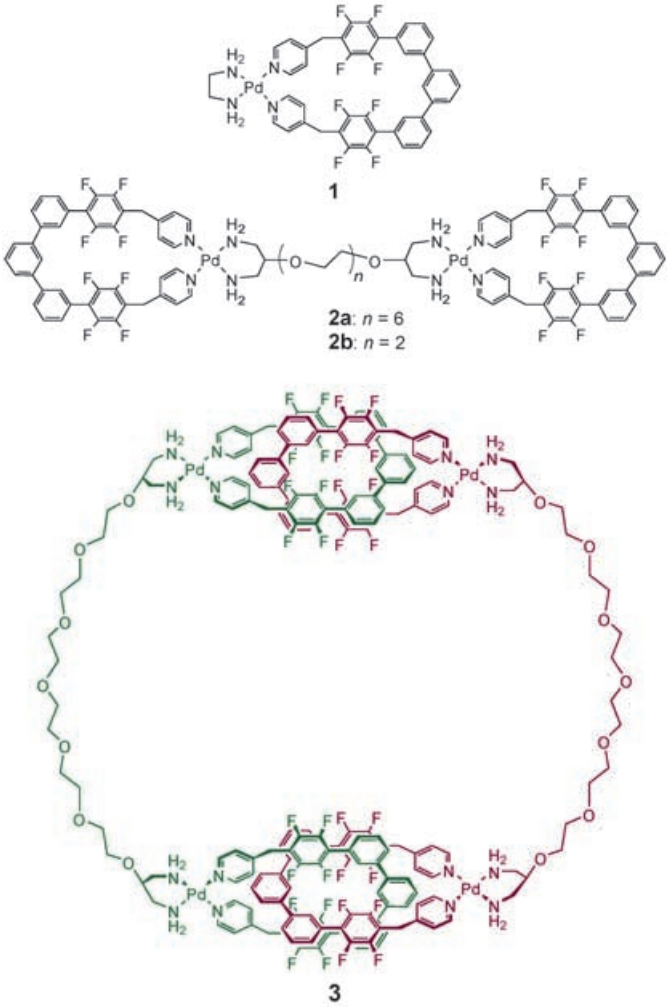


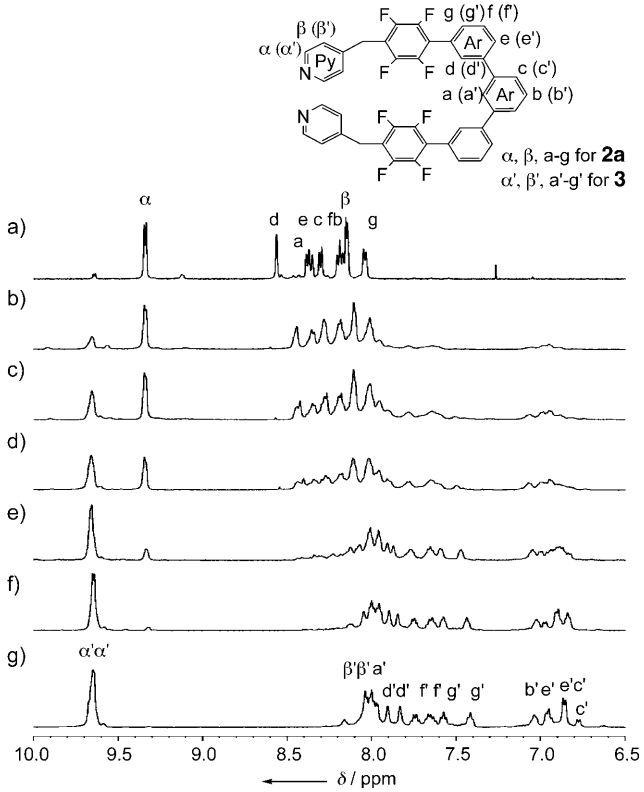
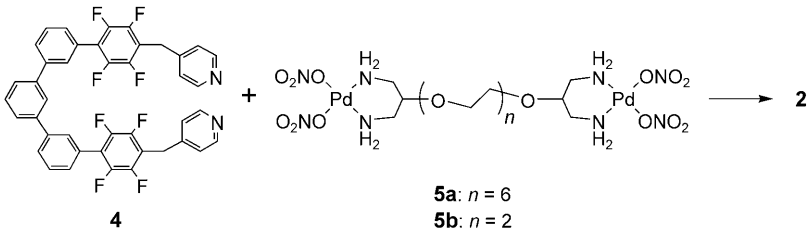


Figure 2. Observation by ^{1}H NMR spectroscopy (aromatic region, 500 MHz, 25 °C) of the ultramacrocyclization of monomer **2a** (5 mM) to dimer **3**. Spectra were obtained by treating the solution of **2a** in DMSO with water at room temperature. Solvent systems: a) [D$_6$]DMSO only, b) [D$_6$]DMSO/D$_2$O (3.5:1), c) [D$_6$]DMSO/D$_2$O (3:1), d) [D$_6$]DMSO/D$_2$O (2.5:1), e) [D$_6$]DMSO/D$_2$O (2:1), f) [D$_6$]DMSO/D$_2$O (1.5:1), and g) [D$_6$]DMSO/D$_2$O (1:1).



Scheme 1. Synthesis of double-loop compounds **2**.

$m/z = 767.5$ corresponds to $[\mathbf{3}-(NO_3)_6+(dmf)_5]^{6+}$; and $m/z = 874.7$ corresponds to $[\mathbf{3}-(NO_3)_5+dmf]^{5+}$ (Figure 3). Whereas the Pd^{II}-clipped ring is achiral, its catenated form is chiral. Therefore, equivalent proton pairs in each Pd^{II}-clipped ring become diastereotopic after catenation and are independently observed (see pairs for $H_{\alpha'}$, $H_{\beta'}$, and $H_{a'}$–$H_{g'}$ in Figure 2g).[11] Probably, **3** is a mixture of two diastereomers because of the chirality of the two catenated moieties, but the diastereomers are not clearly distinguishable.

The solution of catenated species in a mixture of [D$_6$]DMSO/D$_2$O (1:1) was subjected to a DOSY (diffusion-ordered NMR spectroscopy) study[12–14] to confirm the purity of the component (Figure 4). The spectrum clearly showed the appearance of all the signals at the same diffusion coefficient ($\log D = -10.35$) which indicates the selective formation of a single product.[15] It is remarkable that despite the flexible structure of the linker, no other products were formed. Presumably, a cyclic monomer derived from the intramolecular catenation of **2a** is less stable because of the unfavorable orientation of the two Pd^{II}-clip-

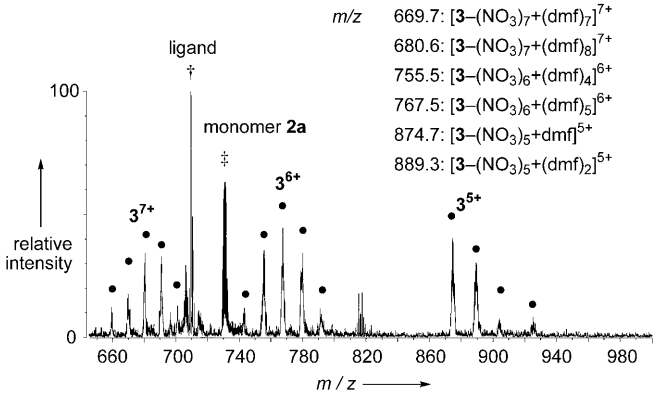


Figure 3. CSI mass spectrum of **3** as a solution in DMF/H$_2$O (1:2).

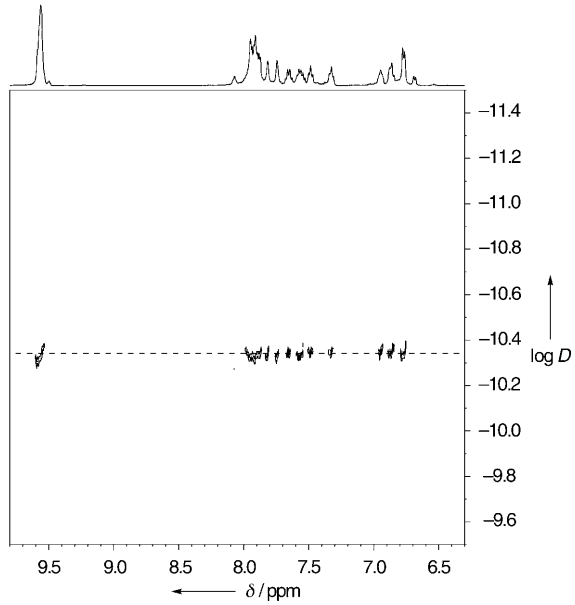


Figure 4. DOSY spectrum of **3** showing the formation of a single product. The spectrum was obtained after treatment of **4** (5 mM) with **5** (5 mM) for 5 minutes at room temperature in $[D_6]DMSO/D_2O$ (1:1).

ped rings, whereas a cyclic trimer or higher oligomers are disfavored because of the higher entropy cost.

CPK modeling showed that an expanded conformation of **3** has an external diameter of approximately 4 nm (Figure 5). The backbone of **3** comprises 238 non-hydrogen atoms ($C_{204}N_{16}O_{14}Pd_4$), and it is one of the largest macrocyclic compounds to be synthesized in reasonable yields and characterized well.

Ultramacrocyclization through double catenation also proceeded smoothly when the length of the oligo(ethylene oxide) chain was limited.[8] The double catenation of **2b** ($n = 2$), which was also quantitatively prepared from **5b** in a polar solvent (Scheme 1), was examined. Upon addition of water, **2b** was efficiently transformed into an ultramacrocyclic dimer as indicated by ^{1}H NMR spectroscopy and CSI-MS studies.[16] Although conformational strain was anticipated to some extent, no other oligomers were detected. From a modeling study, the dimension of the dimer in its extended conformation is estimated to be 3.0 nm.

In the construction of nanoscopic assemblies from extraordinarily large components, close proximity of the reaction centers between the components is entropically unfavorable. As we have demonstrated here, the Pd^{II}-linked coordination ring can be regarded as a nanoscale reaction center. We suggest that the use of such large reaction centers may overcome the entropic disadvantage in nanoscopic molecular manufacturing. Accordingly, we expect that large nanoscopic objects, such as protein molecules or metal nanoparticles, can be easily linked together and aligned through reversible catenation.

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Figure 5. A CPK (Corey–Pauling–Koltun) model for the expanded conformation of molecule **3**. Ar, Py black; O red; N blue; F green; Pd gray; H cream.

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[2] For selected examples of very large covalent macrocycles, see: a) K. S. Lee, G. Wegner, *Makromol. Chem. Rapid Commun.* **1985**, *6*, 203(288-membered ring); b) M. Rothe, M. Lohmüller, U. Breuksch, G. Schmidtberg, *Angew. Chem.* **1994**, *106*, 2047; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1960 (280-membered ring); c) M. Mayor, C. Didschies, *Angew. Chem.* **2003**, *115*, 3284; *Angew. Chem. Int. Ed.* **2003**, *42*, 3176 (304-membered ring).

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[4] a) Large rings with 100 and more ring atoms have been described as "ultralarge rings"[4b] or "ultracycles".[1a] Herein, cyclization with $n > 100$ is termed ultramacrocyclization; b) M. Rothe, M. Lohmüller, U. Breuksch, G. Schmidtberg; *Angew. Chem.* **1994**, *106*, 2047; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1960.

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[8] The dinuclear Pd_2 linker, **5**, was prepared in five steps from commercially available 1,3-diaminopropan-2-ol and isolated as orange microcrystals in 19% overall yield. See Supporting Information for details of the synthesis and physical properties of **5**.
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[10] Compound **2a** was isolated as a white powder upon addition of a large amount of diethyl ether (68% yield). Selected data for **2a**: ^{1}H NMR (500 MHz, [D$_6$]DMSO, TMS): $\delta = 9.34$ (d, $J = 6.0$ Hz, 8H, PyH_α), 8.56 (s, 4H, H_d), 8.38 (d, $J = 8.0$ Hz, 4H, H_e), 8.35 (s, 2H, H_a), 8.30 (d, $J = 8.0$ Hz, 4H, H_c), 8.19 (t, $J = 8.0$ Hz, 4H, H_f), 8.17 (t, $J = 8.0$ Hz, 2H, H_b), 8.15 (d, $J = 6.0$ Hz, 8H, PyH_β), 8.04 (d, $J = 8.0$ Hz, 4H, H_g), 5.42 (br s, 4H, NH), 4.91 (br s, 4H, NH), 4.79 (s, 8H, CH_2), 4.40 (br s, 2H, CH), 4.15–4.03 (m, 24H, OCH_2), 3.14 ppm (br s, 8H, NCH_2); CSI-MS (3:1 DMF/CH_3OH) m/z: 605.6 $[\mathbf{2a}-(NO_3)_4+(dmf)_5]^{4+}$, 705.3 $[\mathbf{2a}-(NO_3)_3]^{3+}$, 1090.4 $[\mathbf{2a}-(NO_3)_2]^{2+}$.
[11] ^{1}H NMR data for **3** (500 MHz, 1:1 [D$_6$]DMSO/D_2O): $\delta = 9.66$ (br s, 16H, PyH_α), 8.05–7.97 (m, 20H, PyH_β, H_a), 7.92 (s, 4H, H_d), 7.85 (s, 4H, H_d), 7.77–7.75 (2t, $J = 8.5$ Hz, 4H, H_f), 7.68 −7.66 (2t, $J = 8.5$ Hz, 4H, H_f), 7.59–7.57 (2d, $J = 8.0$ Hz, 4H, H_g), 7.43–7.41 (2d, $J = 7.0$ Hz, 4H, H_g), 7.05 (br s, 4H, H_b), 6.97 (d, $J = 8.0$ Hz, 4H, H_e), 6.87 (d, $J = 8.0$ Hz, 4H, $H_{c,e}$), 6.79 (d, $J = 8.0$ Hz, 2H, H_c), 4.61 (br s, 4H, CH), 4.52–4.12 (m, 64H, OCH_2, CH_2), 3.39 ppm (br s, 16H, NCH_2). Addition of a large amount of water led to the precipitation of pure **3** in 48% isolated yield (see Supporting Information).
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[15] In the DOSY spectrum, the mixture of **2a** and **3** was clearly resolved. As expected, the diffusion coefficient (D) of **3** is smaller than that of **2a** ($\log D = -10.64$ for **3a** and −10.52 for **2a** in [D$_6$]DMSO/D_2O (2.3:1) mixed solvent).
[16] See Supporting Information for details about the syntheses and physical properties of **2b** and its double-catenated dimer.

