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Synthesis and Supramolecular Association of NCN-Pincer Pd-Complex-bound Norvaline Derivatives toward Fabrication of Controlled Metal Array

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Novel NCN-pincer Pd-complex-bound norvaline derivatives were synthesized. The *N*- and *C*-termini-alkylated Pd–norvalines spontaneously assemble into fibrous aggregates to form supramolecular gels, in which the NCN-pincer Pd complex moieties assemble in a highly oriented manner.

Self-assembly of functionalized amino acids and peptides is currently of interest as a method of fabricating highly ordered arrays of functional components.[1,2] Various amino acids and peptides bearing photo-,[3] electronically,[4] and catalytically[5] active auxiliaries have been synthesized and successfully demonstrated as useful assembly components for supramolecular functional materials consisting of arrayed functionalities. Metalated amino acids and peptides that conjugate to functional organometallics are expected to be useful for this purpose; however, only a few reports on peptides currently exist,[6] and amino-acid-based metal assembly remains largely uninvestigated.[7]

We have found that Pd-complex-bound peptides efficiently self-assemble into fibrous aggregates to afford a supramolecular gel, in which the formation of a well-regulated Pd array was observed.[8] We conjectured that supramolecular gelation of metalated amino acids can also be employed to afford precisely controlled metal arrays. Here we report that the newly synthesized Pd-bound amino acids **1**–**4** (Figure 1a) exhibited an efficient self-assembly ability and afforded a supramolecular gel, in which a highly ordered array of Pd complexes formed. The norvaline derivatives **1**–**4** are covalently conjugated to an NCN-pincer Pd complex, [PdCl(dpb)],[9] at the end of their side chains. The inert C–C covalent linkages to the robust cyclometalated [PdCl(dpb)] complexes were expected to prevent both dissociation and decomplexation of the Pd complexes under acidic, basic, and high-temperature conditions during synthetic transformations.

The Pd-bound norvaline derivative **1** was prepared by a modified procedure based on Taylor's[10] and van Koten's[11] methods. The Suzuki–Miyaura coupling reaction of the 9-BBN adduct of protected L-allylglycine **5** (98% ee) and [PdCl(dpb-Br)] (**6**)[9] gave [PdCl(dpb)]-bound L-norvaline **1** in 72% yield (Scheme 1). Chiral high-performance liquid chromatography (HPLC) analysis confirmed that no loss in optical purity occurred.[12] The absolute configuration around the α-carbon of **1** was unequivocally determined by synchrotron single-crystal X-ray analysis at the BL40XU beam line of SPring-8 (Figure 1b).[13] These results clearly proved the robustness and stability of this norvaline-cyclometalated complex conjugate motif. The bond lengths and angles of the [PdCl(dpb)] moiety of **1** closely resembled those of the parent [PdCl(dpb)] (**7**),[9] which suggests that the NCN–Pd unit retains its original chemical and physical properties after conjugation.

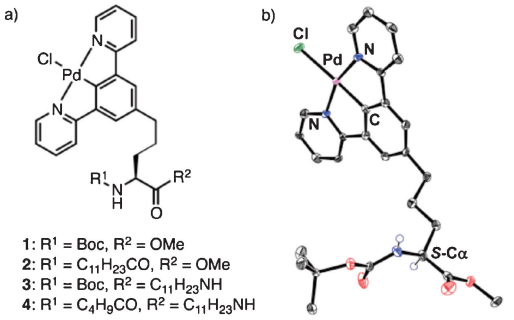
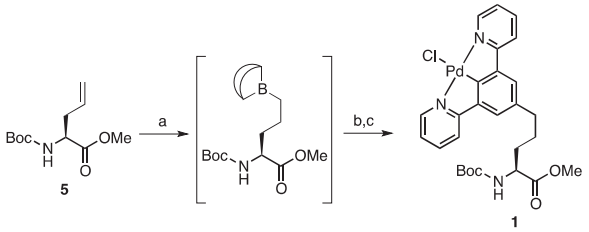
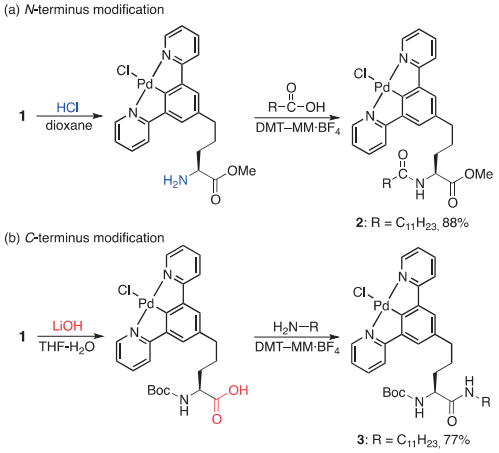


Figure 1. a) NCN-pincer Pd-complex-bound norvaline derivatives. b) X-ray crystal structure of **1**.



Scheme 1. Synthesis of NCN-pincer Pd-complex-bound norvaline **1**. (a) 9-BBN, THF, 0 °C for 5 min then rt for 2 h; (b) [PdCl(dpb-Br)] (**6**), $Pd(OAc)_2$, S-Phos, K_3PO_4, THF–H_2O–DMF, rt, 18 h; (c) KCl, THF–H_2O–DMF, rt, 1 h.

As shown in Scheme 2, various functionalities can be installed at the *N*- and *C*-termini of **1**; *N*-Boc group deprotection was achieved by a conventional HCl–dioxane hydrolysis to produce the corresponding *N*-terminus free form of **1**. Subsequent condensation with dodecanoic acid afforded *N*-(*n*-dodecanoyl)norvaline **2** in 88% yield by using DMT–MM·BF_4 as the condensing reagent.[14,15] The *C*-methyl ester group was transformed into an aliphatic amide by the sequence of LiOH/



Scheme 2. *N*- and *C*-Terminus modification of **1**.

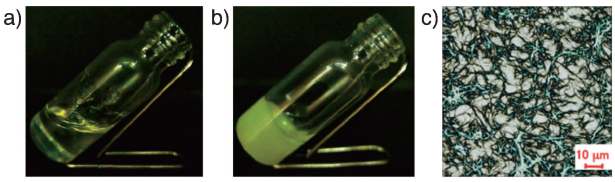


Figure 2. Thermoreversible gelation of **3** in toluene (6.0×10^{-2} M): (a) toluene solution, (b) gel state, and (c) microscopic image of toluene gel (×3000).

THF–H_2O hydrolysis and DMT–MM·BF_4 condensation with an aliphatic amine in one flask: the *C*-alkylamidonorvaline **3** was obtained in 77% yield. The *N*-Boc of **3** can be further transformed to the *n*-pentanoyl group to give double-tail Pd-bound norvaline **4** in 62% yield by the same *N*-terminus modification procedure (Scheme 2a). ^{1}H NMR analysis of the reaction mixture revealed that the [PdCl(dpb)] unit remained unaffected during these *N*- and *C*-terminus transformations.

The alkylated Pd-complex-bound norvalines **3** and **4** in various aromatic organic liquids self-assembled to form stable supramolecular gels.[16] For example, when a hot solution of **3** in toluene was cooled to room temperature, the solution spontaneously lost its fluidity to afford a yellow opaque gel (Figures 2a and 2b). The gel exhibited reversible sol–gel transitions in repetitive heat–cool cycles, indicating that self-assembly through noncovalent interaction is the underlying driving force to gelation.

The entangled fibril network morphology of supramolecular gel **3** was observed by high-performance digital microscopy in the toluene-wet state (Figure 2c). Scanning electron microscopy (SEM) observation of a Pt-coated xerogel of **3** also showed similar fibrous aggregates.[17] To investigate the self-assembled structure of **3** in the gel state, IR and synchrotron X-ray diffraction analyses were conducted. The N–H stretching vibration of a swelling gel of **3** (120 mM) showed a low-frequency shift from 3437 to 3326 cm^{-1} in a toluene solution (15 mM). Two C=O stretching bands also shifted from 1712 and 1674 cm^{-1} in the toluene solution to 1682 and 1650 cm^{-1}, respectively, in the toluene gel. These results strongly support the formation of intermolecular antiparallel amide–amide hydrogen bonds in the gel state. The wide-angle X-ray (WAX) pattern

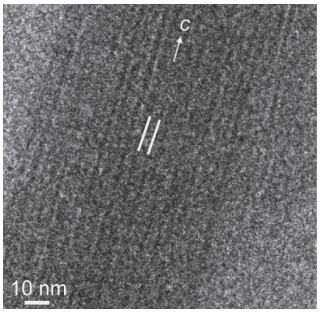


Figure 3. Cryo-TEM images of gel fibril of **3** obtained from toluene gel (6.0×10^{-2} M).

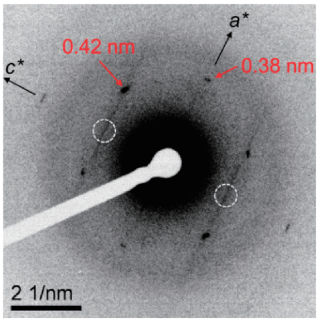


Figure 4. Selected area electron diffraction of the gel fibril.

of a xerogel of **3** prepared by evacuating a 100 mM toluene gel of **3** showed two broad peaks at $2\theta = 13.6$ and 16.6° (*d* spacing 0.42 and 0.35 nm),[18] which represent the distances of hydrogen bonding in the β-sheet and aromatic π–π stacking between the [PdCl(dpb)] moieties, respectively. Indeed, the π–π stacking association of [PdCl(dpb)] moieties was definitely observed in the single-crystal X-ray structure and ^{1}H NMR dilution experiment.[19] Two peaks in the small-angle X-ray scattering (SAXS) pattern at $2\theta = 3.04$ and 1.50° (*d* spacing 1.88 and 3.81 nm, respectively)[18] demonstrated the existence of a periodically layered structure. The layered structure was directly confirmed by cryo-transmission electron microscopy (TEM) observations, which revealed finely striped nanostructure (Figure 3). Selected area electron diffraction showed streaky lines due to the layered structure and diffraction spots corresponding to 0.38 and 0.42 nm, which agree well with the hydrogen bonding and π–π stacking distances obtained from WAX analysis (Figure 4). Unfortunately, higher-order (*hkl*) diffraction could not be obtained; however, the rectangular-like lattice with no (001) diffraction (dashed circles) strongly supported the twofold screw axis symmetry arising from the antiparallel β-sheet self-assembly[20] determined by IR analysis.

Figure 5 illustrates a proposed gelation mechanism. It is reasonable to assume that, as a first step, hydrogen bonding between the amide groups of the norvaline derivatives induces self-assembly, which forms β-sheet-type aggregates. The importance of hydrogen bonding was confirmed in a gelation test of *C*-methyl ester norvaline **2**, which showed no gelation properties because it lacked the *C*-amide group. Importantly, the NCN–Pd units were also assembled along the highly organized β-sheet scaffold because of their π–π stacking interactions. The resulting fibrous self-assembly elongates to form macroscopic

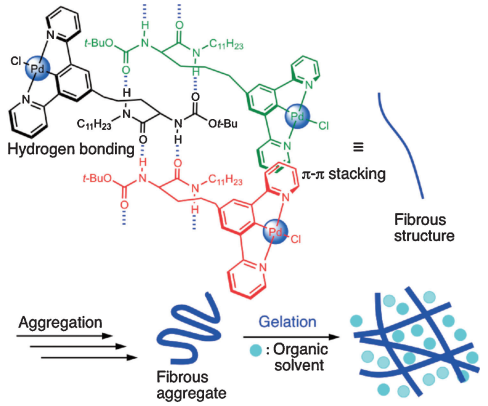


Figure 5. Proposed mechanism of gelation of **3**.

fibril objects as the layered structure grows. Interfiber cross-linking or branching proceeds, forming entangled fibrous networks that become a gel by entrapping solvent molecules in the network.

In conclusion, we successfully prepared chemically and physically stable Pd-complex-bound amino acid derivatives. Hydrogen-bonding-based self-assembly of the metalated amino acids and cooperatively formed π–π stacking of [PdCl(dpb)] moiety enabled us to fabricate well-regulated Pd arrays along with a β-sheet-type supramolecular formation.[19] Metal aggregation based on a supramolecular gel template will provide an efficient methodology for producing functional organometallic materials.

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12 For HPLC data, see SI, Figure S1.[21]

13 For X-ray structural data for **1**, **6**, and **7**, see the SI.[21]

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16 The gelation conditions are summarized in Table S1 in the SI.[21]

17 For an SEM image, see SI, Figure S2.[21]

18 For WAX and SAXS spectra, see SI, Figures S10 and S11.[21]

19 For crystal packing of **1**, see SI, Figures S3 and S4. For NMR data, see SI, Figures S5–S9.[21]

20 For the proposed supramolecular structure resolved by cryo-TEM diffraction, see SI, Figure S12.[21]

21 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

