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1D Nickel Coordination Polymers with an Unnatural Amino Acid Prepared by *in situ* Double Michael Addition of Ethylenediamine to (*E*,*E*)-Muconic Acid

Junghwan Do,[†,*] Jaeun Kang,[†] Yeonsun Jung,[†] Yong Sun Park,[†] and Allan J. Jacobson[‡,*]

[†]*Department of Chemistry, Konkuk University, Seoul 143-701, Republic of Korea.*
**E-mail: junghwan@konkuk.ac.kr*
[‡]*Department of Chemistry and Texas Center for Superconductivity, University of Houston, Houston, TX, 77204-5003, USA. *E-mail: ajjacob@uh.edu*

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In general, the topology of coordination polymers can be designed by controlling the size, shape, and charge of the combination of various organic linkers and/or inorganic metal connectors. Amino acids are well-known organic linkers for readily forming coordination polymers with metal connectors.[1–4] The naturally occurring amino acids acting as metal connectors, however, are limited in number. Among the known 20 proteinogenic amino acids, only aspartic acid and glutamic acid comprise dicarboxylic groups that are needed for constructing rigid polymeric metal–amino acid structures.[5–9] Thus, the synthesis of new amino acids including dicarboxylic groups is of great importance in constructing new polymeric structures. In general, for the synthesis of amino acids, the Michael addition or Mannich reaction typically has been used to form C─N bonds by simple addition of amines to C=C double bonds.[10–13]

We have recently demonstrated a one-step crystal engineering strategy for the formation of several "unnatural", tailor-made α-amino acid–metal complexes containing racemic mixtures of the chiral ligands, piperazinyl succinic acid, *N*-benzyl aspartic acid, *N*-aminoethyl aspartic acid, and *N*-aminopropyl aspartic acid which are formed under mild hydrothermal conditions *in situ* by Michael addition of piperazine, benzylamine, ethylenediamine, and 1,3-diaminopropane to fumaric acid, respectively.[14–16] This type of Michael reaction, *i.e.*, the direct amination of α,β-unsaturated dicarboxylic acid is rarely reported, although the direct amination of α,β-unsaturated monocarboxylic acid can readily be effected, and several synthetic methods for amination of α,β-unsaturated dicarboxylic acid derivatives, such as mono- or diester and monoamide, are well known.[17]

In general, the Michael reaction, that is the regioselective 1,4-addition of nucleophiles to activated olefins, is one of the versatile methods used for C─C, C─N bond formation, and has found wide application in organic synthesis.[18,19] However, few examples are currently known for the two consecutive Michael reactions of the derivatives of muconic acid, a dicarboxylic acid containing a conjugated di-ene group. Only one example was reported in detail of the 1,4-addition of muconaldehyde with two thiols to afford bis-Michael adducts.[20]

We herein expand the scope of this one-step crystal engineering strategy by introducing (*E*,*E*)-muconic acid, a dicarboxylic acid containing a conjugated di-ene group. The Lewis acidic properties of nickel cation promotes the Michael reactions of the nickel complex of (*E*,*E*)-muconic acid with amines. Surprisingly, this has resulted in isolation of a new 1D coordination polymer, Ni(piperazine-2,3-diacetate)$(H_2O)_2$, which is the first example formed *in situ* by double Michael reactions of (*E*,*E*)-muconic acid with ethylenediamine to afford tailor-made β-amino acid, piperazine-2,3-diacetic acid. The heterocyclic product in Ni(piperazine-2,3-diacetate)$(H_2O)_2$ is formed by the Michael addition reaction of an amine group of ethylenediamine followed by intramolecular Michael reaction with the other amine group.

In addition, demetallation of the resulting functionalized piperazine to the corresponding amino acid can be achieved by acidic hydrolysis. The nickel complex has been demetallated in boiling HCl to yield a single diastereomer of 2,3-piperazinediacetic acid and following esterification of the diacetic acid afforded dimethyl 2,3-piperazinediacetate.

The hydrothermal reaction of nickel chloride hexahydrate, (*E*,*E*)-muconic acid, and ethylenediamine in H_2O at 160 °C produced blue polyhedral crystals of Ni(piperazine-2,3-diacetate)$(H_2O)_2$ **1**. The structure of **1** was determined by single crystal X-ray diffraction. Elemental analysis and a comparison of the X-ray powder pattern with one simulated from the single crystal data (Figure S1, Supporting information) confirm the homogeneity and purity of the bulk product.

The product crystallizes in the monoclinic space group *C2/c* with four formula units per unit cell. Crystallographic data for **1** are summarized in Table 1. The piperazine-2,3-diacetate anion positioned on two-fold rotational axis symmetry is a diastereomer containing two chiral carbon atoms, C4. Two carbon atoms, C2 and C3 bonded to the chiral carbon atoms (C4) are disordered over two positions with ~⅔ and ⅓ occupancy ratios, respectively. Therefore, C2 and C3 have four possible configurations, (2*R*, 3*S*), (2*S*, 3*R*), (2*R*, 3*R*), and (2*S*, 3*S*); however, considering unequal number of occupancy factors of C2 and C3, the ordered piperazine-2,3-diacetate anion should be either C2–C4–C4'–C2' (2*R*, 3*R*) or C3–C4–C4'–C3' (2*S*, 3*S*), a *trans* configuration, not C2–C4–C4'–C3'(2*R*, 3*S*) or (2*S*, 3*R*), a *cis* configuration. Lower-symmetric space groups, *C*2 and *Cc* of *C*2/*c* were checked, but the disordering behavior of the piperazine-2,3-diacetate anion was not resolved.

One crystallographically distinct nickel atom located on the center of inversion (¼, ¼, ¼) is coordinated by two nitrogen atoms and two oxygen atoms from two piperazine-2,3-diacetate anions in square planar coordination with the Ni—O and Ni—N distances of 2.030(2) and 2.114(2) Å, respectively. Two additional water molecules in a *trans* configuration complete a distorted octahedron with the distance of 2.125(2) Å, Figure 1. The $NiO_2N_2(H_2O)_2$ octahedron is slightly distorted from regular 90° angles (87.69 (7)–92.31(7)°). In the piperazine-2,3-diacetate anion, two nitrogen and two oxygen atoms (O1) are coordinated to nickel atoms, and two remaining oxygen atoms (O2) in carboxylate groups are terminal. The one unique piperazine-2,3-diacetate acting as tetradentate ligand, bridges two nickel atoms forming infinite zigzag neutral chains, Ni(piperazine-2,3-diacetate)$(H_2O)_2$ along the [101] direction (Figure 2).

Table 1. Crystallographic details for **1**.

Formula	$C_8H_{16}N_2NiO_6$
Formula weight	294.94
T (K)	296 (2)
Crystal size (mm)	0.22 × 0.18 × 0.16
Crystal system	Monoclinic
Space group	*C*2/c
a (Å)	15.141 (3)
b (Å)	7.3287 (15)
c (Å)	10.769 (2)
β (°)	116.41 (3)
V (Å^3)	1070.2 (4)
Z	4
Calculated density (g/cm^3)	1.830
Absorption coefficient (mm^{-1})	1.834
F(000)	616
Independent reflections	969
GOF on F^2	0.971
R indices [I > 2σ(I)]	R_1 = 0.0276, wR_2 = 0.0687
R indices (all data)	R_1 = 0.0422, wR_2 = 0.0722
(Δρ) max:min (e/Å^3)	0.366, −0.173

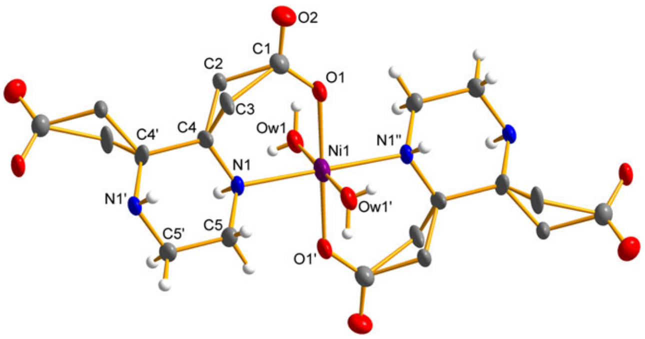

Figure 1. Displacement ellipsoids of the local structure **1** drawn at 50% probability level. Nickel, carbon, oxygen, and nitrogen atoms are purple, gray, red, and blue ellipses, respectively. Hydrogen atoms are represented by white spheres.

The Ni(*rac*-piperazine-2,3-diacetate)$(H_2O)_2$ chains are further stabilized by the presence of hydrogen bonds between the coordinated water molecules and the carboxylate oxygen atoms in a complex arrangement, with the distance of d(Ow1•••O2) = 2.790(3), 3.035(3) Å and d(Ow1•••O1) = 2.879(2), 2.997(3), and 3.030(3) Å within <3.5 Å, which result in the formation of a framework, Figure 3.

The FT-IR spectra exhibits the characteristic absorption bands of the carboxylic unit in the piperazine-2,3-diacetate ligand: 1671 m, 1572s, (ν_{as} CO_2), 1458 m, 1408s, (ν_s CO_2), and 913w, 849w cm^{-1} (δ CO_2). The peak near 3404 s(br) cm^{-1} confirms the presence of H_2O groups. The peaks at 3191 m–2889 w, and 1330 w–956 w cm^{-1} are attributed from the C—N, C—C, O—H, N—H and C—H vibration frequencies (Figure S2).

Compound **1** remains stable upon heating in N_2 up to ~200 °C. On further heating, a weight loss of 12.63% occurs below 300 °C, which corresponds to the loss of two water molecules (calcd 12.21%). Above 300 °C, the material starts decomposing in several steps up to ~500 °C attributable to the loss of piperazine-2,3-diacetate molecules. Assuming that the residue at 800 °C corresponds to NiO, the overall observed weight loss (75.99%) is in good agreement with the calculated value (74.68%) for formation of NiO (Figure 4). The final products after heat treatment were confirmed by powder X-ray diffraction to be NiO (Figure S3).

In conclusion, the racemic piperazine-2,3-diacetate ligand is formed under mild hydrothermal conditions *in situ*

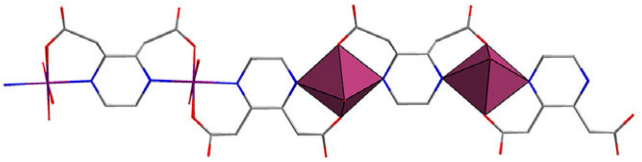

Figure 2. View of the chain in **1**. Purple circles and polyhedral represent Ni atoms, and the other labeling scheme is the same as that in Figure 1.

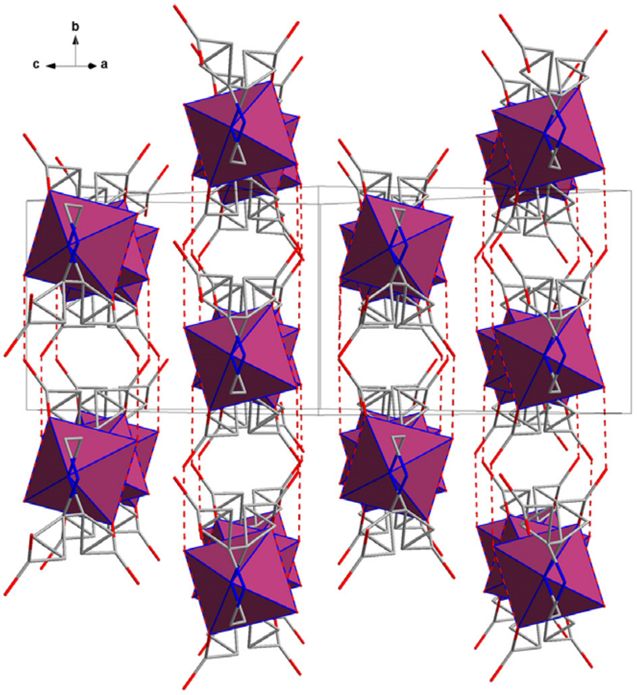

Figure 3. Layer formation of **1** by strong hydrogen bonding within <2.9 Å (dotted red lines) between the chains viewed parallel to [101]. Labeling scheme is the same as that in Figure 2.

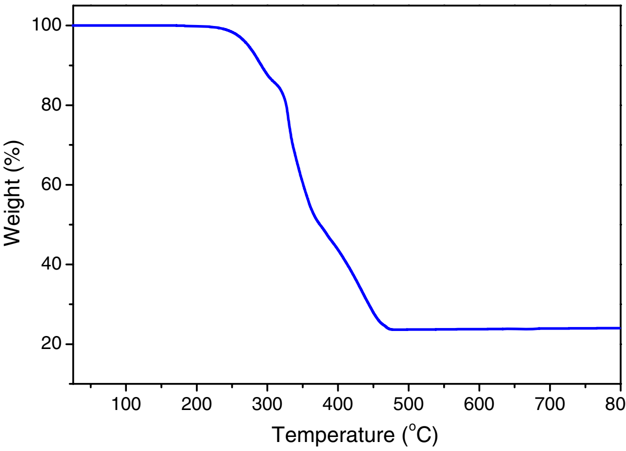

Figure 4. TGA curve of **1**.

by double Michael additions of ethylenediamine to (*E*,*E*)-muconic acid. Previously, we have reported several metal complexes of which the ligands were obtained from the Michael addition of amines to fumaric acid (mono-ene) that possess divalent anions or monovalent anion forming sometimes a zwitterion depending on the amine species and coordination behavior of the terminal nitrogen atoms.[15,16] The successful synthesis of **1** utilizing the direct amination of α,β-unsaturated dicarboxylic acid is not only limited to a mono-ene but also can be extended to di-enes such as a (*E*,*E*)-muconic acid. The charge versatility and coordination behavior of nonproteinogenic amino acids prepared by Michael addition of amine to dicarboxylic acid group containing di-enes as well as mono-enes warrants more systematic investigation. Moreover, successful releasing *trans*-2,3-piperazinediacetic acid from the nickel complex **1** by acidic hydrolysis may suggest an effective approach to synthesize new nonproteinogenic amino acids that detours complicated organic reaction procedures.

Experimental

All chemicals were of reagent grade and used as received from commercial sources without further purification. Powder X-ray diffraction analyses were performed using a Rigaku Ultima IV diffractometer (Cu Kα radiation) (Rigaku, Tokyo, Japan). Thermal analyses were carried out in N_2 at a heating rate of 5 °C/min, using a high-resolution Perkin-Elmer TGA7 Thermal Analyzer (Waltham, MA, USA). Infrared spectra were recorded on a Nicolet 6700 FT-IR spectrometer (Waltham, MA, USA) within a range of 400–4000 cm^{-1} using the KBr pellet method. Galbraith Laboratories, Inc., (Tennessee, USA) performed the element analyses. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopic data were recorded with a Bruker (400 MHz for ^{1}H NMR, 100.6 MHz for ^{13}C NMR) spectrometer (Billerica, MA, USA). Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (δ = 7.26 ppm for ^{1}H NMR, δ = 77.07 ppm for ^{13}C NMR). Multiplicities are reported as s (singlet), d (doublet), t (triplet), q(quartet), and br. (broad signal). Coupling constants (*J*) are reported in Hz. HRMS spectra were recorded with a JEOL JMS-700 (Akishima, Tokyo, Japan) by using the FAB method.

Synthesis of Ni(Piperazine-2,3-Diacetate)(H_2O)$_2$ (1). The product was synthesized from a mixture of nickel chloride hexahydrate (0.071 g, 0.3 mmol), (*E*,*E*)-muconic acid (0.132 g, 0.9 mmol), ethylenediamine (0.02 mL, 0.9 mmol), and distilled water (1.0 mL), which was sealed in a Pyrex tube and heated to 160 °C for 64 h, followed by cooling to room temperature at 20 °C/h. The solution pH values before and after the reaction were ~5 and ~6, respectively. The product was filtered, and blue polyhedral crystals with unidentified yellow powder were found. The yield of the product was ~40%, based on nickel. The product is stable in air and water, and is insoluble in common solvents such as ethanol, DMF, acetone, and THF. EDS analysis confirmed the presence of Ni. The element analyses gave the following results: obsd. (wt %) (C, 32.73; N, 9.68; H, 5.61), calcd (wt %) (C, 32.60; N, 9.50; H, 5.43). IR (KBr): 3404 s(br), 3191 m, 2960 w, 2889 w, 1671 m, 1572 s, 1458 m, 1408 s, 1330 w, 1293 w, 1169 m, 1137 w, 1116 w, 1056 w, 998 w, 956 w, 913 w, 849 w, 795 m, 757 m, 689 m, 629 w, 513 w cm^{-1}. A comparative synthesis without nickel chloride was performed to check the effect of metal salt on the occurrence of the Michael reaction, and the residual solution does not contain the piperazine-2,3-diacetate ligand as proved by NMR.

X-Ray Crystallography. Single-crystal X-ray analysis was performed on a Siemens SMART platform diffractometer outfitted with an Apex II area detector and monochromatized graphite Mo Kα radiation. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares using SHELXTL.[21] The hydrogen atoms in the water molecule were located in difference Fourier maps. Other hydrogen atoms in the piperazine-2,3-diacetate ligand except for the C4 carbon atom connected to disordered carbon atoms (C2, C3) were generated geometrically and allowed to ride on their respective parent atoms. All non-hydrogen atoms were refined anisotropically. Crystallographic data for the structures reported here has been deposited with CCDC (Deposition No. CCDC-1516055 for **1**). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, E-mail: deposit@ccdc.cam.ac.uk.

Isolation of the Ligand, Dimethyl 2,3-Piperazinediacetate by Demetallation of Ni(Piperazine-2,3-Diacetate)(H_2O)$_2$ (1). A solution of complex **1** (100 mg) in 2.0 M-HCl aqueous solution (10 mL) was heated at 80 °C for 1 h and then water was removed under reduced pressure. The residue was dissolved in 10 mL of methanol and treated with 3 mL of acetyl chloride at 0 °C. The mixture was stirred at room temperature for 1 h and then poured into a saturated $NaHCO_3$ solution. After the aqueous layer was thoroughly extracted with methylene chloride, the extracts were dried over anhydrous sodium sulfate, filtered, evaporated to give 29 mg of product as pale yellow oil in 38% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 3.70 (s, 6H, OCH_3), 3.55–3.40 (m, 2H, NCH), 3.02–2.87 (m, 4H, NHCH_2), 2.67–2.56 (m, 2H, CH_2CO$_2$), 2.44–2.39 (m, 2H, CH_2CO$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.1 (CO_2), 56.1 (NCH), 51.9 (OCH$_3$), 45.8 (NCH$_2$), 36.9 (CH_2CO_2); HRMS: calcd. For $C_{10}H_{19}N_2O_4$ [M$^+$ + 1] 231.1345; found 231.1351.

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Supporting Information. Experimental powder X-ray data and simulated powder X-ray patterns of **1** (Figure S1), FT-IR (Figure S2), Powder X-ray data after TGA and simulated powder X-ray patterns of NiO (Figure S3), ^{1}H NMR and ^{13}C NMR of dimethyl 2,3-piperazinediacetate (Figures S4 and S5), and HRMS of dimethyl 2,3-piperazinediacetate information (Figure S6).

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