Two-Step Chiral Transfer from D-Penicillamine to Metallosupramolecular Ionic Crystals

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Two-Step Chiral Transfer from D-Penicillamine to Metallosupramolecular Ionic Crystals

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Treatment of a racemic $Rh^{III}_4Zn^{II}_4$ complex, $(\Delta)_4/(\Lambda)_4$-$[Zn_4O\{Rh(aet)_3\}_4]^{6+}$ (aet = 2-aminoethanethiolate), with D-penicillaminate (D-pen) gave optically pure ionic crystals composed of $(\Lambda)_4$-$[Zn_4O\{Rh(aet)_3\}_4]^{6+}$ and Λ_D-$[Rh(D\text{-}pen)_3]^{3-}$ via intramolecular and intermolecular chiral transfers from D-pen.

The development of synthetic methodologies to prepare optically active coordination compounds, as well as optically active organic compounds, has attracted considerable attention in chemistry and materials science.[1-3] This class of compounds is of interest due to their promising chemical and industrial applications, such as asymmetric catalysts, chiral recognition, non-linear optics, and ferroelectric materials.[4-7] In addition to serendipitous spontaneous resolution and asymmetric autocatalysis,[8,9] two main approaches have been employed to prepare optically active coordination compounds: (1) the combination of enantiopure organic ligands and metal ions[2,10,11] and (2) the optical resolution of a racemic compound with chiral metal complexes.[2,12,13] In the former approach, intramolecular chiral transfer from the ligand to metal occurs to produce central and/or helical chiralities because of the direct coordination of the enantio-pure ligand(s) to a metal center.[14] On the other hand, the latter method is based on intermolecular chiral transfer from an optically active host or counterpart molecules/ions to a target compound.[13] While many optically active coordination compounds have been prepared via one of these two methods, these approaches are not universal and, in some cases, are not applicable for the preparation of optically pure compounds.[15] Herein, we report a unique example that involves both intramolecular and intermolecular chiral transfer events to create an optically pure coordination compound. In this system, a racemic

compound of an S-bridged $Rh^{III}_4Zn^{II}_4$ octanuclear complex, $(\Delta)_4/(\Lambda)_4$-$[Zn_4O\{Rh(aet)_3\}_4](NO_3)_6$ ($[\mathbf{1}](NO_3)_6$; aet = 2-aminoethanethiolate),[16,17] was simply treated with a thiol-containing amino acid, D-penicillamine (D-H_2pen), which led to the production of optically pure crystals (Scheme 1). This compound is a double-salt containing $[\mathbf{1}]^{6+}$, fac-$[Rh(D\text{-}pen)_3]^{3-}$ ($[\mathbf{2}]^{3-}$), and NO_3^-, rather than a simple salt containing $[\mathbf{1}]^{6+}$ and D-pen^{2-}. Remarkably, the Λ chiral configuration was selected not only for $[\mathbf{2}]^{3-}$ due to the intramolecular transfer of D-pen chirality but also for the fac-$[Rh(aet)_3]$ units of $[\mathbf{1}]^{6+}$ due to the intermolecular transfer of the resulting Λ_D-$[\mathbf{2}]^{3-}$ chirality. To the best of our knowledge, this is the first example of the
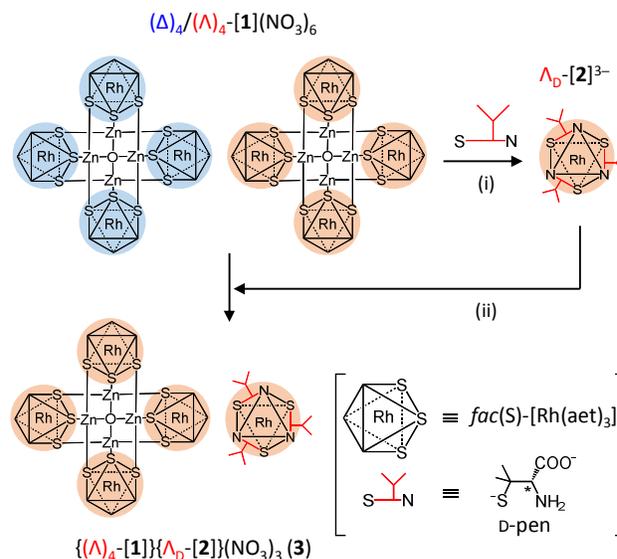
Scheme 1. Simultaneous crystallization of two optically active metal complexes, $(\Lambda)_4$-$[Zn_4O\{Rh(aet)_3\}_4]^{6+}$ ($(\Lambda)_4$-$[\mathbf{1}]^{6+}$) and Λ_D-$[Rh(D\text{-}pen)_3]^{3-}$ (Λ_D-$[\mathbf{2}]^{3-}$), from a racemic metal complex ($(\Delta)_4/(\Lambda)_4$-$[\mathbf{1}]^{6+}$) and D-pen via (i) intramolecular transfer of D-pen chirality to a Rh^{III} center and (ii) intermolecular transfer of Λ_D-$[\mathbf{2}]^{3-}$ chirality to $[\mathbf{1}]^{6+}$.

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simultaneous crystallization of the same configurational cationic and anionic complexes as an optically pure double salt via a two-step chiral transfer.

The initial treatment of racemic [**1**](NO₃)₆ with a large amount of D-H₂pen, neutralized by NaOH, in water at room temperature resulted in the recrystallization of parental [**1**](NO₃)₆. Upon refluxing the mixture for a few hours, a yellow crystalline solid (**3**) was precipitated in a moderate yield.[18]† X-ray fluorescence spectroscopy indicated that **3** contains Rh and Zn as the metal components. The ¹H NMR spectrum of **3** in D₂O displayed two methyl singlets (δ 1.50, 1.21 ppm) and one methine doublet (δ 3.02 ppm) due to the D-pen ligands, along with three broad multiplets (δ 3.30, 2.78, and 2.59 ppm) due to the aet ligands (Figure S1).† The large chemical shifts of the D-pen signals, compared with the corresponding signals for free D-pen, are suggestive of D-pen coordination to a metal center in **3**. The presence of nitrate ions in **3**, as well as fully deprotonated D-pen ligands, was indicate by the IR spectrum that shows intense bands due to N–O and C–O stretching vibrations at 1384 cm⁻¹ and 1584 cm⁻¹, respectively (Figure S2).†[19] Thus, **3** is assumed to be a nitrate salt of a RhZn coordination compound with aet and D-pen ligands, rather than a simple salt of [**1**](D-pen)₃.

The molecular structure of **3** was determined by single-crystal X-ray analysis,† which revealed the presence of one-third of an octanuclear Rh$^{III}_4$Zn$^{II}_4$ complex cation ([**1**]⁶⁺), one-third of a mononuclear Rh^{III} complex anion ([**2**]³⁻), and a NO₃⁻ anion in the asymmetric unit, along with several crystallized water molecules. As shown in Figure 1a, the entire complex cation of [**1**]⁶⁺ has a T symmetrical Rh$^{III}_4$Zn$^{II}_4$ octanuclear structure in [Zn₄O{Rh(aet)₃}₄]⁶⁺, in which a tetrahedral [Zn₄O]⁶⁺ core is covered by four octahedral *fac*-[Rh(aet)₃] units through sulfur bridges. The overall molecular structure of [**1**]⁶⁺ is essentially the same as that in parental [**1**](NO₃)₆.[16] On the other hand, the entire complex anion of [**2**]³⁻ has a mononuclear structure of *fac*-[Rh(D-pen)₃]³⁻, in which a Rh^{III} center is coordinated by three D-pen ligands (av Rh–N = 2.048(13) Å, av Rh–S = 2.312(6) Å) in an octahedral geometry with a *facial* configuration (Figure 1b). Each D-pen ligand in [**2**]³⁻ adopts a bidentate-N,S chelating mode, in which the non-coordinating carboxylate group points in an equatorial orientation. Notably, this is the first preparation and structural characterization of [**2**]³⁻; attempts to prepare [**2**]³⁻ by the reaction of RhCl₃ or *fac*-[Rh(aet)₃] with D-pen were unsuccessful, resulting in the formation of various unidentified species. We assume that the binding of the *fac*-[Rh(aet)₃] units to the [Zn₄O]⁶⁺ core prevents undesirable subsequent reactions after the partial replacement of aet by D-pen in [**1**]⁶⁺. As evidenced by the $R3$ chiral space group and the Flack parameter, crystal **3** contains only the (Λ)₄ enantiomer of [**1**]⁶⁺ and the Λ_D diastereomer of [**2**]³⁻ to afford a homochiral crystal of (Λ)₄Λ_D-[**1**][**2**](NO₃)₃, despite the use of the racemic (Δ)₄/(Λ)₄ isomer of [**1**](NO₃)₆ as the starting complex. In **3**, each Λ_D-[**2**]³⁻ anion is tightly connected to three Λ-*fac*-[Rh(aet)₃] units belonging to three different (Λ)₄-[**1**]⁶⁺ cations through N-H···O-C hydrogen bonds (av. N···O = 2.89 Å).[20] This arrangement leads to the construction of a 2D honeycomb-like sheet structure with a three-fold axis, accommodating three nitrate
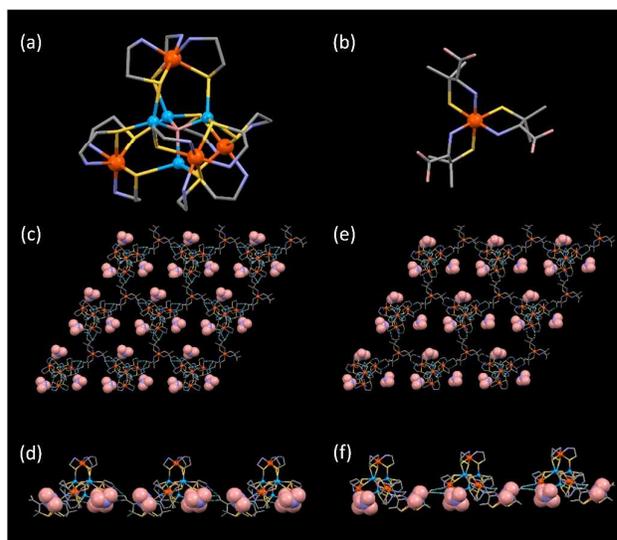

Figure 1. Perspective views of the molecular structures of (a) (Λ)₄-[Zn₄O{Rh(aet)₃}₄]⁶⁺ ((Λ)₄-[**1**]⁶⁺) and (b) Λ_D-[Rh(D-pen)₃]³⁻ (Λ_D-[**2**]³⁻); (c) top and (d) side views of the 2D structure in **3**; (e) top and (f) side views of the 2D structure in **4**. Only one of the disordered part is illustrated in **3**. Hydrogen atoms are omitted for clarity. Color codes: Rh, orange; Zn, blue; S, yellow; O, pink; N, blue; C, gray.

ions in each honeycomb through N-H···O-N hydrogen bonds (N···O = 3.05 Å) (Figures 1c, 1d, S3).† The honeycomb sheets are stacked in a head-to-tail manner through weak N–H···S hydrogen bonds (av. N···S = 3.20 Å), completing a 3D porous metallosupramolecular structure (Figures S4, S5).†

The powder X-ray diffraction (PXRD) pattern of the bulk sample of **3** agreed well with the simulated pattern calculated based on the single-crystal X-ray analysis (Figure S6),† indicative of phase purity and the stability of **3** in air. The optical purity of the bulk sample of **3** was checked by column chromatography. Upon pouring an aqueous solution of **3** onto a cation-exchange column (SP-Sephadex C-25, Na⁺ form), a yellow band containing an anionic species ([**2**]³⁻) was eluted with water, while a yellow band containing a cationic species ([**1**]⁶⁺) was adsorbed on the top of the column. The cationic species was then eluted with a 0.8 M aqueous solution of NaCl. The UV-vis absorption and circular dichroism (CD) spectra of the cationic species are identical to those of (Λ)₄-[**1**]⁶⁺ (Figure S7),† showing two characteristic d-d bands and two positive CD bands in the 300 − 450 nm region. Furthermore, the $\Delta\varepsilon$ value of the main CD band at 375 nm of this species is the same as the reported value for (Λ)₄-[**1**]⁶⁺.†[16] These results imply that the cationic species contains only the (Λ)₄ isomer of [**1**]⁶⁺. The anionic species shows absorption and CD spectral features that are similar to those of the cationic species in the 250 nm - 450 nm region (Figure S7).†,‡ In the ¹H NMR spectrum, this species displays only a single set of signals due to D-pen (Figure S8).† These spectral features imply that the anionic species contains only the Λ_D isomer of [**2**]³⁻.

The reaction solution after the removal of the crystals of **3** was also analyzed by column chromatography, followed by absorption, CD, and ¹H NMR spectral measurements. As a

result, the filtrate was found to contain both the $(\Delta)_4$ and $(\Lambda)_4$ isomers of $[\mathbf{1}]^{6+}$ with an ee value of ~76% for $(\Delta)_4$ (Figure S9).† On the other hand, the presence of $[\mathbf{2}]^{3-}$ in the filtrate was scarcely detected by column chromatography. We estimated that this reaction system contains Δ-[Rh(aet)$_3$], Λ-[Rh(aet)$_3$], and Λ_D-[Rh(D-pen)$_3$]$^{3-}$ in a 40:49:11 ratio, featuring the conversion of the racemic system of $[\mathbf{1}]^{6+}$ to the Λ-rich system by treatment with D-pen (Table S2).†

Molecular model examinations revealed the existence of considerably steric repulsion between the COO$^-$ and methyl groups in the Δ_D isomer of $[\mathbf{2}]^{3-}$ (Figure S10),† which is responsible for the selective formation of the Λ_D isomer via intramolecular chiral transfer from D-pen to a Rh^{III} center. Consistently, only the Λ_D isomer was previously obtained for $[M(D\text{-pen-}N,S)_3]^{n-}$.[21,22] On the other hand, molecular models do not provide valuable information to explain the selective incorporation of the $(\Lambda)_4$ isomer of $[\mathbf{1}]^{6+}$ in **3**. Thus, we attempted to prepare ionic crystals composed of $(\Delta)_4$-$[\mathbf{1}]^{6+}$ and Λ_D-$[\mathbf{2}]^{3-}$ by the 1:1 mixing of $(\Delta)_4$-$[\mathbf{1}](NO_3)_6$[23] and an aqueous solution of Λ-$[\mathbf{2}]^{3-}$ that was obtained by column chromatography of **3**.† Fortunately, this treatment gave yellow block crystals (**4**) that were suitable for single-crystal X-ray crystallography. The X-ray analysis confirmed that **4** contains the $(\Delta)_4$ isomer of $[\mathbf{1}]^{6+}$, the Λ_D isomer of $[\mathbf{2}]^{3-}$, and NO$_3^-$ ions in a 1:1:3 ratio (Figure S11).† In **4**, the $(\Delta)_4$-$[\mathbf{1}]^{6+}$ cations and the Λ_D-$[\mathbf{2}]^{3-}$ anions are connected through N–H···O-C hydrogen bonds, constructing a 2D honeycomb-like sheet structure (Figures 1e, 1f, S3, S4).† This supramolecular structure is very similar to that found in **3**, but this structure is less symmetrical, as indicated by the $P1$ space group. In addition, the N-H···O-C hydrogen bonds between $[\mathbf{1}]^{6+}$ and $[\mathbf{2}]^{3-}$ (av. N···O = 2.97 Å) are appreciably longer than those in **3** (av. N···O = 2.89 Å), and the N-H···S hydrogen bonds between $[\mathbf{1}]^{6+}$ and $[\mathbf{2}]^{3-}$ (av. N···S = 3.40 Å) are also longer than those in **3** (av. N···S = 3.20 Å). We assume that these longer hydrogen bonds, together with the less symmetrical honeycomb structure in **4**, increase the solubility of **4**, which in turn leads to the fractional crystallization of **3** via intermolecular chiral transfer due to Λ_D-$[\mathbf{2}]^{3-}$.

In summary, we showed the preparation of optically pure crystals that exclusively accommodate the $(\Lambda)_4$ isomer of $[Zn_4O\{Rh(aet)_3\}_4]^{6+}$ ($[\mathbf{1}]^{6+}$) and the Λ_D isomer of fac-[Rh(D-pen)$_3$]$^{3-}$ ($[\mathbf{2}]^{3-}$) via a simple one-pot reaction of racemic $(\Delta)_4/(\Lambda)_4$-$[\mathbf{1}]^{6+}$ with the natural amino acid, D-penicillamine. This preparation resulted from a two-step chiral transfer; the intramolecular chiral transfer from D-pen to a Rh^{III} center that led to the diastereoselective formation of Λ_D-$[\mathbf{2}]^{3-}$ and the intermolecular chiral transfer from Λ_D-$[\mathbf{2}]^{3-}$ to $[\mathbf{1}]^{6+}$ that led to the enantioselective incorporation of $(\Lambda)_4$-$[\mathbf{1}]^{6+}$. Recently, we achieved the simultaneous crystallization of two kinds of optically active complexes with opposite chiralities by treating an optically active complex with an achiral organic ligand.[24] However, such a simultaneous crystallization of those species with the same chirality from a racemic complex and an optically active organic ligand has not been reported to date. Inspired by the two-step chiral induction found in the present study, the highly efficient synthesis and separation of optically

active complexes using a simple, commercially available chiral source should be advanced.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ It has been known that tris-chelate type octahedral Rh^{III} centers with the Λ configuration show strong positive CD bands in their first d-d transition band, except for only one unusual example with an axially chiral ligand.[25]

1   R. A. Sheldon, *Chirotechnology: industrial synthesis of optically active compounds*. CRC press, 1993.
2   H. Amouri and M. Gruselle, *Chirality in Transition Metal Chemistry: Molecules, Supramolecular Assemblies and Materials*, J. Wiley & Sons, Chichester 2008.
3   B. L. Feringa and R. A. Van Delden, *Angew. Chem. Int. Ed.*, 1999, **38**, 3418; Z. Chao, Y. Wen and X. Wu. *CrystEngComm*, 2016, **18**, 2792.
4   E. B. Bauer, *Chem. Soc. Rev.*, 2012, **41**, 3153.
5   B. Kesanli and W. Lin, *Coord. Chem. Rev.*, 2003, **246**, 305-326; D. Bradshaw, J. B. Claridge, E, J, Cussen, T. J. Prior and M. J. Rosseinsky, *Acc. Chem. Res.*, 2005, **38**, 273; R. Siedlecka, *Tetrahedron*, 2013, **69**, 6331; E. C. Constable, *Chem. Soc. Rev.*, 2013, **42**, 1637.
6   S.-T. Wu, Z.-W. Cai, Q.-Y. Ye, C.-H. Weng, X.-H. Huang, X.-L. Hu, C.-C. Huang and N.-F. Zhuang, *Angew. Chem. Int. Ed.*, 2014, **53**, 12860.
7   W. Zhang, H.-Y. Ye and R.-G. Xiong, *Coord. Chem. Rev.*, 2009, **253**, 2980.
8   J. Crassous, *Chem. Soc. Rev.*, 2009, **38**, 830.
9   D. K. Kondepudi, R. J. Kaufman and N. Singh, *Science*, 1990, **250**, 975; K. Soai, S. Niwa and H. Hori, *J. Chem. Soc., Chem. Commun.*, 1990, 982; D. K. Kondepudi and K. Asakura, *Acc. Chem. Res.* 2001, **34**, 946; W. K. Rybak, A. Skarzynska and T. Głowiak, *Angew. Chem. Int. Ed.*, 2003, **42**, 1725; R. E. Morris and X. Bu, *Nat. Chem.*, 2010, **2**, 353; J. E. Hein, B. H. Cao, C. Viedma, R. M. Kellogg and D. G. Blackmond, *J. Am. Chem. Soc.*, 2012, **134**, 12629.
10 B. Kesanli and W. Lin. *Coord. Chem. Rev.*, 2003, **246**, 305; O. Mamula and A. von Zelewsky. *Coord. Chem. Rev.*, 2003, **242**, 87.
11 N. Yoshinari, A. Kakuya, R. Lee and T. Konno, *Bull. Chem. Soc. Jpn.*, 2015, **88**, 59; Y. Kurioka, N. Kuwamura, N. Yoshinari, A. Igashira-Kamiyama and T. Konno, *Chem. Lett.*, 2015, **44**, 1330.
12 J. Lacour and V. Hebbe-Viton, *Chem. Soc. Rev.*, 2003, **32**, 373; A. Macchioni, *Chem. Rev.*, 2005, **105**, 2039; J. Lacour and D. Moraleda, *Chem. Commun.*, 2009, 7073.
13 E. Meggers, *Eur. J. Inorg. Chem.*, 2011, **2011**, 2911.
14 P. Lee, H. Q. Yuan, N. Yoshinari, A. Igashira-Kamiyama and T. Konno, *Chem. Lett.*, 2016, **45**, 740.
15 J. Crassous, *Chem. Commun.*, 2012, **48**, 9687.
16 T. Konno, K. Okamoto and J. Hidaka, *Inorg. Chem.*, 1994, **33**, 538.
17 N. Yoshinari, U. Yamashita and T. Konno, *CrystEngComm*, 2013, **15**, 10016.

18 A longer reflux of the mixture for 1 day also gave [Zn$_4$O{Rh(aet)$_3$}$_4$][Rh(D-pen)$_3$](NO$_3$)$_6$ as a yellow powder in a similar yield. However, this product contained both the Δ$_4$ and Λ$_4$ isomers of [**1**]$^{6+}$ with an ee value of ~60% for the Λ$_4$ isomer.

19 K. Nakamoto, *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, Wiley, New York, 1997.

20 T. Steiner, *Angew. Chem. Int. Ed.,* 2002, **41**, 48.

21 M. Taguchi, A. Igashira-Kamiyama, T. Kajiwara and T. Konno, *Angew*. *Chem*. *Int*. *Ed*., 2007, **46**, 2422; Y. Sameshima, N. Yoshinari, K. Tsuge, A. Igashira-Kamiyama and T. Konno, *Angew*. *Chem*. *Int*. *Ed*., 2009, **48**, 8469.

22 T. Konno, A. Toyota and A. Igashira-Kamiyama, *J. Chin. Chem. Soc*., 2009, **56**, 26; Y. Hashimoto, N. Yoshinari, N. Matsushita, T. Konno, *Eur*. *J*. *Inorg*. *Chem*., 2014, 3474; S. Surinwong, N. Yoshinari, B. Yotnoi and T. Konno, *Chem*. *Asian J*., 2016, **11**, 486; S. Surinwong, N. Yoshinari, T. Kojima and T. Konno, *Chem. Commun*., 2016, **52**, 12893.

23 T. Konno, K. Okamoto and J. Hidaka, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 101; S. Aizawa, S. Sone, S. Khajar, Y. Ohishi, S. Yamada and M. Nakamura, *Bull. Chem. Soc. Jpn*., 2000, **73**, 2043; T. Konno, K. Haneishi, M. Hirotsu, T. Yamaguchi, T. Ito and T. Yoshimura, *J. Am. Chem. Soc*. 2003, **125**, 9244.

24 A. Igashira-Kamiyama, A. Fukushima and T. Konno, *Chem*. *Eur*. *J*., 2013, **19**, 16532.

25 N. Yoshinari and T. Konno, *Inorg*. *Chem*., 2008, **47**, 7450.

Optically pure ionic crystals composed of complex cations and anions are created from a racemic complex and an amino acid.