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Chiral Recognition of α-Amino Acids by an Optically Active (2*S*,5*S*,8*S*,11*S*)-2,5,8,11-Tetraethyl Cyclen Cobalt(III) Complex

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The optically active cobalt(III) complex with chiral cyclen, (2*S*,5*S*,8*S*,11*S*)-2,5,8,11-tetraethyl-1,4,7,10-tetraazacyclododecane, preferentially binds to D-phenylglycine (D-Phg) or D-*t*-leucine (D-*t*-Leu) rather than L-Phg or L-*t*-Leu, respectively, with 20% *de* in dimethyl sulfoxide at 293 K. Comparative studies on the crystal structures of cobalt(III) complexes with D-Phg and L-Phg revealed that the diastereoselectivity is due to the difference in the steric hindrance that should occur between the amino group of Phg and the ethyl group of cyclen.

Metal complexes with cyclic polyamine ligands, for example, cyclen and cyclam possessing 12- and 14-membered N_4 macrocyclic structures, respectively, have exhibited specific metal-based functions, such as electrochemical and magnetism, redox reaction, molecular recognition, and catalysis.[1] Chemical modifications of the macrocyclic ligands have been extensively developed to control these properties and to increase novel functions.[2] Of these modifications, asymmetric introduction provides a well-defined functional center for chiral recognition and/or asymmetric catalysis. Among various substrate molecules in the asymmetric chemistry, amino acids have been often used for molecular recognition, optical resolution, and asymmetric reactions.[3] Previously, an optically active cyclen, (2*S*,5*S*,8*S*,11*S*)-2,5,8,11-tetraethyl-1,4,7,10-tetraazacyclododecane (**1**), containing four chiral centers on its framework, was efficiently synthesized by one-pot cyclization.[4] Its optically active cobalt(III) complex, $[Co(\mathbf{1})(H_2O)Br]Br_2$, is an excellent optical resolving agent for a few kinds of racemic amino acids because of the great difference in solubility between a pair of diastereomeric complexes.[5] The bound amino acids are easily released from the complex, and the pure $[Co(\mathbf{1})(H_2O)Br]Br_2$ can be efficiently regenerated. Furthermore, the asymmetric decarboxylation of $[Co(\mathbf{1})(\alpha\text{-amino-}\alpha\text{-methylmalonato})]^+$ to afford alanine was also examined.[6] For a better understanding of the mechanism of stereoselective recognition and thereby improvement of the general versatility of the optically active $[Co(\mathbf{1})]^{3+}$ complex, we examined its stereoselectivity in the amino acid recognition in solution and compared the X-ray crystal structures of both diastereomeric complexes with a pair of D- and L-Phg.

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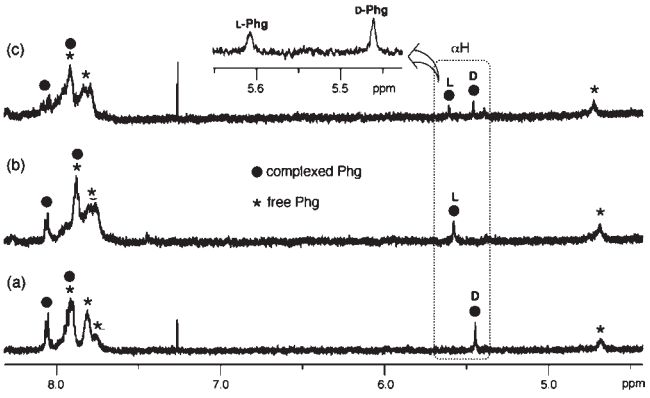
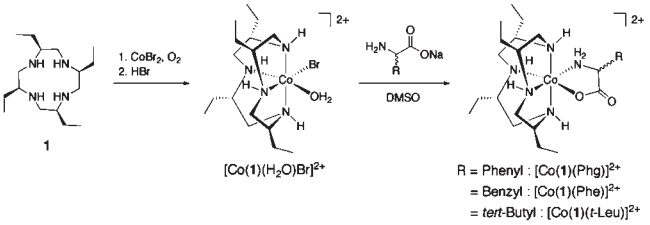


Figure 1. ^{1}H NMR spectra of $[Co(\mathbf{1})]^{3+}$ (500 MHz, DMSO-d_6/D_2O = 30/1, 293 K, $[[Co(\mathbf{1})]^{3+}]$ = 1.3 mM, tetramethylsilane, $Si(CH_3)_4$ in $CDCl_3$ as the external standard) with 2 equiv of sodium salts of (a) D-Phg, (b) L-Phg, or (c) *rac*-Phg, with [Phg] = 2.6 mM.

Scheme 1. Syntheses of $[Co(\mathbf{1})(H_2O)Br]^{2+}$ and Its Amino Acid Complexes



The optically active cobalt(III) complex with cyclen, $[Co(\mathbf{1})(H_2O)Br]Br_2$, was prepared from optically active cyclen **1** and $CoBr_2 \cdot 6H_2O$ (Scheme 1).[7] Among a series of amino acids, D-, L-, or racemic (*rac*-)Phg, *t*-Leu, and phenylalanine (Phe) were examined as amino acids possessing a bulky residue.

The $[Co(\mathbf{1})(H_2O)Br]^{2+}$ complex with two labile sites efficiently binds with bidentate amino acid sodium salts in dimethyl sulfoxide (DMSO). For instance, the reaction of $[Co(\mathbf{1})(H_2O)Br]^{2+}$ with 2 equiv of D-Phg sodium salt in DMSO-d_6/D_2O (30:1, v/v) at 293 K immediately produced a 1:1 complex, $[Co(\mathbf{1})(\text{D-Phg})]^{2+}$,[8] as was confirmed by ^{1}H NMR measurement. Upon complexation, the chemical shift of the αH signal of D-Phg shifted downfield with a 1:1 ratio of complexed and free D-Phg (see the region from 4.5 to 5.5 ppm in Figure 1a).[9] The ^{1}H NMR spectrum also suggested the site-selective binding of D-Phg, that is, four amino nitrogens of **1** and the amino nitrogen and carboxylate oxygen of the amino acid are bound to the central Co^{III} ion in a *cis*-β_1 form,[5] as the αH signal was observed as a single peak. Similarly, a $[Co(\mathbf{1})(\text{L-Phg})]^{2+}$ complex was formed from L-Phg sodium salt and $[Co(\mathbf{1})(H_2O)Br]^{2+}$ (Figure 1b). The formation of $[Co(\mathbf{1})(\text{L-Phg})]^{2+}$ was also confirmed by electrospray ionization time-of-flight (ESI-TOF) mass spectrometry (*m*/*z* 572.2, $[Co(\mathbf{1})(\text{L-Phg})Br]^+$).

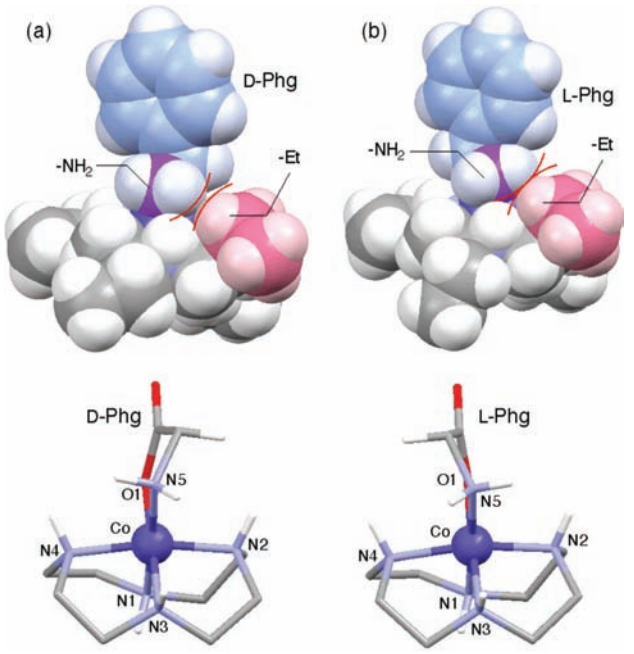


Figure 2. Crystal structures of (a) $[Co(\mathbf{1})(\text{D-Phg})]^{2+}$ and (b) $[Co(\mathbf{1})(\text{L-Phg})]^{2+}$. Molecular structures are represented with space-filling models for the whole structures (top) and stick models for the coordination spheres (bottom). For clarity, ClO_4^- anions are omitted. Selected bond distances [Å]: (a) Co−N1 1.927(7), Co−N2 1.966(7), Co−N3 1.920(7), Co−N4 1.947(7), Co−N5 1.963(6), Co−O1 1.914(5); (b) Co−N1 1.952(2), Co−N2 1.948(2), Co−N3 1.922(2), Co−N4 1.964(2), Co−N5 1.976(3), Co−O1 1.909(2).

The stereoselective recognition of Phg by the $[Co(\mathbf{1})(H_2O)Br]^{2+}$ complex was successfully evaluated by ^{1}H NMR spectroscopy. Because the αH chemical shifts of complexed D-Phg and L-Phg are substantially different from each other, as shown in Figure 1a,b, the diastereoselectivity could be easily estimated from their values of integral. In the ^{1}H NMR spectrum of a solution of $[Co(\mathbf{1})(H_2O)Br]^{2+}$ and 2 equiv of *rac*-Phg, the αH signal ratio of complexed D-Phg/L-Phg stayed constant for several hours at ca. 60:40 (20% *de*) at 293 K in DMSO-d_6/D_2O (30:1, v/v), which is believed to be a result of the thermodynamic equilibrium.

Single crystals of $[Co(\mathbf{1})(\text{L-Phg})](ClO_4)_{1.88}(Br)_{0.12}$[10] and $[Co(\mathbf{1})(\text{L-Phg})](ClO_4)_2$[11] were successfully prepared by exchanging counteranions from Br^- to ClO_4^- in 38% and 35% yields, respectively. Their X-ray analyses first revealed regioselective formations of $[Co(\mathbf{1})(\text{D-Phg})]^{2+}$ and $[Co(\mathbf{1})(\text{L-Phg})]^{2+}$, as expected for the above ^{1}H NMR experiments (Figure 2).[12] Interestingly, one ethyl group of **1** (pink-colored in Figure 2)

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(8) For comparison with the case of *rac*-Phg, 2 equiv of D- or L-Phg was added to the solution.

(9) The addition of a small amount of D_2O to a DMSO-d_6 solution allows the formation of deuterated amines, ND and ND_2, which eliminate the vicinal coupling between the proton signals of amine and αH of Phg in the ^{1}H NMR. Therefore, we could observe the αH signal of complexed Phg as a singlet, and thereby the ratio of complexed D-Phg/L-Phg was clearly estimated from the ratio of the values of integral.

(10) Crystal data for $[Co(\mathbf{1})(\text{D-Phg})](ClO_4)_2$: $C_{24}H_{46}Cl_2CoN_5O_{11}$, F_w = 710.49, orthorhombic, space group $P2_12_12_1$, a = 12.5046(12) Å, b = 12.9421(12) Å, c = 19.3464(18) Å, V = 3130.9(5) Å^3, Z = 4, T = 93 K, λ(Mo Kα) = 0.710 75 Å, R1 = 0.0667 [$I > 2\sigma(I)$], wR2 = 0.1677 (for all data), GOF = 0.985. CCDC reference number 779751.

(11) Crystal data for $[Co(\mathbf{1})(\text{L-Phg})](ClO_4)_{1.88}(Br)_{0.12}$: $C_{24}H_{46}Br_{0.12}Cl_{1.88}CoN_5O_{10.52}$, F_w = 708.15, orthorhombic, space group $P2_12_12_1$, a = 12.5938(6) Å, b = 12.8664(8) Å, c = 19.0257(10) Å, V = 3082.9(3) Å^3, Z = 4, T = 93 K, λ(Mo Kα) = 0.710 75 Å, R1 = 0.0484 [$I > 2\sigma(I)$], wR2 = 0.0990 (for all data), GOF = 1.056. CCDC reference number 779752.

(12) The ^{1}H NMR spectrum of the complexed L-Phg of $[Co(\mathbf{1})(\text{L-Phg})](ClO_4)_{1.88}(Br)_{0.12}$ is almost identical with that of $[Co(\mathbf{1})(\text{L-Phg})]Br_2$, suggesting that the cationic parts of their crystal structures should be maintained in solution (see the Supporting Information).

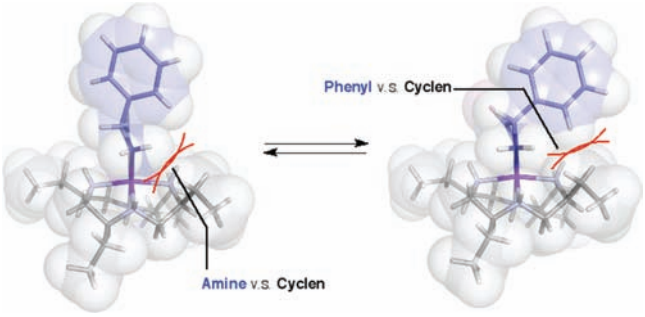

Figure 3. Crystal structure of $[Co(\mathbf{1})(\text{L-Phg})]^{2+}$ (left) and a postulated alternative structure that would reduce the repulsion between the amino group of Phg and cyclen (right). In the postulated structure, the chelate ring formed from L-Phg and Co^{III} is twisted and the repulsive interaction is developed between the phenyl group of Phg and the cyclen ring.

causes steric repulsion with an amino group of L-Phg (purple-colored in Figure 2) in $[Co(\mathbf{1})(\text{L-Phg})]^{2+}$, while $[Co(\mathbf{1})(\text{D-Phg})]^{2+}$ shows only slight steric repulsion between them. This repulsion also lengthens the Co-NH_2 (Phg) bond distance of L-Phg [1.976(3) Å] compared with that of D-Phg [1.963(6) Å]. These results suggest that close contact between an amino group of L-Phg and an ethyl group of **1** must be a main reason for the diastereoselectivity.

The mechanism of steric repulsion in the $[Co(\mathbf{1})(\text{L-Phg})]^{2+}$ complex can be explained by crystal structures and molecular models. As shown in Figure 2, the repulsion is caused by a twist of the five-membered chelate ring formed from the amino acid backbone (−N−C−C−O−) and Co^{III} ion. However, if the repulsion is reduced by the opposite twist of the chelate ring, another repulsion between the phenyl group of L-Phg and the cyclen skeleton appears to be significant (Figure 3). Therefore, it was presumed that the bulky side chain of amino acid interacts with the optically active cyclen skeleton indirectly through the amino acid backbone.

As shown above, the bulkiness of the substituent at the chiral center of amino acid should affect the diastereoselectivity. Other amino acids, *t*-Leu and Phe, were then examined by a ^{1}H NMR study of a solution containing $[Co(\mathbf{1})(H_2O)Br]^{2+}$ and 2 equiv of sodium salts of *rac*-*t*-Leu (or *rac*-Phe). *t*-Leu, possessing a bulky *t*-butyl group at the chiral center, gave a result (D-*t*-Leu/L-*t*-Leu = 60/40, 20% *de*) similar to that of Phg, while Phe, possessing a benzyl group at the chiral center, showed no selectivity (Figure S3 in the Supporting Information). This result strongly supports the proposed mechanism of the diastereoselectivity with the $[Co(\mathbf{1})]^{3+}$ complex. Furthermore, it suggests that **1** can recognize the shape of the amino acid residue through a twist of the amino acid backbone.

In conclusion, chiral recognition of Phg and *t*-Leu was achieved by the cobalt(III) complex of an optically active cyclen, $[Co(\mathbf{1})]^{3+}$. The selectivity mechanism was estimated by a comparison of the crystal structures of $[Co(\mathbf{1})(\text{D-Phg})]^{2+}$ and $[Co(\mathbf{1})(\text{L-Phg})]^{2+}$. In the postulated mechanism, the optically active cyclen skeleton allows chiral recognition of amino acids through a twist of the amino acid backbone that is caused by the repulsion between the bulky amino acid residue and **1**. This finding would encourage the development of molecular functions of $[Co(\mathbf{1})]^{3+}$ such as chiral inversion between L and D, optical resolution, and asymmetric catalysis.

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Supporting Information Available: X-ray crystallographic data of the $[Co(\mathbf{1})(\text{D-Phg})](ClO_4)_2$ and $[Co(\mathbf{1})(\text{L-Phg})](ClO_4)_{1.88}(Br)_{0.12}$ complexes in CIF format, synthetic procedures, ^{1}H NMR spectra, and ORTEP views. This material is available free of charge via the Internet at http://pubs.acs.org.