Characterization of an NH−π Interaction in Co(III) Ternary Complexes with Aromatic Amino Acids

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The NH−π interaction has been detected in the crystal structures of Co(III) ternary complexes with *N*,*N*-bis-(carboxymethyl)-(*S*)-phenylalanine (BCMPA) and aromatic amino acids including (*S*)-phenylalanine ((*S*)-Phe), (*R*)-phenylalanine ((*R*)-Phe), and (*S*)-tryptophan ((*S*)-Trp)). Additionally, this interaction has been studied in solution for Co(III) ternary complexes with BCMPA or NTA (NTA = nitrilotriacetic acid) and several amino acids (AA) by means of electronic absorption, circular dichroism (CD), and ^{1}H NMR spectroscopies. The CD intensities of the Co(III) complexes with aromatic amino acids measured in the d−d region ($\sim 20.5 \times 10^3$ cm^{-1}) are significantly decreased in ethanol solutions relative to water. Analogous complexes with aliphatic amino acids do not exhibit this solvent effect. The ^{1}H NMR spectra of the Co(III) complexes with aromatic amino acids measured in DMSO-d_6 exhibit upfield shifts of the NH peaks compared with those with aliphatic amino acids, which suggest a shielding effect due to the aromaticity. The upshift values coincide with those experimentally evaluated from the crystal structures. The magnitude of the upfield shifts agrees well with Hammett's rule, indicating that the increase of π-electron densities on the aromatic rings leads attractive NH−π interaction that exerts a larger shielding effect for the NH protons. In ligand-substitution reactions of the carbonatocobalt(III) complexes with amino acids, the yields of those with aromatic amino acids are higher than the yields obtained for complexes with aliphatic amino acids. This observation is discussed in connection with the important contribution of the NH−π interaction as one of the promotion factors in the reaction.

Introduction

Noncovalent interactions such as hydrogen bonding, hydrophobic, steric repulsion, aromatic ring stacking, and electrostatic interactions play important roles in chemical reactions, molecular recognition, and regulating biochemical processes.[1−3] The high efficiency and specificity of enzymatic reactions are achieved by a combination of such weak noncovalent interactions.[4] In recent years, NH−π interaction was also recognized as one of the important factors of the molecular recognition and stabilization of molecular structures,[5] and evidence that the π-electrons of aromatic systems act as hydrogen-bond acceptors have been presented from theoretical,[6−8] spectroscopic,[9,10] and crystallographic studies.[5] Although the NH−π interaction has relatively weak bond energy (2−4 kcal mol^{-1},[6] half the strength of a normal hydrogen bond), it is large enough to be biologically significant but difficult to verify its existence and influence on chemical reactions because of its small bond energy.[11−13]

In recent studies on construction of site-selective molecular recognition models of amino acids, we discovered that the complexation of aromatic amino acids to K_2[Co(bcmpa)(CO_3)]

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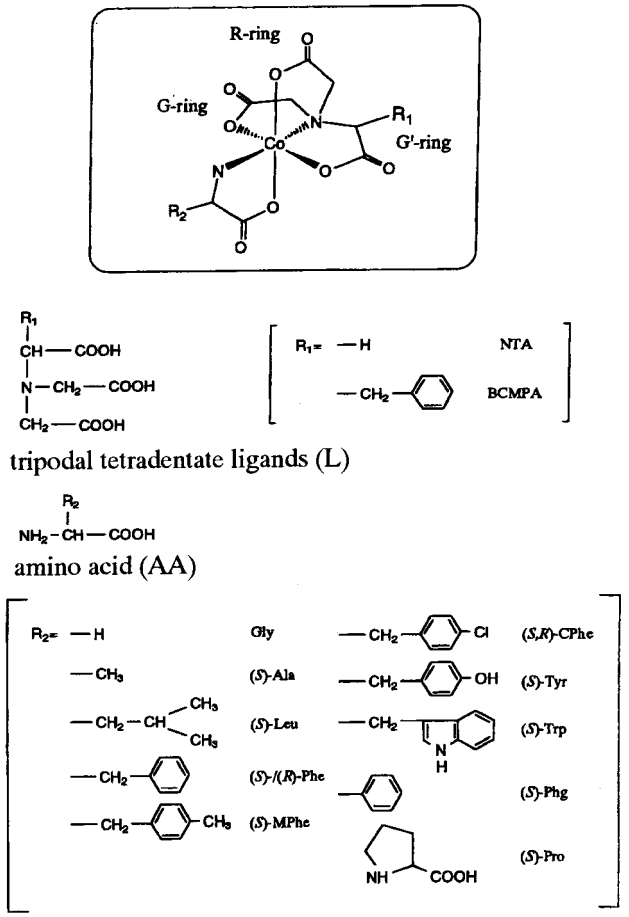
Scheme 1. Structure of *trans*(N)-K[Co(L)(aa)] Complexes Employed



(BCMPA = *N*,*N*-bis(carboxymethyl)-(*S*)-phenylalanine) was much more efficient than complexation of aliphatic amino acids.[14]

To investigate the factors affecting the yield of the ternary complexes in the reaction, we examined the static coordination characteristics of the Co(III) ternary system [Co(III)(bcmpa or nta)(aa)] (NTA = nitrilotriacetic acid, aa = amino acid). We describe herein the crystal and solution structures investigated by electronic absorption, CD, and ^{1}H NMR spectroscopic and X-ray diffraction methods. We have succeeded in obtaining evidence for the NH−π interaction in the Co(III) complexes with aromatic amino acids. In addition, we propose that the NH−π interaction plays an important role as a controlling factor in the complexation of the aromatic amino acids to the Co(III) system.

Experimental Section

Materials and Preparation of Co(III) Complexes. All the chemicals used were purchased from Nacalai Tesque and were of analytical grade or the highest grade available. The tripodal tetradentate ligands (L), NTA, and BCMPA were synthesized according to previously published methods.[15]

The ternary Co(III) complexes with NTA and amino acids (Scheme 1) were prepared and characterized according to the methods in the literature.[14,15] Those with BCMPA were prepared by the modified method of the Co-NTA-AA systems according to the following procedure. To 10 mL of a 0.2 M aqueous solution of K_2[Co(bcmpa)-(CO_3)] prepared from K_3[Co(CO_3)$_3$] and BCMPA in the presence of active charcoal was added an equimolar amount of AA neutralized with KOH, and the resulting mixture was stirred at 50 °C for 4−12 h with adjustment to pH 6−7 by addition of 0.1 M HCl. After filtration, the aqueous solution was poured into a QAE Sephadex A-25 column (Cl^- form), which gave only one reddish violet band. The adsorbed band was eluted with an aqueous 0.1 M KCl solution. The Co(III) complexes with NTA or BCMPA and AA were confirmed by ^{1}H NMR and/or elemental analysis (Tables S1 and S2, Supporting Information).

Table 1. Crystal Data and Experimental Details of *trans*(N)-K[Co(bcmpa)(aa)]

	aa		
	(*S*)-phe	(*R*)-phe	(*S*)-trp
formula	$KCoC_{22}H_{22}N_2O_8\cdot 3.5H_2O$	$KCoC_{22}H_{22}N_2O_8\cdot 2H_2O$	$KCoC_{24}H_{23}N_3O_8\cdot 2H_2O$
formula weight	603.51	576.49	615.52
crystal size/mm	0.20 × 0.30 × 0.20	0.20 × 0.20 × 0.20	0.10 × 0.30 × 0.15
crystal system	monoclinic	tetragonal	tetragonal
space group	$P2_1$ (No. 4)	$P4_3$ (No. 78)	$P4_3$ (No. 78)
a (Å)	13.567(2)	14.055(1)	14.486(2)
b (Å)	11.708(2)		
c (Å)	16.892(5)	12.621(2)	13.061(9)
β (deg)	100.66(7)		
V (Å^3)	2637(1)	2493.2(4)	2741(1)
Z	2	4	4
$2\theta_{max}$/deg	52.6	52.6	52.6
D_{calc}/g cm^{-3}	1.475	1.536	1.562
λ (Mo Kα)	0.71069	0.71069	0.71069
μ (Mo Kα)/cm^{-1}	8.67	9.14	8.47
T/K	293	293	293
F(000)	1212.0	1192.0	1324.0
no. of reflns obsd	5851	2873	6054
no. of reflns used ($\|I_0\| > 3\sigma\|I_0\|$)	3504	2299	1881
no. of variables	674	324	347
R	0.068	0.051	0.052
R_w	0.070	0.053	0.041

[a] $R(F_o) = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $R_w(F_o) = (\sum w||F_o| - |F_c||^2/\sum|F_o|^2)^{1/2}$, $w = [\sigma^2(F_o) + (0.002F_o)^2]^{-1}$.

Spectral Measurements. Electronic absorption and circular dichroism (CD) spectra were measured with a JASCO UVIDEC-660 spectrophotometer and a JASCO J-500C spectropolarimeter, respectively, in the visible region at room temperature in a quartz cell with an optical path length of 1.0 cm. Solvent effects on CD spectra were examined as the differences between intensities in H_2O and in ethanol. ^{1}H NMR spectra were obtained on a JEOL Lambda-500 spectrometer in DMSO-d_6 at 26 °C with TMS as an internal standard. Samples employed for all measurements were freshly prepared at pH ∼7.0 before use with the concentration being adjusted at 5×10^{-5}−2.5×10^{-3} mol L^{-1} with respect to Co(III).

X-ray Crystal Structure Determinations. Single crystals of K[Co-(bcmpa)((*S*)-phe)]·3.5H_2O (**1**), K[Co(bcmpa)((*R*)-phe)]·2H_2O (**2**), and K[Co(bcmpa)((*S*)-trp)]·2H_2O (**3**) suitable for X-ray analysis were obtained from the aqueous solution by slow evaporation at room temperature. Crystals were mounted on a glass capillary. Diffraction data were collected at 295 K with an Enraf Nonius CAD4-EXPRESS four-circle diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.710 69 Å). The crystal data and parameters associated with data collection are given in Table 1. The unit cell parameters were derived from least-squares refinement of 25 well-centered reflections. The reflection intensities were monitored by three standard reflections for every 2 h, and the decays of intensities were within 2%. Reflection data were corrected for Lorentz and polarization effects. An empirical absorption correction, based on Ψ scans, was applied for all the crystals.

The structures of the complexes were solved by the heavy-atom method and refined anisotropically for non-hydrogen atoms by full-matrix least-squares calculations. Refinements were continued until all shifts were smaller than one-third of the standard deviations of the parameters involved. Atomic-scattering factors and anomalous disper-

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Table 2. Selected Interatomic Distances (Å) and Angles (deg)[a]

K[Co(bcmpa)((*S*)-phe)]·3.5H_2O					
Co(a)	O(13a)	1.875(9)	Co(b)	O(13b)	1.881(9)
Co(a)	O(23a)	1.902(8)	Co(b)	O(23b)	1.905(9)
Co(a)	O(33a)	1.887(9)	Co(b)	O(33b)	1.854(9)
Co(a)	O(44a)	1.896(8)	Co(b)	O(44b)	1.908(9)
Co(a)	N(11a)	1.90(1)	Co(b)	O(11b)	1.92(1)
Co(a)	N(41a)	1.93(1)	Co(b)	O(41b)	1.96(1)
K[Co(bcmpa)((*R*)-phe)]·2H_2O					
Co	O(13)	1.909(7)	Co	O(44)	1.883(5)
Co	O(23)	1.903(5)	Co	N(11)	1.923(7)
Co	O(33)	1.876(6)	Co	N(41)	1.921(6)
K[Co(bcmpa)((*S*)-trp)]·2H_2O					
Co	O(13)	1.899(7)	Co	O(44)	1.880(6)
Co	O(23)	1.874(6)	Co	N(11)	1.943(8)
Co	O(33)	1.879(7)	Co	N(41)	1.921(8)

[a] Estimated standard deviations are given in parentheses.

sion terms were taken from the literature.[16] All of the hydrogen atoms were located from the difference Fourier maps, and their parameters were isotropically refined. The R and R_w values were 0.068 and 0.070 for **1**, 0.051 and 0.053 for **2**, and 0.052 and 0.041 for **3**, respectively. The weighting scheme $w^{-1} = (\sigma^2(F_o) + (0.002F_o)^2)$ was employed for all crystals. The final difference Fourier maps did not show any significant features for these crystals. The calculations were performed on an IRIS Indigo XS-24 workstation using the program system teXsan.[17] Tables of atomic coordinates, anisotropic temperature factors, and bond lengths and angles are included as Supporting Information.

Results and Discussion

Preparation of K[Co(L)(aa)] Complexes. As described in the Experimental Section, preparation of the K[Co(L)(aa)] complexes was carried out with the ligand-substitution reaction of a carbonato anion in the K_2[Co(L)(CO_3)] complexes by amino acids (aa). After preliminary observations that complexation of the aromatic amino acids tends to occur more efficiently than complexation of aliphatic amino acids, the reaction rates were measured by HPLC. As is clear from the plots of yields of K[Co(L)(aa)] complexes against reaction time on the basis of K_2[Co(L)(CO_3)] complex (Figure 1), the ligand-substitution reactions of the carbonato anion with the aromatic amino acids (*S*)-/(*R*)-Phe were faster than those with the aliphatic amino acids (*S*)-Ala and (*S*)-Leu. Tendency in the reaction rates does not depend on the identity of the tripodal ligand (NTA or BCMPA). The structural origins of this unique behavior were investigated by electronic absorption, CD, and ^{1}H NMR spectroscopic and X-ray diffraction methods.

Crystal Structures of K[Co(bcmpa)((*S*)-Phe)]·3.5H_2O (1), K[Co(bcmpa)((*R*)-Phe)]·2H_2O (2), and K[Co(bcmpa)((*S*)-Trp)]·2H_2O (3). The crystal structures of **1**, **2**, and **3** are depicted in Figures 2, 3, and 4, respectively, and their selected bond lengths and angles are shown in Table 2. The configurations around the central Co(III) atoms for all the complexes revealed the same octahedral geometries with the tertiary amino nitrogen and the three carboxylate oxygens of BCMPA and the amino nitrogen and carboxylate oxygen of amino acid in *trans*-(N)-arrangement. The metal−ligand bond lengths (Co−O = 1.854−1.904 Å and Co−N = 1.921−1.967 Å) lay in the range of those previously reported for Co(III) complexes with tertiary amine nitrogens, carboxylate oxygens, and amino nitrogens.[15,18,19]

The common structural feature of the complexes presented here is the unique approach of the aromatic ring to the coordinated amino group despite the high degree of free rotation around the β-carbon of amino acid side chains. In all cases, the amino hydrogen atoms are oriented near the mean plane of the aromatic system at distances of 2.81 and 2.61 Å from the phenyl ring of **1**, 2.82 Å from the phenyl ring of **2**, and 2.72 Å from the indole ring of **3**. These geometries agree well with those previously reported.[5,6] Similar orientations have also been observed in the K[Co(*N*,*N*-bis(carboxymethyl)-(*S*)-leucine)((*S*)-phe)] complex reported previously.[19] These observations are indicative of the presence of the attractive interaction between the aromatic ring and the amino hydrogen atoms.

Electronic Absorption and CD Spectra. To further examine the existence of such an interaction, the solution structures of the *trans*(N)-K[Co(L)(aa)] complexes were characterized by electronic absorption, CD, and ^{1}H NMR spectroscopies.

Electronic absorption spectra of the Co(III) complexes (Table S3, Supporting Information), trans(N)-K[Co(bcmpa)(aa)] and *trans*(N)-K[Co(nta)(aa)], in the d−d region showed well-separated first (band 1) and second bands (band 2) near 19.5 × 10^3 and 26.7 × 10^3 cm^{-1}, which are a typical spectral pattern for the *trans*(N)-[CoN_2O_4] chromophore.[20] Their σ_{max} values exhibited similar magnitudes, independent of the identity of the tripodal and amino acid ligands. This indicates that the inner coordination spheres around the Co(III) atoms are almost the same for these complexes.

The CD spectra of the trans(N)-K[Co(bcmpa)((*S*)-ala)] and trans(N)-K[Co(bcmpa)((*S*)-trp)] complexes with (*S*)-Ala and (*S*)-Trp (Table S3, Supporting Information) as typical aliphatic and aromatic amino acids are shown in parts a and b of Figure 5, respectively. The spectra, which are independent of the identity of the tripodal and amino acid ligands, revealed four components in the d−d region. The components can be classified into two bands corresponding to bands 1 and 2 of the electronic absorption spectra. Band 1 is composed of three maxima near 16.3 × 10^3, 18.5 × 10^3, and 20.5 × 10^3 cm^{-1}, and band 2 has one maximum near 26.5 × 10^3 cm^{-1}.[20,21] Only the trans(N)-K[Co(bcmpa)(gly)] complex did not have the intense band near 20.5 × 10^3 cm^{-1}. This is an indication that the band originates from a transition attributable to chiral amino acids. Interestingly, this band exhibited an unambiguous solvent effect that is related to the vicinal effect of chiral amino acids:[22] The Co(III) complexes with the aromatic amino acids (*S*)-Trp, (*S*)-Phe, and (*S*)-Tyr gave intense CD bands in aqueous solution. A significant decrease in CD band intensity was observed for the same complexes in ethanol. On the other hand, the Co(III) complexes

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Table 3. ^{1}H NMR Chemical Shift Values of *trans(N)*-K[Co((*S*)-bcmpa)(aa)] Complexes

	δ/ppm from TMS in DMSO-d_6						
	bcmpa				aa		
aa	G ring	R ring	α-H	side chain	NH	α-H	side chain
gly	3.20 (d) 3.69 (d)	3.50 (d) 4.06 (d)	4.45 (dd)	3.39 (dd): β-CH_2 7.29 (t): *p*-H 7.38 (t): *m*-H 7.53 (d): *o*-H	6.77 (m)	3.25 (m)	-
(*S*)-ala	3.21 (d) 3.72 (d)	3.50 (d) 4.06 (d)	4.46 (dd)	3.39 (dd): β-CH_2 7.29 (t): *p*-H 7.39 (t): *m*-H 7.53 (d): *o*-H	6.27 (dd) 7.24 (dd)	ND[a]	1.35 (d): β-CH_3
(*S*)-leu	3.21 (d) 3.72 (d)	3.49 (d) 4.06 (d)	4.47 (dd)	3.39 (dd): β-CH_2 7.29 (t): *p*-H 7.38 (t): *m*-H 7.53 (d): *o*-H	6.01 (dd) 7.40 (dd)	3.28 (m)	0.92 (d), 0.93 (d): δ-CH_3 1.52 (m), 1.66 (m): β-CH_2 2.15 (m): γ-CH
(*S*)-pro	3.24 (d) 3.73 (d)	3.54 (d) 4.10 (d)	4.43 (dd)	3.39 (dd): β-CH_2 7.29 (t): *p*-H 7.38 (t): *m*-H 7.53 (d): *o*-H	8.20 (m)	3.73 (m)	1.80 (m): γ-CH_2 1.93 (m), 2.16 (m): β-CH_2 3.13 (m), 3.27 (m): δ-CH_2
(*S*)-phg	3.27 (d) 3.80 (d)	3.55 (d) 4.11 (d)	4.52 (dd)	ND[a]: β-CH_2 7.30 (t): *p*-H 7.39 (t): *m*-H 7.56 (d): *o*-H	6.12 (dd) 7.91 (dd)	4.45 (m)	7.31−7.37 (m): *o*,*m*,*p*-H
(*S*)-phe	3.22 (d) 3.74 (d)	3.50 (d) 4.06 (d)	4.46 (dd)	3.38: β-CH_2 7.29 (t): *p*-H 7.38 (t): *m*-H 7.53 (d): *o*-H	5.79 (dd) 7.07 (dd)	3.54 (m)	3.05 (dd), 3.14 (dd): β-CH_2 7.25 (t): *p*-H 7.34 (t): *m*-H 7.39 (d): *o*-H
(*R*)-phe	3.19 (d) 3.70 (d)	3.51 (d) 4.05 (d)	4.50 (dd)	N. D.[a]: β−CH_2 7.29 (t): *p*-H 7.39 (t): *m*-H 7.54 (d): *o*-H	5.80 (dd) 7.02 (dd)	3.50 (m)	3.07 (dd), 3.14 (dd): β-CH_2 7.25 (t): *p*-H 7.34 (t): *m*-H 7.40 (d): *o*-H
(*S*)-trp	3.21 (d) 3.73 (d)	3.49 (d) 4.05 (d)	4.47 (dd)	3.38 (dd): β-CH_2 7.30 (t): *p*-H 7.39 (t): *m*-H 7.53 (d): *o*-H	5.34 (dd) 7.26 (dd)	3.62 (m)	3.12 (dd), 3.26 (dd):β-CH_2 7.01 (t), 7.09 (t): 5,6-H 7.32 (s): 2-H 7.37 (d), 7.63 (d): 4,7-H 10.96(s): 1-H

[a] Not determined because of overlap with water signal.

Table 4. ^{1}H NMR Chemical Shift Values of *trans(N)*-K[Co(nta)(aa)] Complexes

	δ/ppm from TMS in DMSO-d_6				
	nta		aa		
aa	G ring	R ring	NH	α-H	side chain
gly	3.87 (d) 4.21 (d)	3.82 (s)	6.77 (t)	3.27 (t)	-
(*S*)-ala	3.86 (d), 3.88 (d) 4.23 (d), 4.24 (d)	3.82 (s)	6.29 (dd) 7.39 (dd)	3.36 (m)	1.37 (d): β-CH_3
(*S*)-leu	3.86 (d), 3.87 (d) 4.23 (d), 4.24 (d)	3.82 (s)	6.03 (dd) 7.39 (dd)	3.26 (m)	0.93 (d), 0.94 (d): δ-CH_3 1.55 (m), 1.68 (m): β-CH_2 2.18 (m): γ-CH
(*S*)-phe	3.85 (d), 3.88 (d) 4.23 (d), 4.26 (d)	3.82 (s)	5.81 (dd) 7.05 (dd)	3.52 (m)	3.07 (dd), 3.16 (dd): β-CH_2 7.25 (t): *p*-H 7.35 (t): *m*-H 7.41 (d): *o*-H
(*S*)-Mephe	3.85 (d), 3.87 (d) 4.23 (d), 4.25 (d)	3.81 (s)	5.65 (dd) 7.04 (dd)	3.50 (m)	2.30 (s): *p*-CH_3 3.02 (dd), 3.10 (dd): β-CH_2 7.15 (d): *m*-H 7.28 (d): *o*-H
(*S*)-,(*R*)-Clphe	3.85 (d), 3.88 (d) 4.23 (d), 4.26 (d)	3.81 (s)	6.02 (dd) 7.16 (dd)	3.48 (m)	3.07 (dd), 3.15 (dd): β-CH_2 7.37 (d): *m*-H 7.44 (d): *o*-H
(*S*)-tyr	3.85 (d), 3.88 (d) 4.23 (d), 4.25 (d)	3.81 (s)	5.52 (dd) 7.02 (dd)	3.46 (m)	2.94 (dd), 3.03 (dd): β-CH_2 6.74 (d): *m*-H 7.18 (d): *o*-H 9.26 (s): *p*-OH
(*S*)-trp	3.86 (d), 3.88 (d) 4.24 (d), 4.25 (d)	3.81 (s)	5.38 (dd) 7.25 (dd)	3.61 (m)	3.14 (dd), 3.28 (dd): β-CH_2 7.02 (t), 7.10 (t): 5,6-H 7.35(s): 2-H 7.38(d), 7.65(d): 4,7-H 10.97(s): 1-H

with aliphatic amino acids (*S*)-Ala, (*S*)-Leu, and (*S*)-Pro did not exhibit the solvent effect. This fact clearly indicates that the Co(III) complexes with aromatic side chains may intramolecularly aggregate between hydrophobic groups in aqueous solution (e.g., hydrophobic hydration) and that it is weakened by the less polar solvent. This, in turn, may suggest the existence of the NH−π interaction in solution which is proposed from the crystal structures of complexes **1**, **2**, and **3** and that of K[Co(*N*,*N*-bis(carboxymethyl)((*S*)-leucine)((*S*)-phe)] reported previously.[19] This is also supported from the finding that the Co(III) complex including phg, which cannot stereochemically form the intramolecular NH−π interaction, did not show such a solvent effect.

^{1}H NMR Spectra of Co(III) Ternary Complexes. Since NMR spectroscopy is a powerful method for studying weak interactions in solution, ^{1}H NMR spectra of the Co(III) complexes were measured to obtain detailed structural information of the NH−π interaction in solution. If the NH protons closely approach an aromatic system, they will be expected to shift toward higher field region by the ring current effect. Since

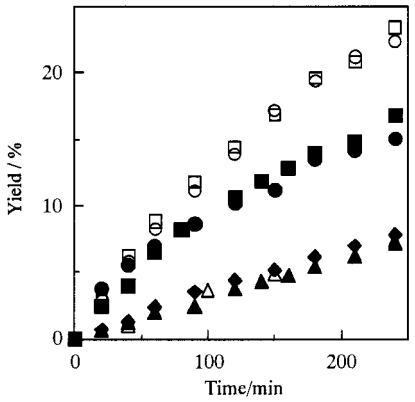


Figure 1. Plots of yields of *trans*(N)-K[Co(L)(aa)] complexes against time on the basis of $K_2[Co(L)(CO_3)]$ complex as followed by HPLC: K[Co(bcmpa)((*S*)-phe)] (■); K[Co(bcmpa)((*R*)-phe)] (●); K[Co(bcmpa)((*S*)-leu)] (◆); K[Co(bcmpa)((*S*)-ala)] (▲); K[Co(nta)(*S*)-phe)] (□); K[Co(nta)(*R*)-phe)] (○); and K[Co(nta)(*S*)-ala)] (△).

the NH_2 protons of the coordinated amino acids are not detected in D_2O because of its H−D exchange, the ^1H NMR resonances of K[Co(L)(aa)] complexes were measured in DMSO-d_6 solution, and their data are listed in Tables 3 and 4 for *trans*(N)-K[Co((*S*)-bcmpa)(aa)] and *trans*(N)-K[Co(nta)(aa)], respectively. The spectral patterns of the Co(III) complexes in DMSO-d_6 agree well with those in D_2O previously reported.[14,20,21] This indicates that the complexes apparently have similar structural conformations in DMSO and aqueous solutions.

The proton NMR spectra of the NH_2 group for the Co(III) complexes in DMSO-d_6 were observed as two sharp doublet−doublet signals with an ABX pattern in the range of 5.3−7.4 ppm, except for that of the Gly complex, which includes two amino hydrogen atoms with a chemically equivalent environment (6.77 ppm). The split proton signals in the amino acid complexes with different vicinal coupling constants due to α-H indicates that the environments of the two hydrogen atoms are not chemically equivalent. This finding suggests that the C(α)−N(amino) bond is resistant to rotation and that it is possible to assign the two NH_2 proton signals from the magnitude of the vicinal couplings with α-H according to the Karplus equation;[22] the signals at higher- and lower-field sides are assigned to the protons at the anti and gauche positions for the α-H, respectively.

Tables 3 and 4 include the following interesting information. First, the NH proton chemical shifts are dependent not on the tripodal ligands, BCMPA or NTA, but on the amino acid ligands. Second, the two split proton peaks of the amino protons were observed at higher- and lower-field regions in comparison with those of the Gly complexes. The average values of the two peaks for the aromatic amino acid complexes showed an upfield shift compared with that of the Gly complex, although those with aliphatic amino acids were almost the same as the Gly complex. Especially, the peaks at the higher-field side exhibited significant upfield shifts as described below, although the lower-side peaks did not show any meaningful shift. Third, the chemical shift values of the higher-side peaks for the Co(III) complexes with *p*-X-substituted phenylalanine (X = −OH, $-CH_3$, −H, −Cl) demonstrated a significant substituent effect. Plots of the chemical shift values vs the substituent constants of the *para*-substituted groups, X (Figure 6), exhibit a clear linear relationship that agrees well with Hammett's rule.[23] Complexeswith electron-releasing groups in the aromatic system showed a larger upfield shift compared with those with electron-

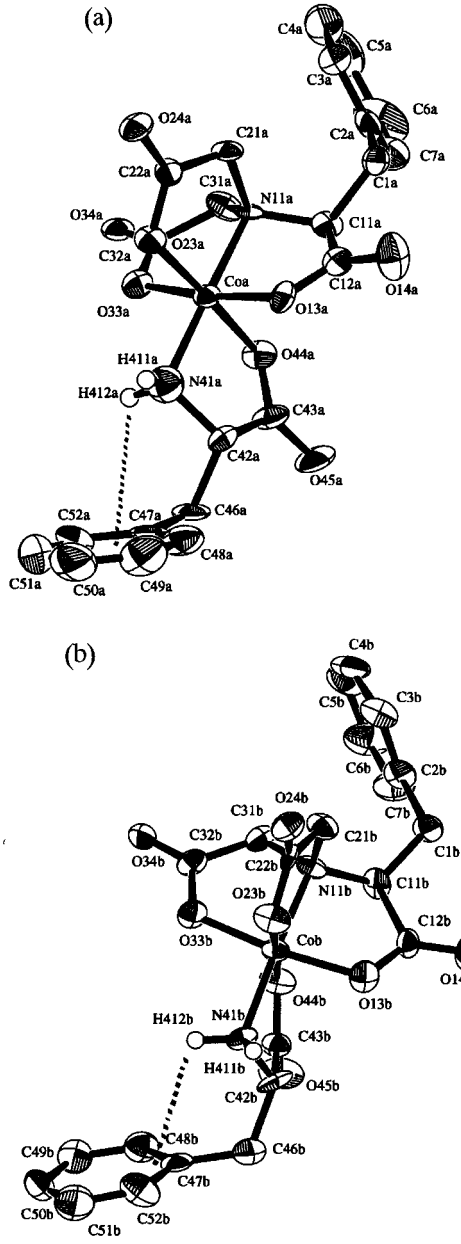


Figure 2. ORTEP drawing of *trans*(N)-[Co(bcmpa)((*S*)-phe)]$^-$ anion. The two complex anions revealed, (a) and (b), are independent molecules in the unit cell. The dotted line denotes NH−π interaction.

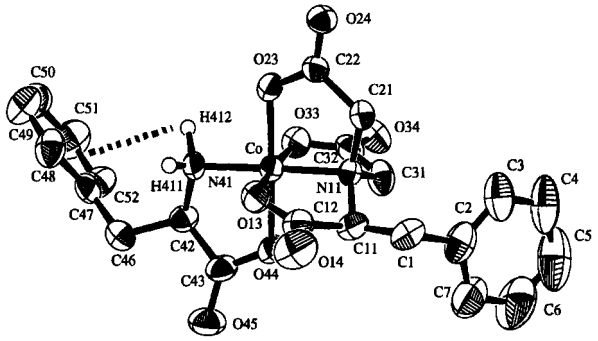


Figure 3. ORTEP drawing of *trans*(N)-[Co(bcmpa)((*R*)-phe)]$^-$ anion. The dotted line denotes NH−π interaction.

(23) *Physical Organic Chemistry*, 2nd ed.; Hammett, L. P., Ed.; McGraw-Hill: New York, 1970.

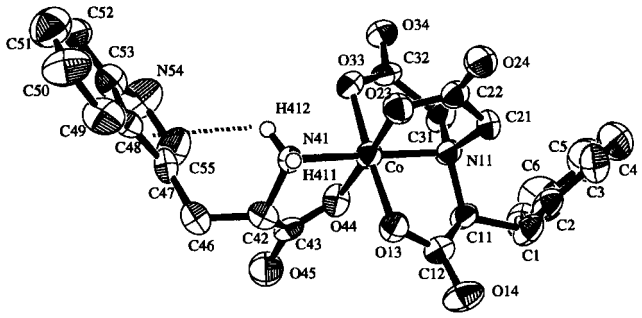


Figure 4. ORTEP drawing of *trans*(N)-[Co(bcmpa)((*S*)-trp)]$^-$ anion. The dotted line denotes NH−π interaction.

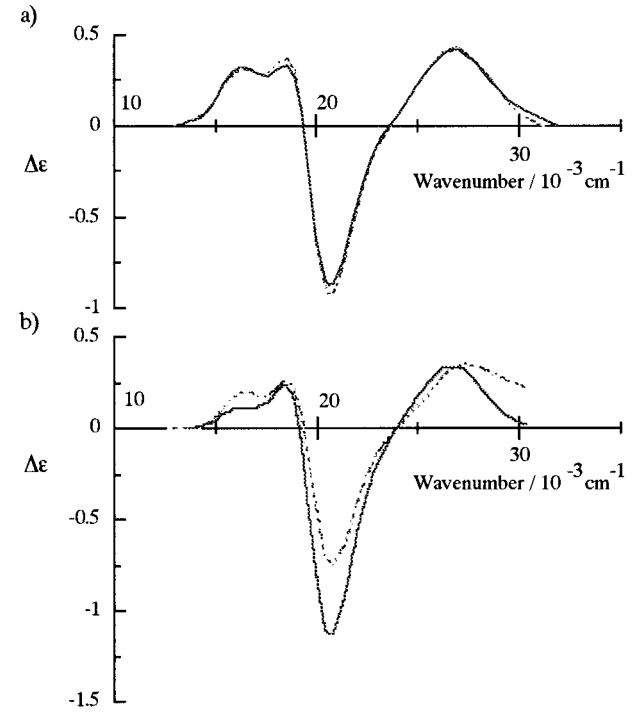


Figure 5. CD spectra of *trans*(N)-K[Co(bcmpa)((*S*)-ala)] (a) and *trans*(N)-K[Co(bcmpa)((*S*)-trp)] complexes (b): in aqueous (---) and ethanol solutions (···).

withdrawing groups, indicating that greater electron density on the aromatic ring results in a larger shielding effect.

As indicated above, the two amino proton peaks at the higher and lower sides for the Co(III) complexes with aromatic amino acids such as (*S*)-Trp, (*S*)-Phe, (*R*)-Phe, (*S*)-Mephe, and (*S*)-Tyr were observed in the ranges of 5.34−5.81 ppm and 7.02−7.26 ppm, respectively, while those for the Co(III) complexes with aliphatic amino acids such as (*S*)-Ala and (*S*)-Leu were detected in the ranges of 6.01−6.29 ppm and 7.22−7.40 ppm, respectively. It is obvious that complexes with aromatic amino acids showed significant upfield shifts compared with those with aliphatic ones. The higher-side peaks undergo larger ring current effect in comparison with the lower-side ones. The shielding effect may be estimated from the crystal structures according to Bovey's equation[24] if the conformations of the amino acid residues established in the crystal structures are maintained also in the solution. In the crystal structure, one of the two coordinated amino protons is located just at the position exerting the shielding effect of aromatic ring, but another one slightly

(24) (a) Johnson, C. E.; Bovey, F. A. *J. Chem. Phys.* **1958**, *21*, 1012. (b) Bovey, F. A. *Nuclear Magnetic Resonance Spectroscopy*; Academic Press: New York, 1969.

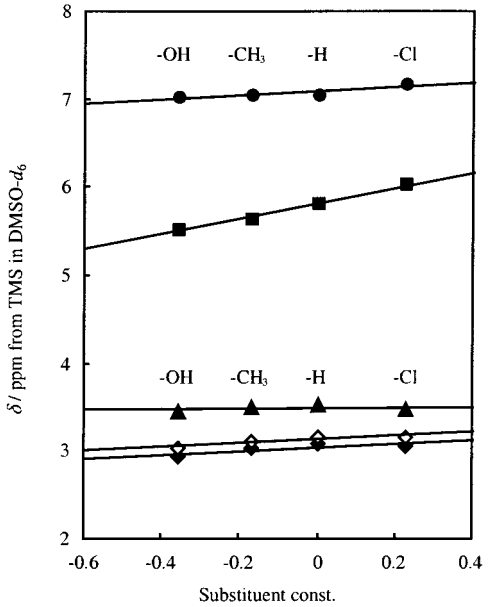


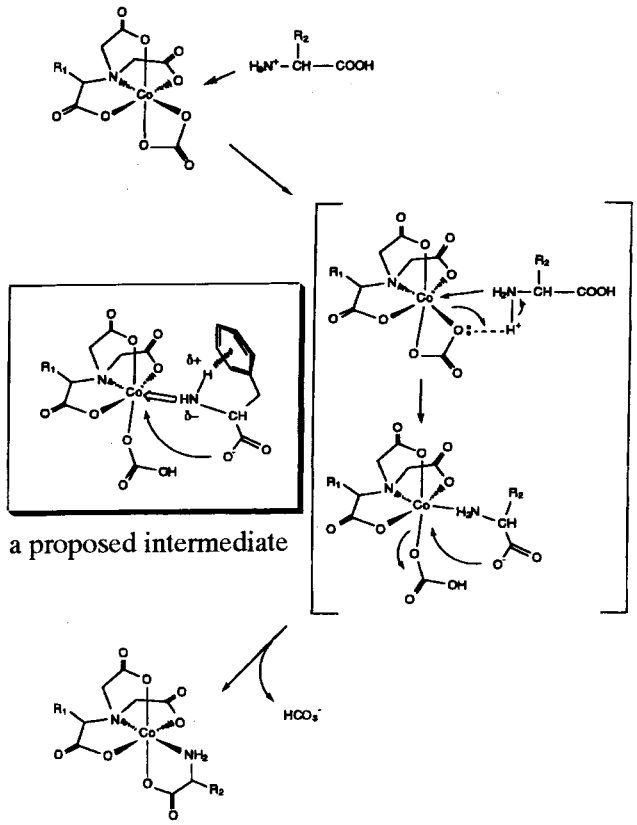
Figure 6. Relationship between the ^{1}H NMR chemical shift values of *trans*(N)-K[Co(nta)(*p*-Xphe)] and the substituent constants (Hammett's rule). ■ and ● denote two NH proton peaks at the higher- and lower-field sides, ▲ α-H, and ◇, ▼ two β-Hs.

deviates from such a position. From the calculation, the former allows us to estimate an 0.5−0.7 ppm upfield shift and the latter a −0.05 to −0.01 ppm shift. The upfield shift values experimentally obtained from NMR, ∼0.35 and ∼0.20 ppm upfield shifts of higher- and lower-side peaks, respectively, agree rather well with the calculated values, even taking into consideration of the free rotation around the amino acid side chains. The results obtained from Bovey's equation reflect only the geometry of the hydrogen atoms for the aromatic ring and do not estimate the strength of the hydrogen bond. However, the geometries of the NH−π interaction, which is defined as the angle and distance of N−H bond vector on the aromatic ring, is considered to be almost the same for all cases of the compounds treated in this study, on the basis of the crystal structures. Thus, we can consider that the hydrogen bond strength in NH−π interaction depends on the distance between the NH hydrogen and aromatic ring center. The tendency in upfield shifts according to Hammett's rule (Figure 6) indicates that the NH−π interaction is an attractive force such as hydrogen bonding.

The above findings suggest that the attractive force found in the crystal structures may be maintained even in polar solvents such as DMSO, although it may be weaker than a hydrogen bond. In fact, these data show greater correspondence with Hammett's rule.

NH−π Interaction in the Ligand-Substitution Reaction of the Carbonato Cobalt(III) Complex with Amino Acids. The ligand-substitution reaction of the $K_2[Co(L)(CO_3)]$ complex with amino acids described above proceeded efficiently in the case of the aromatic amino acids. Although the reaction mechanism is currently not clarified in detail, the mechanism may reasonably be speculated as follows: Under neutral conditions in aqueous solution, the substitution reaction of the carbonato ligand by the amino acids may proceed through a nucleophilic attack of the amino group of the amino acids on the central Co(III) atom as shown in Scheme 2. At this stage, the basicity of the amino nitrogen atom may significantly contribute to the ligand-substitution reaction of the Co(III) complex with amino acids. The attractive interaction occurring

Scheme 2



between the N−H and the aromatic system, as depicted in Scheme 2, will cause the electron density to increase on the amino group through a polarization effect. This should lead to rapid reaction of the Co(III) complexes with aromatic amino acids. Considering that the NH−π interaction between the amino NH_2 group and aromatic amino acid side chain proximal to each other is necessarily more enhanced in an aqueous solution because of hydrophobic hydration, it is reasonable to conclude that the ligand-substitution reaction of the Co(III) complexes with the aromatic amino acids proceeds efficiently in comparison with those with aliphatic ones.

Conclusion

The NH−π interaction has been detected in the crystal structures of the Co(III) ternary complexes with tripodal tetradentate ligand, BCMPA, and aromatic amino acids such as (*S*)-Phe, (*R*)-Phe, and (*S*)-Trp. The CD and ^{1}H NMR spectra gave effective supporting data for the NH−π interaction: Only the Co(III) complexes with aromatic amino acids demonstrated an unambiguous solvent effect in their CD spectra and specific upfield shifts of the coordinating amino proton peaks in the NMR spectra. These findings clearly indicate the existence of NH−π interaction also in solution. The efficient formation reaction of the Co(III) complexes with aromatic amino acids in comparison with those with aliphatic amino acids was interpreted in terms of contribution of the NH−π interaction as one of the most important promotion factors. It is of importance that the NH−π interaction was characterized in the complexes involving aromatic amino acids. Future studies should be undertaken to understand the role of this interaction in the biological systems.

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Supporting Information Available: ^{1}H NMR spectral data for *trans*(N)-K[Co(nta)(aa)] and *trans*(N)-K[Co(bcmpa)(aa)] (Tables S1 and S2, respectively), electronic absorption and CD spectral data of *trans*(N)-K[Co(bcmpa)(aa)] complexes (Table S3), and X-ray crystallographic data (atomic coordinates, isotropic and anisotropic thermal parameters, and selected bond lengths and angles) for complexes K[Co(bcmpa)((*S*)-phe)]·3.5H_2O, K[Co(bcmpa)((*R*)-phe)]·2H_2O, and K[Co(bcmpa)((*S*)-trp)]·2H_2O. This material is available free of charge via the Internet at http://pubs.acs.org.

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