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Enhanced Stability of Binary and Ternary Copper(II) Complexes with Amino Acids: Importance of Hydrophobic Interaction between Bound Ligands

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Formation of binary or ternary copper(II) complexes with amino acids is enhanced by the noncovalent interaction between side chains of the amino acids. The enhanced stability was discussed on the basis of the mechanistic considerations for copper(II) complex formation. The extra stabilization was linearly correlated to the hydrophobicity of the side chains of both aromatic and aliphatic amino acids. The optical selectivity of the formation of copper(II) dipeptide was also successfully correlated to the hydrophobicity of the side chains of coordinated peptides.

Noncovalent interactions between coordinated ligands in binary or ternary metal complexes have recently received much attention, and they have been the subject of extensive studies on specific interactions such as intercalation occurring in proteins, enzymes, DNA, and RNA.[2] Among the noncovalent interactions, the aromatic ring stacking has been discussed extensively, on the basis of equilibrium, CD, and NMR studies.[3-6] Sigel et al. observed the enhanced stability constant of ternary complexes involving 1,10-phenanthroline, copper(II) or zinc(II), and phenylalkanecarboxylates and attributed the enhancement to the stacking between aromatic ligands.[3b] The increased stability of stacked palladium complexes involving bipyridine and aromatic dipeptides has been evaluated as 0.2-1.7 logarithmic units by Yamauchi et al.[6c] The stacking also enhances the rate of complex formation.[7] These investigations reasonably indicate the importance of hydrophobic ligand-ligand interactions involving aromatic ring stacking.

We have reported the enhanced rate of metalloporphyrin formation in the presence of amino acids, which has been interpreted as being due to the hydrophobic interaction of the side chain of the amino acid with the porphyrin plane.[8] The present paper describes the extra stabilization of binary and ternary copper(II) complexes resulting from hydrophobic interactions of amino acid side chains.

We have proposed the following equations for the formation constants of ternary complexes of copper(II) CuAL and higher complexes CuL_n, on the basis of mechanistic considerations:[9-11]

$$\log K_{CuAL}^{L} = \log K_{CuL}^{L} + (\log K_{os(CuA,L)} - \log K_{os(Cu,L)}) + \sum_{I<}^{I}\sum_{J}^{J}\delta_{ij}X_i(A)\ Y_j(L) \quad (1)$$

$$\log K_{CuL_n}^{L} = \log K_{CuL}^{L} + (\log K_{os(CuL_{n-1},L)} - \log K_{os(Cu,L)}) + \sum_{I<}^{I}\sum_{J}^{J}\delta_{ij}X_i(L)\ Y_j(L) - \log n \quad (2)$$

where $K_{os(CuA,L)}$ and $K_{os(Cu,L)}$ denote formation constants of the outer-sphere complexes [CuA,L] and [Cu,L], respectively, δ_{ij} denotes the effect of the donor atom X_i in the ligand A (or L) on the donor atom Y_j in the ligand L, and $X_i(A)$ (or $X_i(L)$) and $Y_j(L)$ denote the number of the donor atoms X_i in A (or L) and Y_j in L, respectively. The term log n provides the statistical correction for the number of ways that CuL_n can dissociate. Formation constants are defined as

$$K_{CuAL}^{L} = [CuAL][CuA]^{-1}[L]^{-1}$$

$$K_{CuL_n}^{L} = [CuL_n][CuL_{n-1}]^{-1}[L]^{-1}$$

$$K_{CuL}^{L} = [CuL][Cu]^{-1}[L]^{-1}$$

Charges are omitted for simplicity.

The first step of the coordination of amino acids to copper(II) is the coordination of the noncharged amino nitrogen.[10] Then, for amino acids, the second term involving formation constants of outer-sphere complexes may be dropped:

$$\log K_{CuAL}^{L} = \log K_{CuL}^{L} + \sum_{I<}^{I}\sum_{J}^{J}\delta_{ij}X_i(A)\ Y_j(L) \quad (3)$$

$$\log K_{CuL_n}^{L} = \log K_{CuL}^{L} + \sum_{I<}^{I}\sum_{J}^{J}\delta_{ij}X_i(L)\ Y_j(L) - \log n \quad (4)$$

We have the following donor atom-donor atom interaction terms: $\delta_{N(al)N(al)} = -0.35(+2.00\ kJ)$; $\delta_{N(al)O} = -0.26(+1.48\ kJ)$; $\delta_{OO} = -0.29(+1.65\ kJ)$. N(al) and O denote aliphatic nitrogen and carboxylate oxygen donors, respectively. The preceding equations (eq 3 and 4) enabled us to predict formation constants of a number of copper(II) complexes involving amines and amino acids.[10-12] The formation constants of copper(II) complexes involving 2,2'-bipyridine and oxygen donor(s) have also been quantitatively accounted for in terms of donor atom-donor atom interactions according to the proposed equations. However, we notice extra stabilization of some binary or ternary copper(II) complexes as compared to the cases where the constants are predicted from eq 3 and 4. We attempted to correlate the extra stabilization given by the following with the hydrophobicity scale:[13]

$$\Delta \log K_{CuAL}^{L} = \log K_{CuAL}^{L}(obsd) - \log K_{CuAL}^{L}(calcd) \quad (5)$$

$$\Delta \log K_{CuL_n}^{L} = \log K_{CuL_n}^{L}(obsd) - \log K_{CuL_n}^{L}(calcd) \quad (6)$$

Formation constants of some copper(II) complexes with amino acids are summarized in Table I together with the hydrophobicity scale for side chains of amino acids.[13] In Figure 1, the enhanced formation constant is plotted against the hydrophobicity scale of

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Table I. Enhanced Stability Constants of Binary and Ternary Copper(II) Complexes with Amino Acids[a]

no.	HL	HA	$\log K_{CuL}^{L}$ obsd	$\log K_{CuAL}^{L}$ obsd	$\log K_{CuAL}^{L}$ calcd	$\log K_{CuAL}^{L}$ diff	$\sum\Delta G_t$,[b] kJ/mol	ref.
1	Gly	Gly	8.22	6.89	6.76	0.13	0	15
2	Gly	Ala	8.22	7.18	7.06	0.12	2.1	15
3	Gly	Ser	8.22	7.17	7.06	0.11	−1.3	15
4	Gly	Thr	8.22	7.21	7.06	0.15	1.7	15
5	Gly	Tyr	8.22	7.43	7.06	0.37	9.6	15
6	Gly	Phe	8.22	7.44	7.06	0.38	10.5	15
7	Ala	Ala	8.18	6.81	6.72	0.09	4.2	15
8	Ala	Ser	8.18	7.19	7.02	0.17	0.8	15
9	Ala	Thr	8.18	7.20	7.02	0.18	3.8	15
10	Ala	Tyr	8.18	7.42	7.02	0.40	11.7	15
11	Ala	Phe	8.18	7.38	7.02	0.36	12.6	15
12	Val	Val	8.05	6.86	6.59	0.27	12.6	16
13	Val	Tyr	8.05	7.50	6.89	0.61	15.9	6a
14	Leu	Leu	8.19	6.94	6.73	0.21	15.0	3d
15	Ser	Ser	7.93	6.64	6.47	0.17	−2.6	15
16	Ser	Thr	7.93	6.92	6.77	0.15	0.4	15
17	Ser	Tyr	7.93	7.15	6.77	0.38	8.3	15
18	Ser	Phe	7.93	7.14	6.77	0.37	9.2	15
19	Met	Met	7.85	6.68	6.39	0.29	10.8	16
20	Thr	Thr	8.03	6.74	6.57	0.17	3.4	15
21	Thr	Tyr	8.03	7.25	6.87	0.38	11.3	15
22	Thr	Phe	8.03	7.23	6.87	0.36	12.2	15
23	Tyr	Tyr	7.81	6.93	6.35	0.58	19.2	15
24	Tyr	Phe	7.85	7.37	6.69	0.68	20.1	6a
25	Tyr	Trp	7.85	7.45	6.69	0.76	23.8	6a
26	Phe	Phe	7.86	6.91	6.40	0.51	21.0	15
27	Trp	Trp	8.02	7.54	6.56	0.98	28.4	16

[a] HL and HA denote the neutral form of the amino acid, and abbreviations of amino acids are as follows: Gly, glycine; Ala, alanine; Val, valine; Leu, leucine; Ser, serine; Met, methionine; Thr, threonine; Tyr, tyrosine; Phe, phenylalanine, Trp, tryptophan. [b] Total hydrophobicity scale of amino acid side chains.

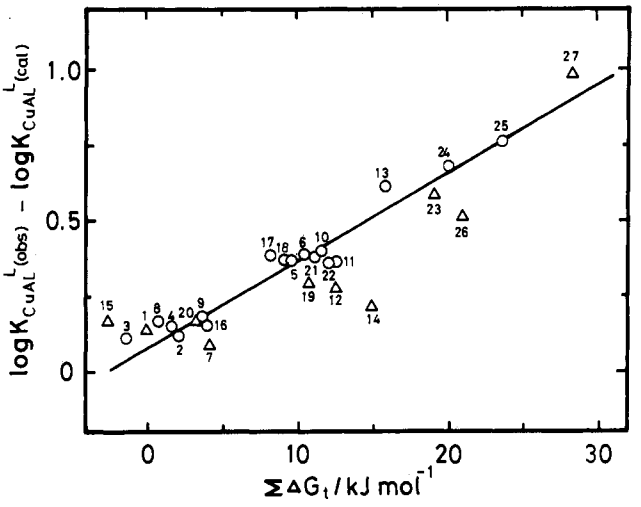

Figure 1. Correlation between enhanced stability of binary or ternary copper(II) complexes involving amino acids and hydrophobicity scale of amino acid side chains ($\Sigma\Delta G_t$/kJ mol^{-1}): CuAL, ○; CuL_2, △. Refer to Table I for an explanation of the numbers.

amino acid side chains. Table I and Figure 1 tell us clearly the following points: (1) In complexes **1–4**, **7–9**, **15**, **16**, and **20** no extra stabilization occurs. (2) In complexes **5**, **6**, **10–12**, **14**, **17–19**, and **22** the extra stabilization is small but evident. (3) Enhanced stability of complexes **13** and **23–27** is appreciable because of the significant hydrophobic interaction between the bound ligands. (4) The increased stability is linearly correlated with the hydrophobicity scale of amino acid side chains: L-Trp gives the largest increase in the formation constant among them. These findings are in agreement with the qualitative observation that the extent of the intramolecular interaction in the complexes increases in the order aliphatic–aliphatic < aliphatic–aromatic < aromatic–aromatic.[3d]

Structural factors are important in the ligand–ligand interaction. Since the hydrophobicity scale is determined from the solubility of amino acids in various mixed aqueous solutions of ethanol or dioxane,[13] the scale seems to be independent of the structure of amino acid side chains. However the ligand–ligand interaction is favored for aromatic or bulky aliphatic side chains with high hydrophobicity scales, while it is not favored for small aliphatic chains with low hydrophobicity scales. Thus the extra stabilization correlates with the hydrophobicity scale even for somewhat sterically different amino acids, as shown in Figure 1.

Interestingly, a small but definite extra stabilization is observed for CuAL (L = Gly, A = Tyr or Phe), where no hydrophobic interaction is anticipated between bound ligands. In these cases the extra stabilization may result from other factors such as change in water structure around complexes and/or easy access of tyrosine and phenylalanine to the hydrophobic part of $Cu(gly)^+$ in complexation. Nevertheless, in this case too, the hydrophobicity of the side chain has an influence on the stability increase. Similar extra stabilization was also observed for $Cu(en)(tyr)^+$ and $Cu(en)(phe)^+$ compared to $Cu(en)(ala)^+$ (where en denotes 1,2-diaminoethane).[6b]

Yamauchi et al. reported that ternary complexes involving aromatic amines, copper(II), and amino acids are stabilized in the order alanine < valine < phenylalanine < tyrosine < triptophan < 5-hydroxytriptophan.[6b] The order is parallel to the hydrophobicity scale of amino acid side chains. Similar stabilization by the hydrophobic interaction of side chains has also been found in a series of aliphatic and aromatic unidentate amines coordinated to dipeptide–Pd complexes.[4]

Recently Bonomo et al. have shown the preferential formation of copper(II) complexes of optically homogeneous depeptides compared to D,L-dipeptides.[14] The increased overall stabilities of copper(II) dipeptides ($\Delta \log \beta_{1-11} = \log \beta_{1-11}$(L,L-dipeptide) $- \log \beta_{1-11}$(D,L-dipeptide) are 0.07, 0.27, 0.37, 0.73, 0.47, and 0.62 for copper(II) complexes with alanylalanine, methionylmethionine, methionylvaline, leucylleucine, methionylphenylalanine, and le-

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ucylisoleucine, respectively. The increased stability ($\Delta \log \beta_{1-11}$) is also linearly correlated with the hydrophobicity scale.

The present paper confirms the importance of hydrophobic interactions between aliphatic as well as aromatic ligands in the complex formation and correlates successfully the enhanced stability of both binary and ternary copper(II) complexes with the hydrophobicity of side chains of coordinated amino acids.

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Variable-Pressure Oxygen-17 NMR Studies on Acetic Acid Exchange of Manganese(II) Perchlorate and Manganese(II) Acetate[1]

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Acetic acid exchange of manganese(II) perchlorate and manganese(II) acetate in acetic acid (HOAc) involving dichloromethane-d_2 as a diluent has been studied at various pressures up to 180 MPa by the variable-pressure ^{17}O FT-NMR line-broadening method. The activation volumes at 258 K are $+0.4 \pm 0.7$ cm^3 mol^{-1} for $Mn(ClO_4)_2$ and $+6.7 \pm 0.6$ cm^3 mol^{-1} for $Mn(OAc)_2$, respectively. These positive values are unusual for the solvent exchange on manganese(II) studied so far and are discussed in terms of the bulkiness of acetic acid molecules and the effect of the ligand bound to the manganese(II).

Introduction

The activation volume, ΔV^*, is now accepted as a criterion of the activation mode of a variety of inorganic reactions in solution such as the solvent exchange on metal cations and the formation of metal complexes.[2-5] We have measured the activation volumes for the formation of some metal complexes by the high-pressure stopped-flow method, and the following results were obtained.[6-9] The activation volume for the complex formation of iron(III) greatly depends on the bulkiness of both the solvent molecule and the ligand; the bulkier the solvent molecule or the ligand, the less associative the activation mode. These findings indicate that it is difficult for the bulky entering ligand to enter into the inner-coordination sphere of a metal cation and that the activation mode becomes less associative for bulkier solvents or bulkier entering ligands, which make the inner-coordination sphere of metal cation sterically more crowded in the activation state. This phenomenon would be significant for the reactions of metal ions such as high-spin d^5 iron(III) that proceed via an associative activation mode in a nonbulky solvent such as water.[6,7] On the other hand, the activation volumes for the complexation of the d^8 nickel(II) ion are positive even in a nonbulky solvent such as water, acetonitrile, or methanol and are not as sensitive to the bulkiness of solvent and ligand molecules as in the case of iron(III); the complex formation of nickel(II) always proceeds via a dissociative interchange (Id) mechanism.[8]

Recently, the exchange of *N*,*N*-dimethylformamide (DMF) on high-spin d^5 manganese(II) was studied[10,11] and a small but positive value was observed, though the solvent exchange on this cation is known to proceed via an associative interchange mechanism in nonbulky solvents such as water,[12] methanol,[13] and acetonitrile.[14] We have already reported the kinetic parameters, except for the activation volume, for the acetic acid exchange of manganese(II) perchlorate[15] and manganese(II) acetate.[16] We have measured the activation volumes for these reactions at 258 K by the variable-pressure ^{17}O FT-NMR line-broadening method. On the basis of the activation volumes, we will discuss the effect of the bulkiness of acetic acid and the bound ligand effect on the activation mode of the solvent exchange of manganese(II).

Experimental Section

Variable-Pressure NMR Measurements. For variable-pressure ^{17}O NMR experiments, a high-pressure NMR probe fitted with the electromagnet (2.34 T) of a JEOL JNM-FX100 FT-NMR spectrometer operating at 13.50 MHz was constructed. The probe consists of two separable parts: an aluminum support with a tuning network, shim coils, etc. and a pressure vessel. The pressure vessel consisting of three separable parts is illustrated in Figure 1A. The pressure cylinder (1) made of nonmagnetic titanium alloy is covered with a copper cylinder inside of which a spiral is cut. The thermostating nitrogen gas is circulated along the spiral in order to adjust the temperature in the pressure vessel. An adapter (2) made of titanium alloy is attached to facilitate insertion and withdrawal of the sample tube. The pressure cylinder is connected to an electrical terminal (3) into which the leading wires for the radio-frequency coil and copper–constantan thermocouple are introduced with small cones soldered separately to seal the pressure. The pressure sealing in other parts is achieved with a cone-type seal and O-ring seals.

The sample tube, illustrated in Figure 1B, is filled with the sample solution. The flexible Teflon cap (j) and the piston (k) transmit the hydrostatic pressure to the sample solution. The piston and the contractive Teflon tube (l) completely protect the sample solution in the glass tube (m) from contamination by the surrounding pressure-transmitting liquid.

The pressure vessel is connected through the flexible tube (SUS316; 1.702-mm o.d., 0.305-mm i.d.) to a pressure-generating system consisting

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