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Structural and Electronic Effects on Complex Formation of Copper(II) and Nickel(II) with Sulfhydryl-Containing Peptides

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Potentiometric and visible spectral measurements in aqueous solutions have been performed on Ni(II) and Cu(II) complexes containing a series of sulfhydryl peptides. The peptide ligands used were those which revealed the effect of stereo- and electrochemical variations on the formation of the deprotonated metal complexes. The formation constants (log K_1K_c) of the Ni(II) and Cu(II) complexes increase in the order 6–6 < 6–5 < 5–6 < 5–5 fused-ring systems. The d–d band of the Cu(II) complexes shifts linearly to a shorter wavelength with the order $(CH_3)_2CH < CH_3 < Ph–CH_2 < Ph$, consistent with the order of Taft's polar substitution constants. Some additional coordinated heterocyclic bases give a linear blue shift of the original bands with the order of the basicity of the bases. Complexes differing only in donor atoms more readily increase the stability in the order NNO < SNO < SNS donor sets.

Introduction

Considering the importance of sulfhydryl groups of cysteine residues in active sites of metalloproteins, it is surprising that only a few studies have been reported concerning the interaction of the sulfhydryl-containing peptides with biologically interesting metal ions. Holm and his colleagues[1] have reported some electronic and reactivity properties of Fe_4S_4–glycyl-L-cysteinylglycyl oligopeptide complexes as synthetic analogues of the active sites of iron–sulfur proteins. We have also found that reaction of a dicysteinyl peptide with a Fe(III) salt and sulfide in a aqueous solution yielded a species whose electronic spectrum was similar to that of two-iron ferredoxins.[2] Molybdenum(V)–glutathione complexes have been investigated as a model for molybdenum–enzyme interaction.[3] However, the copper(II)–sulfhydryl–containing peptides interaction which is of interest insofar as it is connected with the "blue" copper center has never been studied. Although the constitutions of the "blue" copper coordination groups have yet to be clarified, possible ligand atoms are nitrogen, oxygen, and sulfur. Sulfhydryl coordination has been suggested by *p*-mercuribenzoate binding studies on azurin,[4] plastocyanin,[5] and stellacyanin[6] and confirmed for stellacyanin by spectroscopic characterization of a Co(II) derivative.[7] Resonance Raman spectra of the "blue" copper proteins consisted of three or four bands between 350 and 470 cm^{-1}, which are assignable to Cu–N or Cu–O bond stretching, and a weak band near 270 cm^{-1}, which probably arises from Cu–S stretching.[8,9] Miskowski et al.[8] have proposed that the "blue" copper site involves approximately trigonal-bipyramidal coordination, with a sulfur and two nitrogen ligands in the equatorial plane and less strongly bound nitrogen or oxygen ligands at axial positions. On the basis of the model system approach for reduction potentials of the "blue" copper proteins, Patterson and Holm[10] have suggested a ligand structure including one thiolate sulfur and some histidyl groups. A suitable model sulfur–copper(II) chromophore has never been reported, however, presumably because of the instability of copper(II)–sulfhydryl complexes. Thiolate sulfur ordinarily reduces Cu(II), with production of disulfide.

Recently, we have isolated and characterized stable α-mercaptopropionylglycine–nickel(II) and –copper(II) complexes which involve sulfhydryl, neighboring deprotonated peptide nitrogen, and terminal carboxylate groups as the coordination sites.[11] Of special note was the fact that the spin-Hamiltonian parameters and the bonding parameters of the Cu(II) complex are very similar to those of the chromophore in the "blue" copper proteins. In devising models of the "blue" copper sites, it would be advantageous to have knowledge of the effect of structural and electronic variations of the ligand on the reaction of Cu(II) and Ni(II) ions with sulfhydryl-containing peptides. Some controlling factors, fused chelate-ring members, substituent groups of the ligand, additional ligands, and chelate donor sets, were investigated herein.

Experimental Section

Materials. A series of sulfhydryl-containing peptides were synthesized by the Schotten–Bauman reaction between the corresponding bromo-substituted aliphatic acid chloride and amino acid (glycine, β-alanine, etc.) followed by a condensation with thiobenzoic acid and then hydrolysis in an ammonia solution.[12] The peptide ligands were recrystallized with ethyl acetate and determined by elemental analysis and iodometric titration. A freshly prepared solution of the ligand was used in each experiment. The nickel and copper solutions (0.01 M) were prepared by dissolving metal(II) nitrate in water and standardized with 0.01 M EDTA solution. A carbonate-free potassium hydroxide solution (0.1 M) was prepared by the method of Armstrong[13] and standardized with potassium hydrogen phthalate. All other reagents used were of commercial reagent grade, and deionized water was used throughout.

Methods. Exactly equimolar amounts of a ligand and Cu(II) (or Ni(II)) were mixed in 18 ml of water and to this was added 2 ml of 1 M KNO_3 to make the concentration 0.004 M. The mixture was titrated with 0.1 N KOH at 20 °C under a nitrogen atmosphere, and the pH values were measured. The ligands were titrated in the absence of Cu(II) or Ni(II) under the same conditions to determine their acid dissociation constants. Potentiometric pH measurements were carried out with a Radiometer titrator, Type TTT-1C. Optical absorption spectra of the complexes were determined in an aqueous solution (pH 6–11) at 20 °C using a Shimadzu recording spectrophotometer, Model Double-40R.

Calculations. When the sulfur peptide reacts with an equimolar amount of Cu(II) or Ni(II), the following two reactions have been shown to occur in solution[11]

$$M^{2+} + L^{2-} \overset{K_1}{\rightleftharpoons} ML \tag{1}$$

$$ML \overset{K_c}{\rightleftharpoons} MA^- + H^+ \tag{2}$$

where L^{2-}, ML, and MA^- denote respectively the free ligand, the neutral complex, and the negative complex formed upon the dissociation of the peptide NH of ML. The equilibrium constants K_1 and K_c are defined as

$$K_1 = [ML]/[M^{2+}][L^{2-}] \tag{3}$$

$$K_c = [MA][H^+]/[ML] \tag{4}$$

Following the modified method of Datta and Rabin,[14] we calculated the K_1 and K_c values from

$$K_1 = \frac{[H^+](\alpha Z - \gamma[L_t])\{K_c(3\alpha-\gamma) + [H^+](2\alpha-\gamma)\}}{K_c\{[M_t](3\alpha-\gamma) - (\alpha Z - \gamma[L_t])\} + [H^+]\{[M_t](2\alpha-\gamma) - (\alpha Z - \gamma[L_t])\}} \times \frac{1}{K_c(3[L_t]-Z) + [H^+](2[L_t]-Z)} \tag{5}$$

Table I. Effect of Fused-Ring Members on Absorption Spectra and Formation Constants

	Fused-ring members	Acid dissociation const pK_1-(COOH)	pK_2-(SH)
α-Mercaptopropionylglycine	5-5	3.60	8.74
α-Mercaptopropionyl-β-alanine	5-6	3.77	8.81
β-Mercaptopropionylglycine	6-5	3.71	9.60
β-Mercaptopropionyl-β-alanine	6-6	3.82	9.69

Formation const: Ni(II) complex			Cu(II) complex[a]			Optical absorption max, nm (ε)	
log K_1	pK_c	log K_1K_c	log K_1	pK_c	log K_1K_c	Ni(II) complex	Cu(II) complex
5.44	6.88	−1.44	7.6	6.2	+1.4	375 (2750), 475 (410)	605 (260)
4.56	7.37	−2.81	7.0	6.7	+0.3	390 (1400), 497 (320)	620 (120)
4.49	7.63	−3.14	6.9	7.0	−0.1	400 (1020), 510 (290)	630 (100)
4.15	8.01	−3.86	6.1	7.6	−1.5	412 (800), 523 (200)	645 (80)

[a] Since the reaction solution has a slight turbidity from $a = 0$ to $a = 2$, the constants obtained are approximate values.

where $\alpha = 1 + [H^+]/K_{a1} + [H^+]^2/K_{a1}K_{a2}$, $\gamma = 2 + [H^+]/K_{a2}$, and $Z = [K^+] + [H^+] - [OH^-]$; K_{a1} and K_{a2} are the acid dissociation constants of the carboxyl and sulfhydryl groups of the peptides, and $[L_t]$ and $[M_t]$ are the total concentrations of ligand and metal, respectively. All of the computations were made with the use of a FACOM 230-60 computer at the Data Processing Center, Kyoto University.

Results and Discussion

Effect of Fused Chelate Ring Members. The acid dissociation and the formation constants for the Ni(II) and Cu(II) complexes of mercaptopropionylglycine and mercaptopropionyl-β-alanine are listed in Table I along with the optical absorption data. From the following relationship obtained by combining eq 3 and 4, the relative stability among the negative complexes, MA^-, is discussed at a constant pH

$$[MA^-]/[M^{2+}][L^{2-}] = K_1K_c/[H^+] \quad (6)$$

Contrary to the order of the basicity of the sulfhydryl groups (pK_2), the K_1K_c values decrease in the order α-MPG > α-MPA > β-MPG > β-MPA in both the Ni(II) and Cu(II) complexes. The 5–5 membered complex is considerably more stable than the 5–6, 6–5, and 6–6 membered complexes. According to the molecular models a greater strain exists if the thiolate of β position and/or the carboxylate of β-alanine moiety are coordinated to the metal ions. On the other hand, it is known that the stability constants of a similar deprotonated Cu(II) complex decrease in the order glycylglycine (log K_1K_c = 1.50) > β-alanylglycine (1.32) > glycyl-β-alanine (1.06) > β-alanyl-β-alanine (-1.3).[15] In this case, however, a difference in the stability between the 5–5 and 6–5 (or 5–6) membered complexes is less than that in the case of the sulfhydryl-containing peptide–copper(II) complexes. We are of the opinion, therefore, that the order is largely related to the steric strain of the fused-ring systems and that the most favored structural choice is the 5–5 fused ring in the chelate formation by the sulfhydryl-containing peptides and the metal ions, especially in the rigid negative complex (MA^-).

The observed stability sequence of the complexes is also in agreement with their absorption maximum wavelength in the visible region. The relative effectiveness in the magnitude of the ligand field around the central metal(II), which is reflected in the λ_{max} values, is found to be 5–5 > 5–6 > 6–5 > 6–6 fused-ring systems. Of interest is a linear correlation between

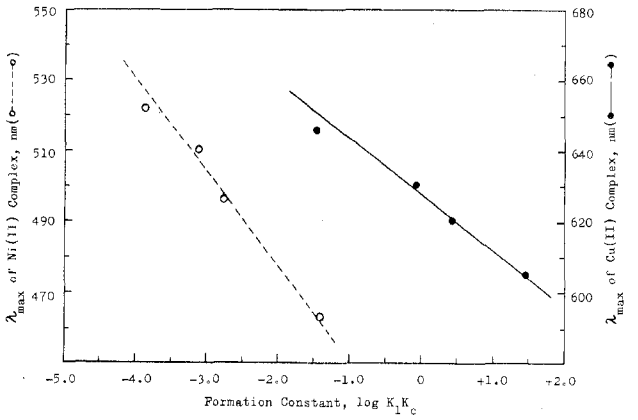

Figure 1. Correlation between absorption bands and formation constants.

Table II. Effect of Substituent Groups on Acid Dissociation Constants and Optical Absorption Characteristics

R in R-CH(SH)CONH-CH_2COOH	Taft's polar substituent σ^*[a]	Acid dissociation const pK_1(COOH)	pK_2(SH)
$(CH_3)_2CH$	−0.19	3.77	9.07
CH_3	0	3.60	8.74
	+0.22	3.47	8.41
	+0.60	3.20	7.80

Optical absorption max, nm (ε): Ni(II) complex	Imidazole adduct of Ni(II) complex	Cu(II) complex	Imidazole adduct of Cu(II) complex
375 (2800), 478 (420)	370 (680), 465 (350)	610 (280)	583 (270)
375 (2750), 475 (410)	370 (650), 463 (350)	605 (260)	580 (250)
375 (2900), 470 (420)	370 (700), 462 (370)	597 (290)	575 (270)
375 (3500), 466 (480)	370 (720), 460 (370)	590 (330)	570 (330)

[a] R. W. Taft, *J. Am. Chem. Soc.*, 75, 4231 (1953).

the K_1K_c values and λ_{max} values of the sulfhydryl-containing peptide–metal(II) complexes (see Figure 1).

Effect of Substituent Groups of Ligand. The effect of substituent variation on complex formation of the metal(II) ions with the 5–5 fused-ring forming ligands was studied. Several features are evident in the data of Table II. The acid dissociation constants of the ligands increase to more basicity in the order Ph < Ph–CH_2 < CH_3 < $(CH_3)_2CH$, consistent with increasing electron-releasing tendencies of the groups as expressed by Taft's polar substituent constants. Especially in the Cu(II) complex, the d–d band near 600 nm is obviously affected by the substituents in a manner which affords linear correlations of λ_{max} values with the appropriate substituent constants. The shift to a shorter wavelength in the order $(CH_3)_2CH$ < CH_3 < Ph–CH_2 < Ph is in the reverse order of the basicity of the sulfhydryl groups. The result indicates that the electron-withdrawing groups have an effect on stabilization of the complex MA^-. The stability of the green color and the facility with which these Cu(II) complexes can be isolated are apparently in good keeping with the order. It was reported very recently that the Cu(II)–Cu(I) redox potentials shift to more negative values in the order CF_3 < Ph < CH_3, consistent with increasing electron-releasing tendencies of the groups as expressed by Hammett σ_p, σ_m, or inductive constants

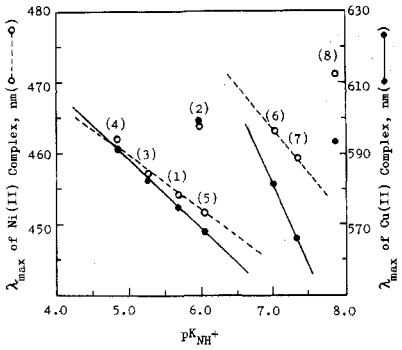

Figure 2. Correlation between shift of main absorption bands and basicity of heterocyclic bases. The numbers indicate ligands: (1) pyridine; (2) 2-methylpyridine; (3) 3-methylpyridine; (4) 4-methylpyridine; (5) quinoline; (6) imidazole; (7) 1-methylimidazole; (8) 2-methylimidazole.

exclusive of resonance.[10] Of interest is the fact that electron-withdrawing groups, as well as sulfur donors and unsaturated nitrogen-donor ligands such as imidazole and bipyridine, promote positive shifts of the potentials, because of the high redox potentials (0.2–0.8 V) of the "blue" copper proteins.

Effect of Additional Ligands. An additional binding of some heterocyclic bases to the original sulfhydryl-containing peptide–nickel(II) and –copper(II) complexes was investigated by the visible spectra. It was found, in both the Ni(II) and Cu(II) complexes, that the maximum absorption bands shift linearly to a shorter wavelength with the order of the basicity in pyridine and imidazole ligands added, except for the case of 2-methyl derivatives (see Figure 2). Replacement of aquo ligand by pyridine or imidazole ligand leads to a high ligand field and causes a shift of the visible bands to a higher frequency. A greater shift of 4(or 3)-methyl derivatives is attributed to the inductive effect of 4(or 3)-methyl group and a smaller shift of 2-methyl derivatives to the steric interference. On the contrary, the addition of 4-chloro(or cyano)pyridine involving a electron-withdrawing group and of 2,2-bipyridine, *o*-phenanthroline, and acridine involving complicating steric factors had no effect on the original spectra of the Ni(II) and Cu(II) complexes.

Effect of Chelate Donor Sets. The influence of donor atom changes in the planar Ni(II) and Cu(II) complexes is expressed in Table III where the species with SNO donor sets are taken as references. The order of increasing ligand field is NNO < SNO < SNS, where the donor atom portion of the ligand has been varied. The most interesting feature is the blue shift of 25–30 nm upon replacing nitrogen or oxygen by the sulfur donor in the Cu(II) complexes. It is apparent, therefore, that the sulfhydryl group of the square plane has more influence of the ligand field than does the amino or carboxyl group. In the Cu(II) complexes of nitrogen-containing peptides, on the other hand, Bryce and Gurd[16] have indicated the relative effectiveness in lowering the λ_{max} values of the three nitrogen-containing groups to be α-amino > peptide > imidazole nitrogens.

In conclusion, these structural and electronic effects can be summarized as follows: (i) the tendency of forming the deprotonated Ni(II) and Cu(II) complexes was increased in the order 6–6 < 6–5 < 5–6 < 5–5 fused-ring systems, and the replacement of 6- by 5-membered ring gave a blue shift of 10–15 nm; (ii) the visible band of the Cu(II) complexes shifted linearly with the order $(CH_3)_2CH$ < CH_3 < Ph–CH_2 < Ph, and the substituent groups of the ligands gave a blue shift of 10 nm/0.4 of σ^*; (iii) the visible bands of the Ni(II) and Cu(II) complexes shifted linearly with the order of the basicity in the heterocyclic bases added, and the additional ligands gave a blue shift of 10–20 nm/log unit of acid dissociation constants in the pyridine ligands; (iv) the ligand field was increased in the order NNO < SNO < SNS donor sets, and the replacement of N or O by S donor gave a blue shift of 25–30 nm in the Cu(II) complexes. In particular, it is emphasized that the sulfhydryl sulfur donors have high binding affinity not only for Cu(I), being a "soft" metal,[17] but also for Cu(II), being a "hard–soft" borderline metal. Accordingly, if the "blue" copper center has a Cu–S bond, it would be favorably maintained upon redox process.

Table III. Effect of Donor Sets on Absorption Spectra and Formation Constants

	Donor set	Absorption max, nm (ϵ) Ni(II) complex	Cu(II) complex
α-Mercaptopropionyl-cysteine	SNS	410 (1200), 567 (450)	405 (700), 580 (280)
α-Mercaptopropionyl-glycine	SNO	375 (2750), 475 (410)	400 sh, 605 (260)
α-Mercaptopropionyl-phenylglycine	SNO	375 (2600), 475 (470)	400 sh, 603 (240)
Alanylglycine[a]	NNO	*b*	635 (90)

Acid dissociation const			Formation const: Ni(II) complex			Cu(II) complex		
pK_1	pK_2	pK_3	log K_1	pK_c	log K_1K_c	log K_1	pK_c	log K_1K_c
3.29	8.48	10.22	11.38	8.59	+2.79	14.7	8.0	+6.7
3.60	8.74		5.44	6.88	−1.44	7.6	6.2	+1.4
3.08	8.66		5.21	6.57	−1.36	7.4	6.0	+1.4
3.23	8.15		*b*	*b*	*b*	5.48	4.28	+1.20

[a] G. F. Bryce, J. M. H. Pinkerton, L. K. Steinrauf, and F. R. N. Gurd, *J. Biol. Chem.*, 240, 3829 (1965). [b] The reaction between Ni(II) and alanylglycine, as well as glycylglycine [H. C. Freeman, "Inorganic Biochemistry", G. L. Eichhorn, Ed., Elsevier, Amsterdam, 1973, pp 121–166], is apparently anomalous and forms a blue-green octahedral complex.

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Registry No. Ni(II)–α-MPG complex, 57719-54-7; Ni(II)–α-MPA complex, 57719-55-8; Ni(II)–β-MPG complex, 57719-56-9; Ni(II)–β-MPA complex, 57719-57-0; Cu(II)–α-MPG complex, 57719-58-1; Cu(II)–α-MPA complex, 57719-59-2; Cu(II)–β-MPG complex, 57719-60-5; Cu(II)–β-MPA complex, 57719-41-2; Ni(II)–$(CH_3)_2CHCH(SH)CONHCH_2COOH$ complex, 57719-42-3; Ni(II)–$PhCH_2CH(SH)CONHCH_2COOH$ complex, 57719-43-4; Ni(II)–$PhCH(SH)CONHCH_2COOH$ complex, 57719-44-5; Cu(II)–$(CH_3)_2CHCH(SH)CONHCH_2COOH$ complex, 57719-45-6; Cu(II)–$PhCH_2CH(SH)CONHCH_2COOH$ complex, 57719-46-7; Cu(II)–$PhCH(SH)CONHCH_2COOH$ complex, 57719-47-8; imidazole–Ni(II)–$(CH_3)_2CHCH(SH)CONHCH_2COOH$ complex, 57761-87-2; imidazole–Ni(II)–α-MPG complex, 57719-48-9; imidazole–Ni(II)–$PhCH_2CH(SH)CONHCH_2COOH$ complex, 57719-49-0; imidazole–Ni(II)–$PhCH(SH)CONHCH_2COOH$ complex, 57719-50-3; imidazole–Cu(II)–$(CH_3)_2CHCH(SH)CONHCH_2CO_2H$ complex, 57761-84-9; imidazole–Cu(II)–α-MPG complex, 57719-51-4; imidazole–Cu(II)–$PhCH_2CH(SH)CONHCH_2COOH$ complex, 57719-52-5; imidazole–Cu(II)–$PhCH(SH)CONHCH_2COOH$ complex, 57719-53-6; pyridine, 110-86-1; 2-methylpyridine, 109-06-8; 3-methylpyridine, 108-99-6; 4-methylpyridine, 108-89-4; quinoline, 91-22-5; 1-methylimidazole, 616-47-7; 2-methylimidazole, 693-98-1.

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Molecular Orbital Studies on the Optical Activity of Chiral Four-Coordinate Copper(II) Systems

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The chiroptical properties associated with the d–d and low-lying charge-transfer transitions in several types of dissymmetric four-coordinate Cu^{2+} systems are calculated on a semiempirical molecular orbital model. Of particular interest are systems in which the metal ion–donor group cluster are inherently dissymmetric and metal–ligand π interactions are expected to be significant. Spectra–structure relationships based on correlations of d–d and charge-transfer rotatory strengths with various stereochemical features of chiral Cu^{2+} complexes are developed and discussed. The results demonstrate the sensitivity of both the signs and magnitudes of the chiroptical properties to donor atom sets, configurational distortions of chelate ring systems, chelate ring conformation, and chelate ring substitution (vicinal effects). Useful and reliable correlations between structure parameters and the rotatory strengths of individual transitions are not readily apparent in the calculated results. However, strong correlations between various structure variables and the *net* d–d (and charge-transfer) rotatory strengths were found.

I. Introduction

Chiroptical spectroscopy has been used extensively to probe the structural details of complexes formed by transition metal ions with a variety of ligand types.[1] The optical activity exhibited by the metal ion d–d transitions and the low-lying (near-ultraviolet) charge-transfer transitions in these systems has been of special interest for developing spectra–structure relationships from which both stereochemical and electronic structural information can be obtained. Although most of the spectra–structure relationships developed and applied so far are based on purely empirical or semiempirical correlations, some effort has been expended in developing a purely theoretical basis for these relationships within the framework provided by various quantum mechanical models of molecular optical activity. These theoretical studies, however, have not produced a fully satisfactory model or theory capable of providing widely applicable and reliable spectra–structure correlations.

Chirality in transition metal complexes is generally attributed to one or more of the following structural features: (1) chiral distortions within the metal ion–donor group cluster ("inherent dissymmetry"); (2) chiral distributions of chelate rings about the metal ion ("configurational dissymmetry"); (3) chiral conformations of chelate rings ("conformational dissymmetry"); (4) asymmetric centers within the ligands (including, in some cases, asymmetric donor atoms). Most theoretical analyses and spectra–structure correlations (such as those based on sector or regional rules) have focused on the latter three sources of chirality, although the possible importance of inherent dissymmetry within the metal ion–donor group cluster has been examined in several studies.

Theoretical treatments of optical activity in chiral transition metal complexes have generally developed along three different lines. In one approach an independent-systems representation of the complex is adopted wherein the complex is partitioned into an achiral chromophoric group (which includes the metal ion) and a set of extrachromophoric groups distributed throughout the ligand environment.[2] Interactions between the chromophoric group and extrachromophoric groups are treated by perturbation techniques, and optical activity in the chromophoric transitions is assumed to arise from dissymmetric terms in these interactions. The theoretical bases for the several sector or regional rules which have been proposed and applied in making spectra–structure correlations in chiral transition metal complexes derive from various forms of the independent-systems model. On this model the chromophore–extrachromophore coupling is assumed to arise from purely electrostatic interactions between nonoverlapping charge distributions on the chromophoric and extrachromophoric groups. Dissymmetry in these interactions can originate with (1) chiral distributions of achiral extrachromophoric groups about the chromophoric center, (2) chiral centers within the perturbing extrachromophoric groups, and (3) a combination of both (1) and (2).

The second approach to examining the origins of optical activity in transition metal complexes focuses on chiral distortions of donor atom orbitals. These distortions reflect the chiral nature of the ligand environment beyond the donor atom set and communicate chirality to the chromophoric electrons of the metal ion via direct bonding (or antibonding) interactions. Liehr[3] and Karipides and Piper[4] adopted this approach and employed a LCAO–MO model for representing the dissymmetrically distorted electronic structure of the metal ion–donor atom cluster. Strickland and Richardson[5] performed a series of calculations based essentially on Liehr's and Piper's models. Schäffer[7] adopted a similar approach in his study of optically active transition metal complexes, but instead of an LCAO–MO model for the electronic structure of the chromophore he employed the angular overlap model.[7]

In the independent-systems model, the chromophoric electrons of the metal ion sense the chirality of the complex via "through-space" electrostatic interactions with the ligand