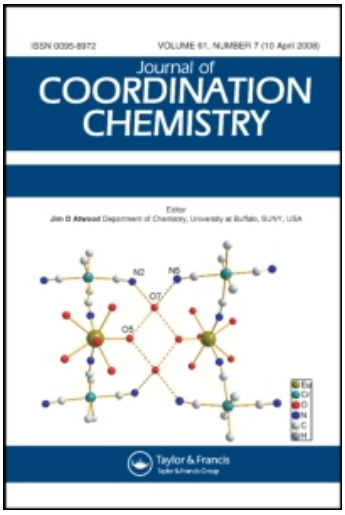

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OPTICAL ROTATION STUDIES OF COPPER (II)-TRIPEPTIDE COMPLEXES†

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Copper(II) complexes of various optically active di- and tripeptides have been studied with the aid of optical rotatory dispersion (ORD) and circular dichroism (CD) techniques. The magnitudes of the molecular rotations related to the d–d transitions of the complexes fall into three different ranges, depending on the positions of asymmetric carbon atoms of the ligands. The molecular rotations of GAG and GLG complexes are greater than those of GGA, GGL, and GGV complexes, which are again greater than those of AGG, LGG, and VGG complexes (G, A, L, and V are glycine, alanine, leucine, and valine residues, respectively, in the tripeptides investigated, the N-terminal residue being the first residue in each abbreviation). The structures of these complexes, deduced from their potentiometric equilibrium curves and from the known crystal structure of the copper(II)-triglycine complex, show that the asymmetric carbon atoms of the second and third amino acid residues (counting from the N-terminal amino acid residue) are in the plane composed of the central metal ion, the nitrogen atoms of the amino and peptide groups, and the oxygen atom of the carboxylate group. The magnitude of the Cotton effect increases with the planarity of the chelate rings which include the asymmetric carbon atom and the metal ion, and with increasing strength of the coordinate bonds that form these chelate rings. Further support for this interpretation is found in the CD spectra of the copper(II) and nickel(II) complexes of AGG, GAG, GGA, and AAA. Analysis of the CD spectra of LL and DL alanylalanine complexes also demonstrate the influence of planarity and coordinate bond strength on the magnitude of the Cotton effect. Schiff base formation of aldehydes and ketones with dialanines causes fundamental changes in the geometries of the copper(II) complexes and reverses the relative contributions of the chelate rings to the total CD absorption intensities of the complexes.

INTRODUCTION

Previous studies of copper(II) complexes of glycine peptides[1–4] are extended in the present work to optically active di- and tripeptide ligands with the aid of circular dichroism (CD) and optical rotatory dispersion (ORD) measurements. The ligands selected for study have one or more optically active amino acid residue(s) in the molecule, and are expected to form metal complexes which have structures similar to those of diglycine and triglycine complexes. Since the disymmetric centers of the metal complexes of these ligands are in the metal chelate rings, it is of interest to study the interactions of the optical activities of the ligands with the d–d electronic transitions of the complexes. Because several complex species are formed at various pH values detailed studies in the present work are restricted to the predominant species at pH ~ 9, in which both peptide protons are dissociated to form strong metal-nitrogen coordinate bonds. The resulting metal chelate structures are basically the same for all the peptides investigated, in which the metal ion is coordinated through the terminal amino and carboxylate groups, and to one or two negatively-charged trigonal nitrogen atoms, in a tetradentate structure containing three fused chelate rings. The formulas of these complexes may be represented by type formulas $MH_{-1}L$ for dipeptide complexes and $MH_{-2}L^{-1}$ for tripeptide complexes, where M^{2+} represents copper(II) or nickel(II) ions and HL represents the ligand.

EXPERIMENTAL

Method

The potentiometric measurements employed have been described previously.[1] Optical rotatory dispersion curves were obtained with a Cary 60 spectropolarimeter, with cells of 1.000 cm thickness. Sample solutions were made of equimolar amounts of copper (II) or nickel(II) nitrate, the di- or tripeptide (0.004–0.008 M), and two or three molar proportions of sodium hydroxide, as required by the stoichiometry involved in the formation of the complexes with peptide proton neutralization. Visible

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spectra of the same simple solutions were taken with a Cary Model 14 Spectrophotometer. CD spectra were measured with a JASCO Model J-20 spectropolarimeter. Ionic strengths of all solutions were adjusted to 0.10 M by adding potassium nitrate. In this research pH is defined as the negative logarithm of the hydrogen ion concentration ($pH = -\log [H^+]$).

Materials

L-alanylglycylglycine (AGG), glycylglycyl-L-alanine (GGA), L-leucylglycylglycine (LGG), glycyl-L-leucylglycine (GLG), L-leucylglycyl-L-leucine (LGL), and L-leucyl-L-leucyl-L-leucine (LLL) were M.A. grade chemicals purchased from Mann Research Laboratories, New York, N.Y. Glycyl-L-alanylglycine (GAG), L-valyl-glycylglycine (VGG), glycylglycyl-L-valine (GGV) and D-alanyl-L-alanine were purchased from Cyclo Chemical Corporation, Los Angeles, Calif. Glycylglycyl-L-leucine (GGL) was purchased from National Biochemical Corporation, Cleveland, Ohio. L-alanyl-L-alanine was purchased from Nutritional Biochemical Corporation. Before sample solutions were prepared the peptides were dried over phosphorus pentoxide in a vacuum desiccator for at least a day. All peptides were found to be at least 99.9% pure on the basis of potentiometric titrations with and without metal ions.

RESULTS

Potentiometric equilibrium curves for copper(II) complexes of these optically active ligands are very similar to that of the copper(II)-triglycine complex. The presence of a leucyl or a valyl group slightly reduces the degree of formation of the complexes at each corresponding step, presumably because of the lowering of the formation constant relative to that of the parent tripeptide complex.

The optical rotatory dispersion curves of the 1:1 complex formed when three moles of base are added to each mole of ligand are shown in Figures 1, 2, 3 and 4. Two Cotton effect curves are seen in the visible spectral region with their maxima at 490–500 nm and 300–320 nm. The latter is not well defined since the strong absorption of the metal complex interferes with the optical rotatory dispersion curves. The values of molecular rotation at 490–500 nm are listed in Table I. Molecular rotation is defined as $[M] = \alpha/(b \cdot X_M)$ where α is observed rotation in degrees, b is cell length in decimeters, and X_M represents moles of solute per 100 ml of solution.

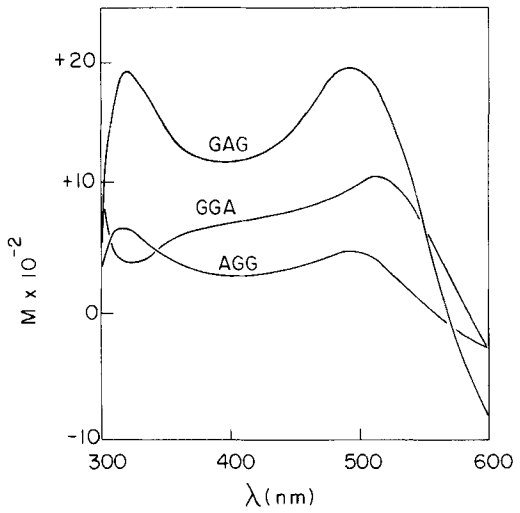


FIGURE 1 Optical rotatory dispersion of copper(II) complexes of GAG, GGA, and AGG.

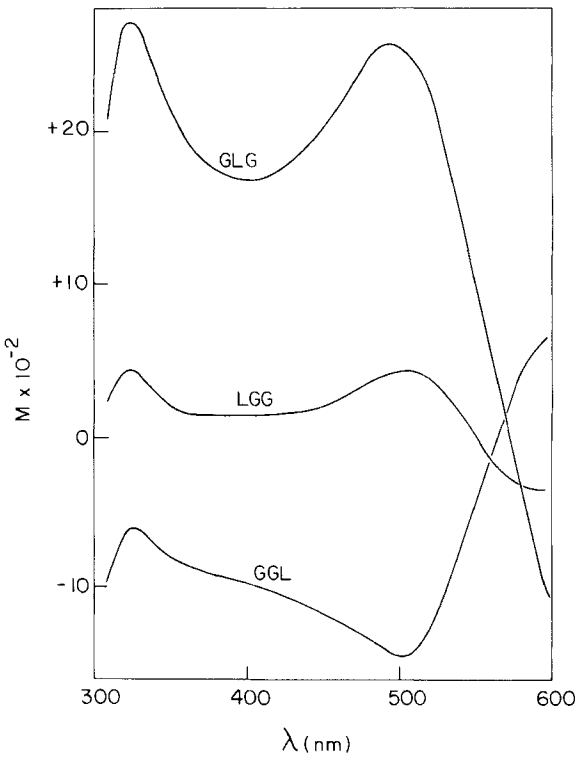


FIGURE 2 Optical rotatory dispersion of copper(II) complexes of LGG, GLG, and GGL.

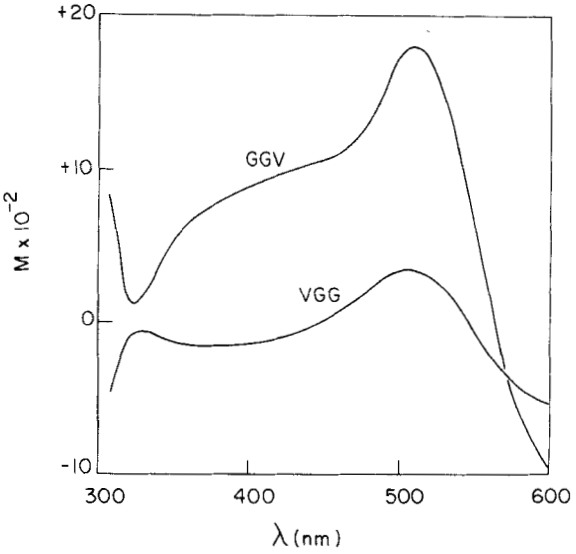


FIGURE 3 Optical rotatory dispersion of copper(II) complexes of VGG and GGV.

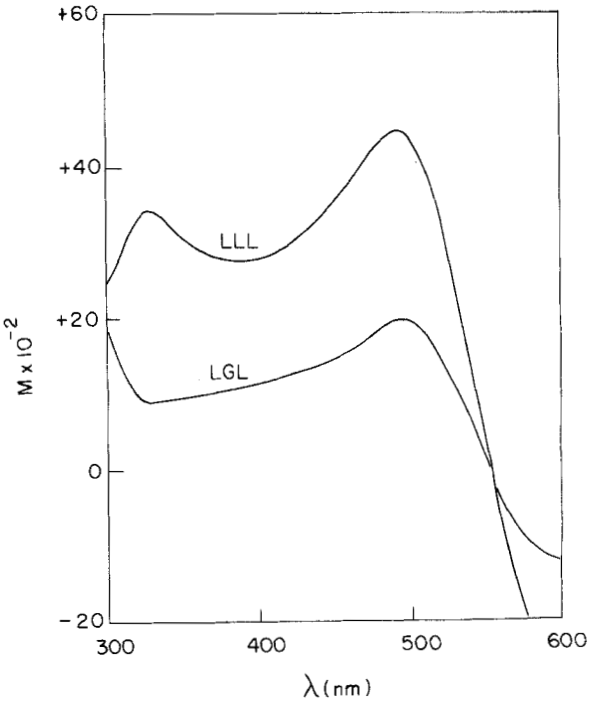


FIGURE 4 Optical rotatory dispersion of copper(II) complexes of LGL and LLL.

The visible spectra of all these complexes have absorption maxima at 550 nm with absorptivities of ~150 cm^{-1} M^{-1}.

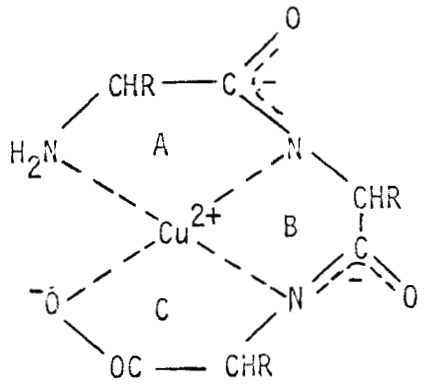
TABLE I
Molecular rotation of copper(II)-tripeptide complexes[a]

Ligand	*Molecular Rotation, [M] x 10^{-2}* [b]
AGG	5
GAG	19
GGA	11
LGG	5
GLG	26
GGL	15
LGL	20
LLL	44
VGG	4
GGV	18

[a]Corresponding to the formula $CuH_{-2}B^-$ where $HB^{\pm}$ is the dipolar species of the tripeptide.
[b]Rotation measured at 500 nm.

DISCUSSION

The potentiometric equilibrium curves show that all the ligands lose two peptide protons in addition to the terminal ammonium proton to form chelate compounds having the general structure:



I Isomeric copper(II) tripeptide complexes, $CuH_{-2}L^-$

As in the case of the triglycine complexes,[2] this species is predominant (almost 100 per cent) in the pH region where three moles of alkali metal hydroxide have been added to an equimolar metal to ligand solution. Therefore, it is clear that all metal complex species exist in this form under the conditions employed in this study.

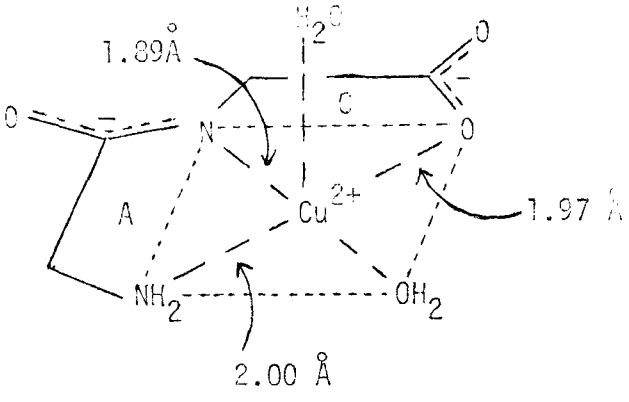
Although the electronic spectra and potentiometric titration curves of isomeric sets of metal complexes studied in this investigation are quite

similar the ORD spectra seem to be very sensitive to the position of the side-chain R substituent. As shown in Figures 1, 2, and 3, the magnitudes of molecular rotation of complexes differing only in the position of a single side chain "R" group are different for different complexes. It is noted that the complexes formed with the substituent in the A ring have the lowest molecular rotation, ~500, whereas moving the substituent to the B ring produces peptide complexes having the greatest value of molecular rotation, 2000–2500. Those formed with the substituent in the C ring gives complexes having intermediate values of molecular rotation, 1000–2000.

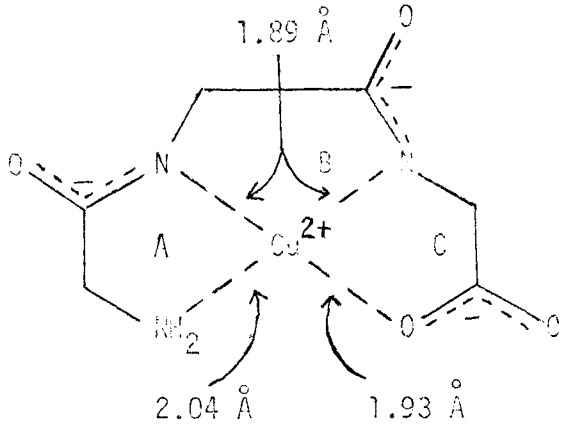
From molecular models of these complexes, it is found that the tetrahedral nature of the N-terminal nitrogen atom forces the adjacent carbon atom slightly out of the plane composed of the central metal ion, the nitrogen atoms of the amino and peptide groups, and the coordinated carboxylate oxygen atom. On the other hand, the two other alpha carbon atoms in the B and C chelate rings lie in this plane because of the trigonal nature of the bonding of the negative peptide nitrogen atoms. The Cotton effect curve at 550 nm is related to the absorption maxima of these copper(II) complexes at the same wavelength. Since this latter absorption band is due to the $d_{x^2-y^2} \rightarrow d_{xy}$ electronic transition of the complex, the optical rotatory dispersion curve should be influenced to the greatest extent by asymmetric carbon atoms in the plane of the metal ion. On the basis of this interpretation for the vicinal effect in the ORD spectra of copper(II) complexes, the low values found for the molecular rotations of AGG, LGG, and VGG are therefore not surprising. In a previous study,[2] it was shown that the coordination of the metal ion to a peptide nitrogen is stronger than that of the metal ion to a carboxylate oxygen. Thus the substituent in the B ring is linked to the metal ion much more strongly than the same substituent would be if it were present in the C ring, and would be expected to have the greater molecular rotation, as observed.

In order to further test these conclusions, analogous copper(II) complexes of the ligands LGL and LLL were studied. Their optical rotatory dispersion curves are illustrated in Figure 4 and their measured values of molecular rotation are listed in Table I. Comparison of the values of 500 for LGG and 1500 for GGL, to that of 2000 for LGL indicates remarkable additivity of the Cotton effects of the chelate rings in these complexes. The same is true for the measured value of the molecular rotation of 4400 for LLL, which may be approximated by LGG + GLG + GGL = 4600.

Since the coupling of the asymmetry of the ligand to the metal ion is primarily a function of the strength of the coordinate bonds involved, it is of interest to compare the magnitude of the Cotton effect to parameters directly related to bond strength. Perhaps the best evidence for coordinate bond strength in peptide complexes available at the present time comes from metal-ligand distances obtained by X-ray crystal structure analysis. Formulas II and III indicate the coordinate bond distances deduced for the copper(II)-diglycine complex,[5] $CuH_{-1}L \cdot 3H_2O$, and for the copper(II)-triglycine complex, $NaCuH_{-2}L \cdot 2H_2O$[6]. On the basis of these models, and with bond distance as a measure of relative bond strength and electronic coupling it is seen that the bond between the trigonal negatively-charged peptide nitrogen and the copper(II) ion is much stronger than the coordinate bond involving the N-terminal tetrahedral nitrogen atom, and considerably stronger than the coordinate bond formed with the carboxylate oxygen.



II



III

It is also seen that in the tripeptides, the asymmetric carbon atom in the B ring is adjacent to one of the strongest coordinate bonds and one atom removed from the other. The asymmetric carbon atom in the C ring is adjacent to the other strongest coordinate bond, and is one atom removed from a much weaker coordinate bond. The asymmetric carbon atom in the A ring is adjacent to the weakest coordinate bond, and one atom removed from the strongest coordinate bond. Taking into consideration relative bond strengths and positions of the asymmetric carbon atoms with respect to the coordinate bonds, it becomes apparent that the magnitudes of the Cotton effect for these compounds should be B > C > A, where A, B and C represent the N-terminal, central, and C-terminal chelate rings, respectively, as indicated in formula III. It is thus seen that the relative magnitudes of the Cotton effects listed in Table I parallel the strengths of the coordinate bonding linkages between the asymmetric (carbon) center and the chromophore (i.e., the metal ion).

Similar relationships have been found in the CD spectra of copper(II) and nickel(II) complexes of di- and tri-peptides. The CD spectra of tripeptides containing one alanyl and two glycyl residues are listed in Table II. All of these complexes are in the form $MH_{-2}L^-$, in which two peptide protons are dissociated from each ligand anion. For both the copper(II) and nickel(II) complexes, it is seen that the relative magnitudes of the Cotton effect are GAG > GGA > AGG, with the B ring having the highest value, and the A ring the lowest. The data in Table II also indicate additivity of the Cotton effects attributed to each chelate ring in the tripeptides, the sum of values for the nickel(II) complexes showing remarkable agreement with the experimental value for the nickel(II)-trialanine complex.

TABLE II
Molar circular dichroism of tripeptide complexes containing L-alanine residues[a]

	Complex	
Ligand	$CuH_{-2}L^{-}$[b]	$NiH_{-2}L^{-}$[c]
GGA	−0.48	−0.85
GAG	−0.75	−1.12
AGG	−0.19	−0.11
Sum	−1.42	−2.08
AAA	−1.03	−2.10

[a]A represents the alanine residue; G represents the glycine residue.
[b]Data compiled from Good *et al.*[7]
[c]Data compiled from Martin *et al.*[8]

Dipeptides

The similarity of bond distances in formulas II and III makes it reasonable to assume that strengths of the coordinate bonds in the dipeptide complexes of the type $MH_{-1}L$ are approximately equivalent to the corresponding bonds in the tripeptide complexes. On this basis, the contribution of the N-terminal ring C to the total Cotton effect of the alanylalanine complex may be considered to be about 2.5 times that of the N-terminal ring A, as calculated from the molar circular dichroism values of the copper(II)-GGA and copper(II)-AGG complexes in Table II. Therefore it is seen that the introduction of a D-amino acid residue in the A ring (positive circular dichroism) should not overcome the contribution of an L-amino acid in the C ring (negative circular dichroism) and that the combination should give a net negative value of the circular dichroism of the copper(II) complex of the D,L isomer. For example, it is seen in Table III that the net magnitude of the circular dichroism of the D,L isomer of $CuH_{-1}L$ is only somewhat more than half that of the L,L isomer. This relationship also holds with other complex species such as $CuH_{-1}LOH^-$, $NiH_{-1}L$, etc.

As the C ring contribution increases, the molar circular dichroism, $\Delta\epsilon$, of the D,L-isomer should become more negative. A convenient parameter for comparing chelate ring contributions to the total circular dichroism of dipeptide complexes is $\Delta\epsilon_{D,L}/$

TABLE III
Relative contributions of C-rings to the circular dichroism of alanylalanine complexes of the type $CuH_{-1}L$

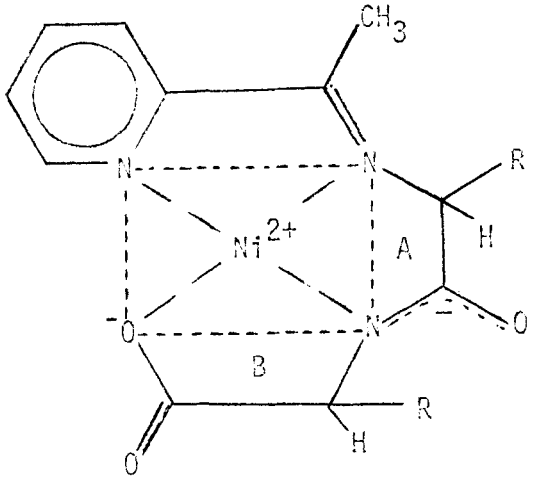
	D,L		L,L		
Complex	λ_{max}	$\Delta\epsilon$	λ_{max}	$\Delta\epsilon$	$\Delta\epsilon\Delta\epsilon_{D,L}/\Delta\epsilon_{L,L}$[a]
$CuH_{-1}L$	530	−0.05	530	−0.14	0.65
$CuH_{-1}LOH^-$	495	−0.15	515	−0.12	0.67

[a]Computed at 650 nm.

$\Delta\epsilon_{L,L}$, which gives the relative C ring contribution. The quotient varies from +1 for 100% contribution by the C ring to −1 for 0% contribution, with the value passing through zero and changing sign at 50% contribution. Values of these parameters for the complexes listed in Table III all show predominant contribution to the total circular dichroism by the C ring, amounting to more than 75% in both cases.

Ni(II)-Schiff base Complexes

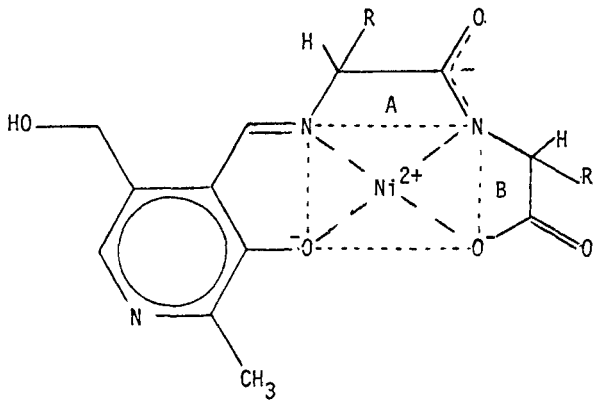
The Schiff bases of optically active dipeptides formed from 2-acetylpyridine and pyridoxal form nickel(II) complexes in which the N-terminal amino group is converted to a trigonal nitrogen, which coordinates strongly in the plane of the metal ion. The above arguments concerning the effect of planarity and strength of binding on the vicinal effect would predict predominance of the A rings in the Schiff base complexes indicated by formulas IV and V. The asymmetric center in the A rings now are adjacent to



IV Ni(II) complex of Schiff base of alanylalanine and 2-acetylpyridine, $NiH_{-1}L$; R = CH_3.

a coordinated trigonal nitrogen and one atom removed from the second, while the B ring has a strongly-bound in-plane trigonal nitrogen atom and a more weakly bound carboxylate oxygen. These complexes differ from the Ni(II)-dipeptide complexes in that they are yellow and diamagnetic, and the CD spectra corresponding to the d–d electronic transitions (435 nm for IV and 450 nm for V) are almost completely dominated by the optically active amino acid residue on the A ring (A ≫ B). This large effect results in the negative CD spectra of the L,L Schiff bases being almost mirror images of the positive CD spectra of the D,L isomers. The fact that the almost complete predominance of the A rings is more than would have been predicted from the bonding and orientation of the donor groups in the peptide residues may be rationalized on the basis of the participation of the additional aromatic nitrogen donor in IV and the phenolic-type group in V. These additional donor groups are resonance-linked to the asymmetric carbon atoms of the A rings and would therefore be expected to enhance considerably the effect of the N-terminal asymmetric center.

Although further investigations of the effects described in this paper are needed, the present work clearly indicates that, as also suggested by Gillard,[9] the magnitude of the vicinal (Cotton) effect in polypeptide complexes depends on the number of chelate rings and the presence of unsaturation in the ligands. Moreover, for chelate rings of the same type, this work shows that the total effect of a number of



V Ni(II) complex of Schiff base of alanylalanine and pyridoxal, $NiH_{-1}L^{-}$; R = CH_3.

asymmetric centers is approximately additive. More specifically, the present work also demonstrates the importance of planarity of the ligand (induced by unsaturation), and the strength of the coordinate bonding of the metal ion to the ligand. Extension of this type of investigation to tetrapeptides would be very interesting since in this case the C-terminal asymmetric center, while still in the plane of the metal ion, would not be part of a metal chelate ring, it having been shown that the carboxylate group is not coordinated in such complexes.

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