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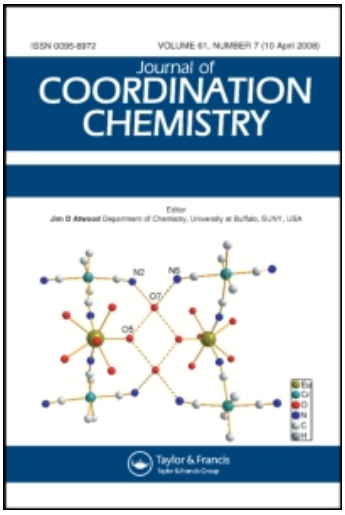

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TRANSITION METAL COMPLEXES OF OPTICALLY ACTIVE AZETIDINE-2-CARBOXYLIC ACID

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TRANSITION METAL COMPLEXES OF OPTICALLY ACTIVE AZETIDINE-2-CARBOXYLIC ACID

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Complexes of D- and L-azetidine-2-carboxylic acid have been prepared with Cu(II), Ni(II), and Co(III). Absorption and circular dichroism spectra of these complexes are similar to those obtained for the corresponding proline complexes.

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INTRODUCTION

In a previous publication from this laboratory, we described the synthesis and characterization of several transition metal complexes of DL-azetidine-2-carboxylic acid (DL-AzCOOH).[1b] The naturally occurring L-isomer of azetidine-2-carboxylic acid (L-AzCOOH) is of interest because of its ability to inhibit protein metabolism by substituting for L-proline in the protein chain.

In a continuing study of this amino acid, we have prepared complexes of D and L-AzCOOH with Cu(II) and Co(III). The complex, $Co(L\text{-}AzCO_2)_3$, was previously isolated by Lin and Douglas.[2] Like proline, AzCOOH is interesting because the amino group is contained within a ring. Thus, upon coordination of AzCOOH to a metal ion, an optically active center is produced at the nitrogen atom. The optical properties of the above complexes have been investigated by means of absorption and circular dichroism (CD) spectroscopic methods.

EXPERIMENTAL

Preparation of the ligands DL-Azetidine-2-carboxylic acid was prepared by the method of Phillips and Cromwell.[3] The racemic mixture was resolved into its optical isomers by the procedure of Rodebaugh and Cromwell.[4] L-Tyrosine hydrazide was used as the resolving agent. This procedure produced analytically pure samples of D-AzCOOH and L-AzCOOH.

Preparation of the Complexes

Preparation of Ni(II) and Cu(II) complexes The Ni(II) and Cu(II) complexes with D and L-AzCOOH were prepared by a method similar to that used for the DL-AzCOOH complexes.[1] The metal hydroxides (1.18 mmoles) and the amino acid (2.1 mmoles) were stirred in about 5 ml of deionized water for four hours. The solutions were filtered and the filtrate removed under reduced pressure on a rotoevaporator. The products were dried under vacuum at room temperature. This procedure produced analytically pure complexes.

Preparation of $Co(D\text{-}AzCO_2)_3 \cdot 2H_2O$ This complex was prepared by refluxing $[Co(NH_3)_4CO_3]NO_3$ (0.12 g, 0.5 mmoles) and D-AzCOOH (0.16 g, 1.6 mmoles) in 5 ml of water for 24 hours. After 24 hours, no evolution of ammonia could be detected with moist litmus paper. The solution was evaporated to a volume of 1–2 drops, cooled to 0°C and filtered. The pink product was washed with methanol, redissolved in water and then filtered to remove a very small amount of insoluble material. The water was removed on a rotoevaporator under reduced pressure. The resulting product was dried under vacuum at room temperature. Yield = 5 mg (2.5%).

Elemental analysis Carbon, hydrogen and nitrogen analyses were performed by PCR, Inc., Gainesville, Florida.

Absorption spectral measurements The absorption spectra were obtained for aqueous solutions. The spectra were recorded on a Cary Model 14 Recording Spectrophotometer using matched one cm. quartz cells.

Circular dichroism spectral measurements The circular dichroism spectra were also obtained for aqueous solutions. They were determined on a Cary

TABLE I
Analytical data for azetidine-2-carboxylic acid complexes[a]

Compound	% Carbon		% Hydrogen		% Nitrogen		% Yield
	Calcd	*Found*	*Calcd*	*Found*	*Calcd*	*Found*	
$Ni(L\text{-}AzCO_2)_2(H_2O)_2$	32.55	32.30	5.47	5.55	9.50	9.32	71.9
$Ni(D\text{-}AzCO_2)_2(H_2O)_2$	32.55	32.37	5.47	5.67	9.50	9.59	71.9
$Cu(L\text{-}AzCO_2)_2(H_2O)$	34.07	34.06	5.01	5.09	9.94	10.16	75.0
$Cu(D\text{-}AzCO_2)_2(H_2O)_2$	32.02	31.83	5.38	5.19	9.35	9.18	84.4

[a]all complexes are blue

Model 6001 Recording ORD/CD Spectrometer. The automatic slit adjustment for this instrument does not operate beyond 600 nm. Therefore, the slit was adjusted manually for spectra obtained above 600 nm.

RESULTS AND DISCUSSION

The optical spectra obtained for D and L-azetidine-2-carboxylic acid complexes are similar to those obtained for the corresponding proline complexes. As with proline, when AzCOOH coordinates to a metal ion, an asymmetric center is produced at the nitrogen atom. Also, coordination of AzCOOH produces a configuration at the nitrogen atom which rotates light in a direction opposite to that resulting from the α-asymmetric carbon atom. Because the nitrogen atom is attached directly to the metal ion, the vicinal effect from the activated nitrogen atom is stronger than that produced by the indirectly

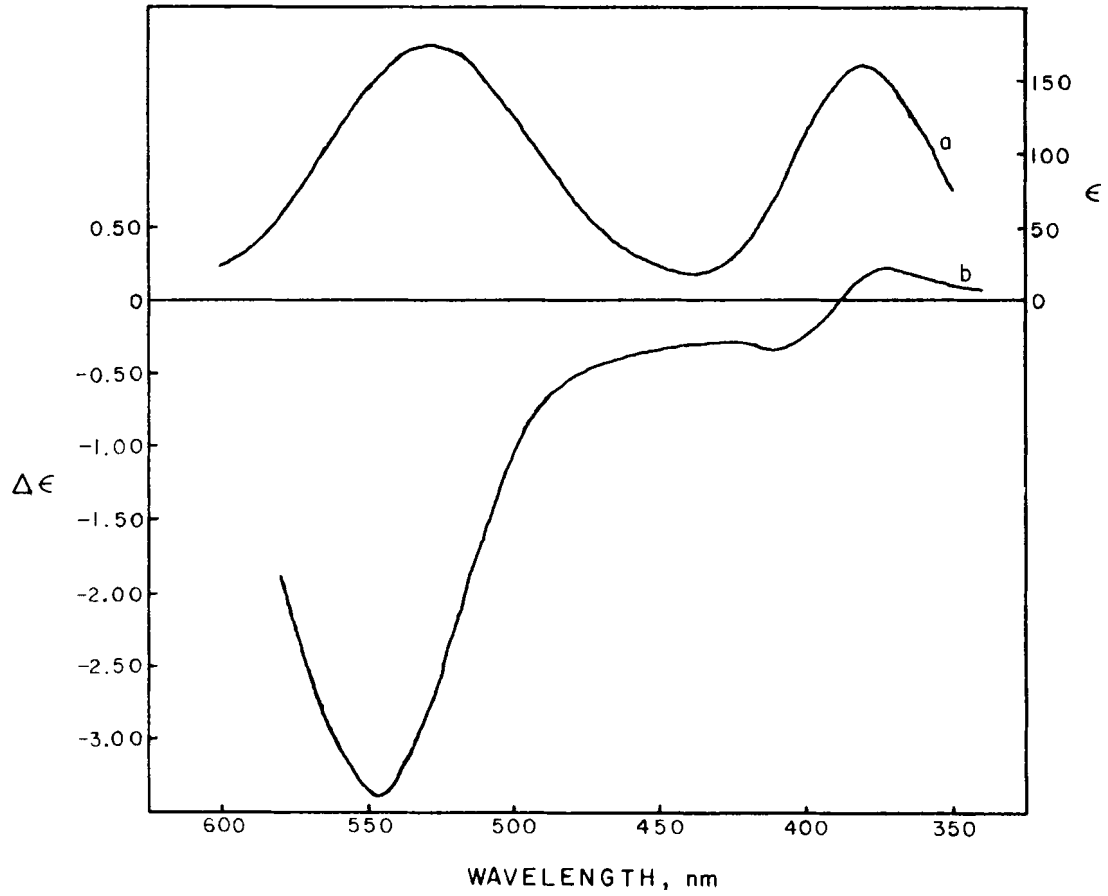

FIGURE 1 Absorption (a) and circular dichroism (b) spectra of $Co(D\text{-}AzCO_2)_3 \cdot 2H_2O$.

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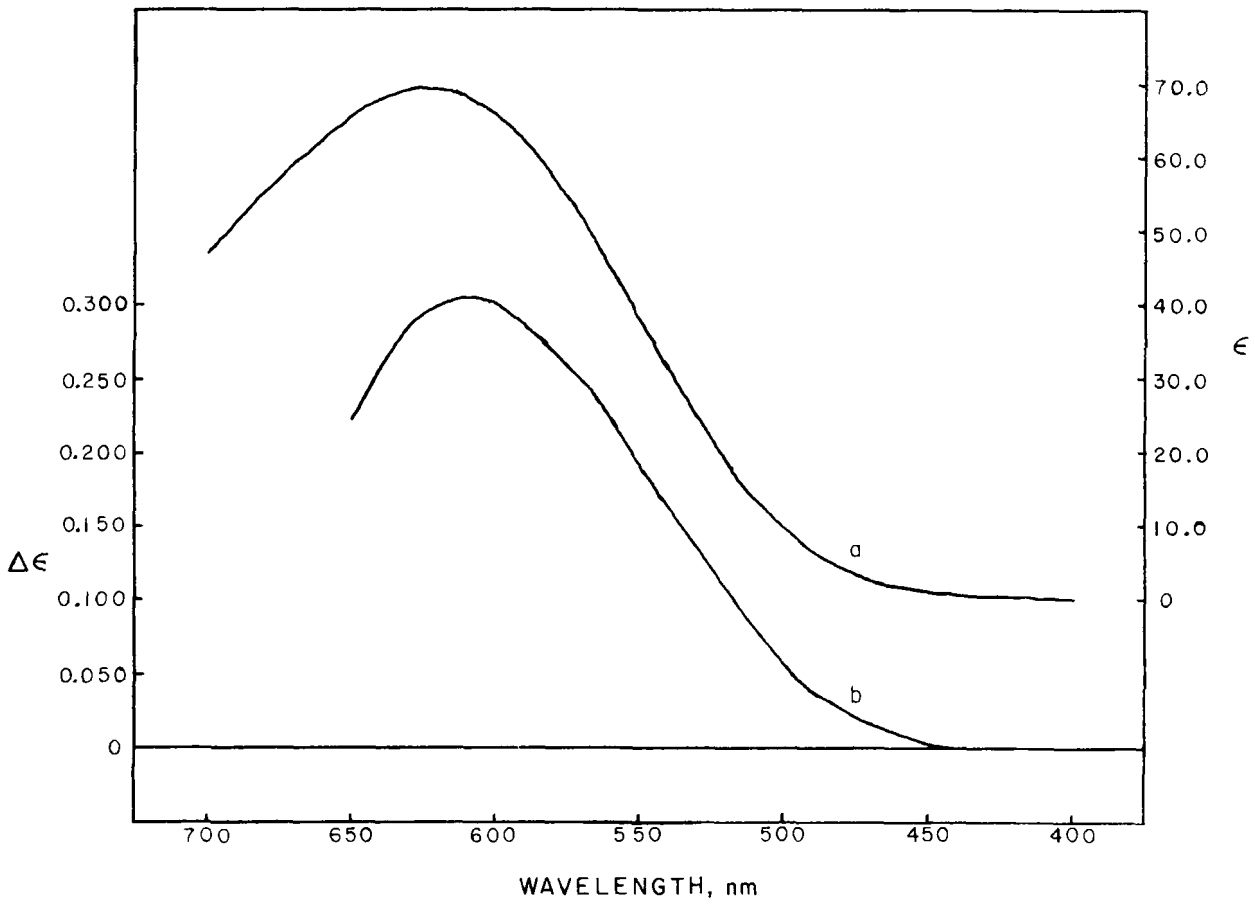

FIGURE 2 Absorption (a) and circular dichroism (b) spectra of $Cu(L\text{-}AzCO_2)_2(H_2O)$.

attached α-asymmetric carbon atom. These properties of optically active AzCOOH produce circular dichroism (CD) spectra for the complexes which have a strong band with a sign opposite to that expected from the α-asymmetric carbon.

Analytical data The stoichiometries of the complexes were determined by carbon, hydrogen and nitrogen analyses. The analytical data, color and percentage yield of the complexes are listed in Table I. The yield of the Co(III) complex of D-AzCOOH was too low to permit an elemental analysis. After purification, the complex produced absorption and CD spectra very similar to those of the corresponding complex of L-AzCOOH. An infrared analysis for water was performed on this complex by comparing the relative peak areas of the water band and the asymmetric carboxyl stretching band with those of $Co(DL\text{-}AzCO_2)_3 \cdot 3H_2O$. The results indicate that there are two equivalents of water present in this complex. Thus, its empirical formula is $Co(D\text{-}AzCO_2)_3 \cdot 2H_2O$. The L-AzCOOH complex of Cu(II) is slightly hygroscopic. The complex was dried under vacuum at room temperature before analysis and the analysis results indicate one equivalent of water. The Cu(II) complexes of proline were shown to exhibit a similar property.[5,6] However, the proline complexes required gentle heating to remove the first equivalent of water.

Absorption and Circular Dichroism Spectral Data

$Co(D\text{-}AzCO_2)_3 \cdot 2H_2O$ The absorption spectrum for $Co(D\text{-}AzCO_2)_3 \cdot 2H_2O$ is similar to that found for $Co(DL\text{-}AzCO_2)_3 \cdot 3H_2O$ and $Co(L\text{-}AzCO_2)_3$.[1,2] The absorption spectrum for this complex is shown in Figure 1. The maxima occur at 528 nm ($\epsilon = 174$) and 380 nm ($\epsilon = 160$). These values are similar to those found for the complex of the racemic ligand, 528 nm

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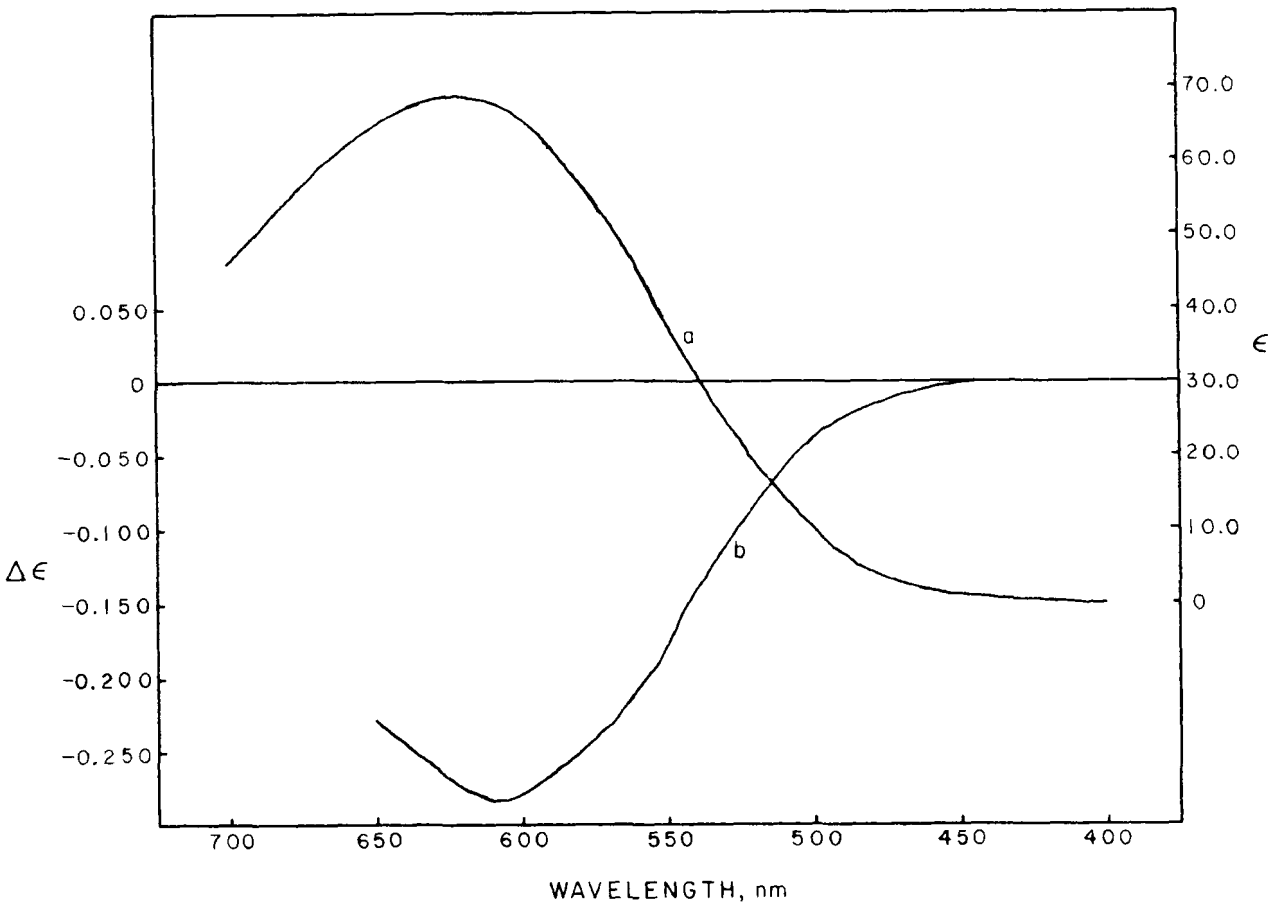

FIGURE 3 Absorption (a) and circular dichroism (b) spectra of $Cu(D\text{-}AzCO_2)_2(H_2O)_2$.

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(ϵ = 160) and 380 nm (ϵ = 152). The greater intensity of the absorption peak at longer wavelength as compared to the shorter wavelength peak is characteristic of the N-facial isomer of amino acid-Co(III) complexes.[7] Also, the corresponding meridional isomers show splitting of the longer wavelength absorption band which does not occur for the facial isomer.

The circular dichroism (CD) spectrum for $Co(D\text{-}AzCO_2)_3 \cdot 2H_2O$ is also shown in Figure 1. It is exactly opposite in sign to the spectrum found for $Co(L\text{-}AzCO_2)_3$.[2] The strong negative band at 546 nm results from the vicinal effect of the activated nitrogen atom of the amino acid ring. This complex can thus be identified as fac-(-)-$[Co(D\text{-}AzCO_2)_3 \cdot 2H_2O]$ where the sign refers to the sign of the low energy CD band as outlined by Denning and Piper.[7]

Three of the four possible isomers of Co(L-proline)$_3$ were isolated by Denning and Piper.[7] From steric hindrance and relative yield considerations, they were able to assign absolute configurations to each of these isomers. By their method the isomer with the least steric hindrance is the most stable and, therefore, should be obtained easier in higher yields. By using these considerations, Lin and Douglas identified the L-AzCOOH complex they isolated to be the fac-Λ-isomer.[2] Because of the similarity of peak intensities in the CD spectra of $Co(L\text{-}AzCO_2)_3$ and $Co(D\text{-}AzCO_2)_3 \cdot 2H_2O$, the isomer of $Co(D\text{-}AzCO_2)_3$ isolated must be of pure absolute configuration. By building molecular models of each of the isomers of $Co(D\text{-}AzCO_2)_3$, it was found that the fac-Δ-isomer had no interaction of the amino acid rings and, therefore, was not sterically hindered. Therefore, it can be concluded that the complex prepared for this study exists in the Δ configuration. This does not imply that the other isomers of $Co(D\text{-}AzCO_2)_3$ can not be isolated. The very small scale preparation performed diminishes the chances of isolating the sterically hindered isomers.

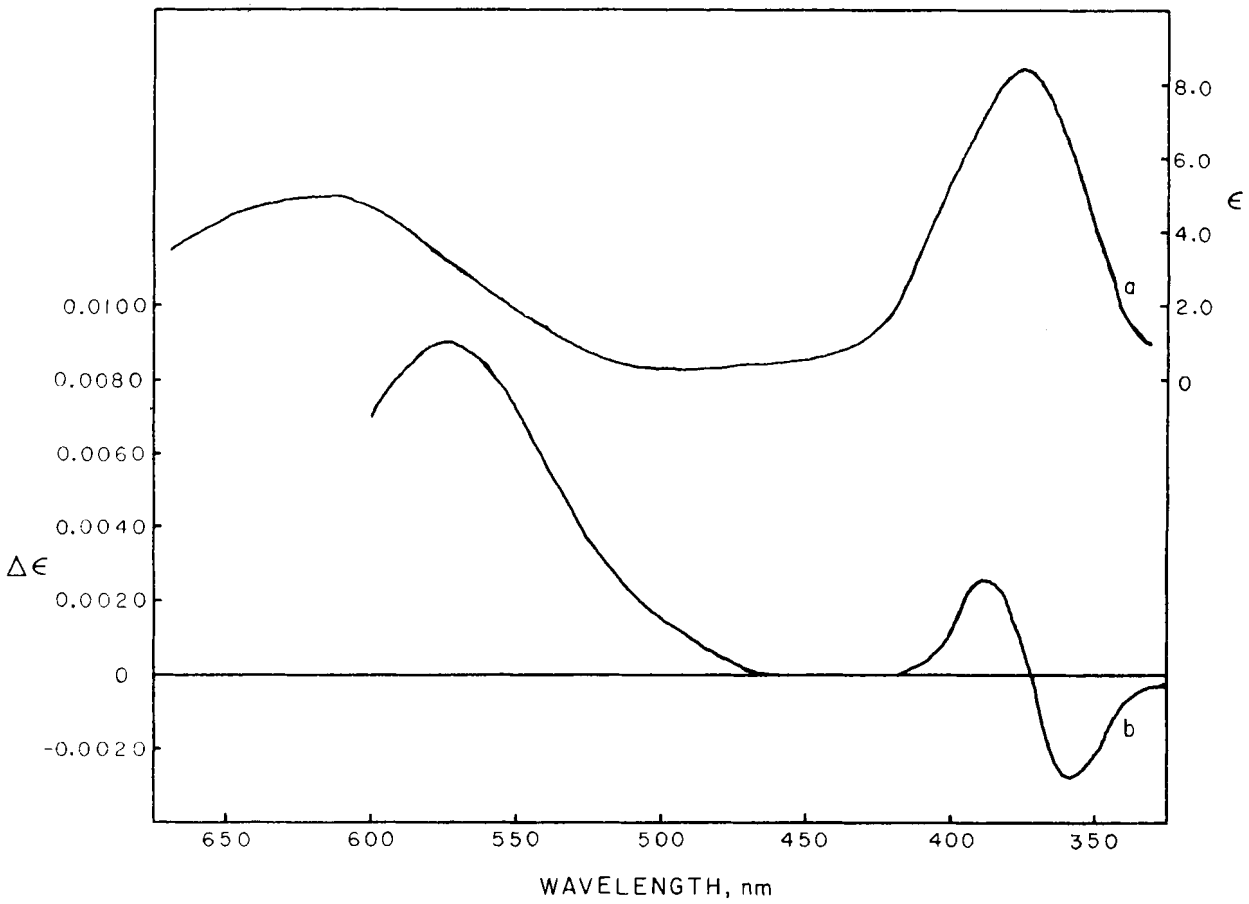

FIGURE 4 Absorption (a) and circular dichroism (b) spectra of $Ni(L\text{-}AzCO_2)_2(H_2O)_2$.

Cu(II) complexes The absorption and CD spectra of $Cu(L\text{-}AzCO_2)_2(H_2O)$ and $Cu(D\text{-}AzCO_2)_2(H_2O)_2$ are shown in Figures 2 and 3, respectively. Each of the complexes shows a single broad band at 625 nm in the absorption spectrum. The racemic complex, $Cu(DL\text{-}AzCO_2)_2(H_2O)_2$, also produced a similar band at 625 nm.[1] These spectra are very similar to those found for the corresponding proline complexes. The proline complexes have been shown to exist in an N-*trans* octahedral configuration with the two water molecules occupying axial positions.[6,8,9] This suggests that the AzCOOH complexes should also form a similar structure.

$Cu(L\text{-}AzCO_2)_2(H_2O)$ produced a broad band with a maximum at 612 nm in the CD spectrum. The corresponding complex with D-AzCOOH produced the mirror image of this spectrum. As in the Co(III) complexes, the vicinal effect of the asymmetric nitrogen atom produces a spectrum opposite in sign and more intense than is expected from the α-asymmetric carbon atom. These spectra are similar to those found for $Cu(L\text{-proline})_2(H_2O)_2$.[10] However, the latter complex has a small negative CD band at about 525 nm which was not found for the AzCOOH complexes.

Ni(II) complexes The CD and absorption spectra of $Ni(L\text{-}AzCO_2)_2(H_2O)_2$ and $Ni(D\text{-}AzCO_2)_2(H_2O)_2$ are shown in Figures 4 and 5, respectively. As in the Co(III) and Cu(II) complexes, the vicinal effect produced by the asymmetric nitrogen atom is observed in the CD spectra for these complexes. The CD spectra consist of a strong band at longer wavelength and two weak bands at shorter wavelength. Haines and Reimer reported the CD spectrum of $Ni(L\text{-proline})_2(H_2O)_2$.[11] Some distinct differences exist between the CD spectra of $Ni(L\text{-}AzCO_2)_2(H_2O)_2$ and $Ni(L\text{-proline})_2(H_2O)_2$. The spectrum of the L-proline complex includes a small positive band at about 500 nm which is not evident in the spectrum of

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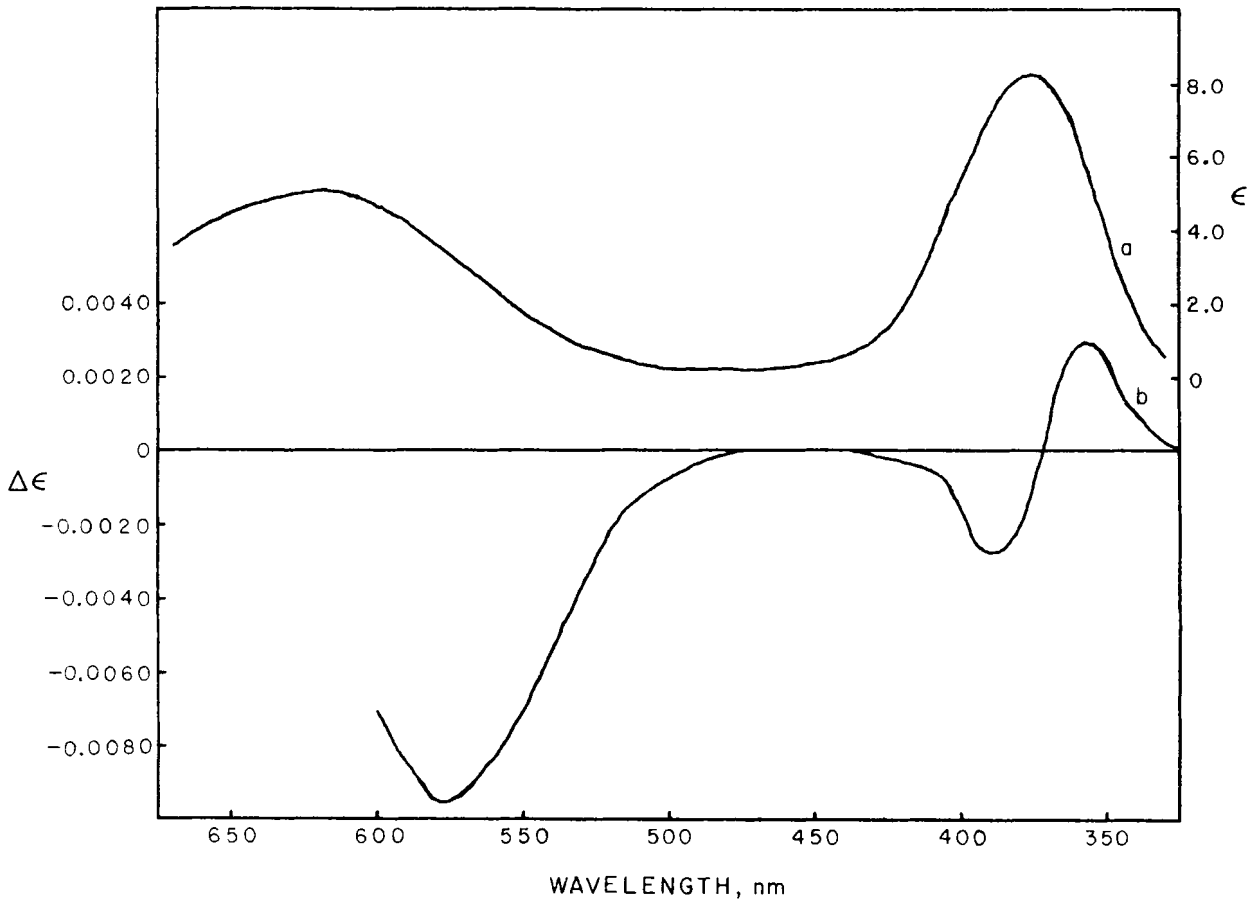

FIGURE 5 Absorption (a) and circular dichroism (b) spectra of $Ni(D\text{-}AzCO_2)_2(H_2O)_2$.

$Ni(L\text{-}AzCO_2)_2(H_2O)_2$. It is possible that this band could be hidden under the much stronger long wavelength CD band. Also, the band at about 390 nm for the L-proline complex is approximately equal in intensity to the long wavelength band. The corresponding band for the AzCOOH complexes is less intense.

CONCLUSIONS

Five new complexes of azetidine-2-carboxylic acid have been prepared and characterized. The electronic spectra of the optically active complexes are very similar to those found for the racemic complexes.[1] The CD spectrum of each of the optically active complexes has been reported and discussed. The vicinal effect of the asymmetric nitrogen atom dominates the CD spectrum of each of the complexes. Because of its direct attachment to the metal ion, the asymmetric nitrogen atom has a greater effect than the indirectly attached α-asymmetric carbon upon the CD spectra of the complexes. Also, the signs of the CD spectra produced are opposite to that expected from the α-asymmetric carbon atom. These phenomena have been observed fro the complexes of L-proline.[10,11] An S configuration is enforced upon the nitrogen atom of the L-amino acid upon coordination to a metal ion. However, a negative rotation of light, which would be expected for an S-asymmetric carbon atom, is not produced. Although we have demonstrated that the signs of CD spectra for complexes of optically active azetidine-2-carboxylic acid are also opposite to that expected, we cannot offer an explanation of the results.

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