effects" have been noted in various metalloporphyrin systems.[21] The experimental data presented here support these ideas since both nickel(II) and copper(II) complexes containing the 14-membered rings ($x = 2, y = 3$) have been prepared in both forms I and II, while complexes with the 15-membered ring ($x = 3, y = 2$) have been isolated only for nickel(II) and only in form II. No copper(II) complexes with 15-membered rings have been isolated which may reflect increased steric crowding due to the slightly larger size of the copper(II) ion. In addition, neither nickel(II) nor copper(II) seemed to form a complex with the 16-membered ligands. We therefore conclude that the $M(dienoN_4)X$ and $M(dieneN_4)X_2$ complexes become less stable as steric crowding increases in the larger macrocyclic rings and that sterically strained configurations containing adjacent six-membered rings are most stable in form II which contains the neutral ligands while those less strained can exist in both forms I and II. Measurements of stability constants for these complexes should provide more definitive evidence for the explanations given here.

(21) J. L. Hoard in "Structural Chemistry and Molecular Biology," W. H. Freeman, San Francisco, Calif., 1968, pp 573-594, and references therein.

Registry No. $Ni([14]\ dienoN_4)NO_3$, 39556-33-7; $Ni([14]\ dienoN_4)Br$, 39556-34-8; $Ni([14]\ dienoN_4)I$, 39556-35-9; $Ni([14]\ dienoN_4)PF_6$, 39042-83-6; $Ni([14]\ dieneN_4)I_2$, 39561-15-4; $Ni([14]\ dieneN_4)(PF_6)_2$, 39561-16-5; $Ni([15]\ dieneN_4)(PF_6)_2$, 39561-23-4; $Cu([14]\ dienoN_4)NO_3$, 39561-17-6; $Cu([14]\ dienoN_4)Br$, 39561-18-7; $Cu([14]\ dienoN_4)I$, 39561-19-8; $Cu([14]\ dienoN_4)PF_6$, 39561-20-1; $Cu([14]\ dieneN_4)(PF_6)_2$, 39561-21-2; $Cu([14]\ dieneN_4)I_2$, 39561-22-3; $[16]\ dieneN_4 \cdot 2HPF_6$, 39526-74-4; acac, 123-54-6; 2,3,2-tet, 4741-99-5; 3,2,3-tet, 10563-26-5; 3,3,3-tet, 4605-14-5.

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Circular Dichroism of Amino Acid Complexes of Nickel(II)

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Quantitative circular dichroism (CD) data are presented for a series of bis(amino acid) complexes of nickel(II). The complexes prepared were those of alanine, valine, isoleucine, proline, histidine, serine, asparagine, ornithine, glutamic acid, and aspartic acid. Certain differences from previous qualitative spectra have been found in some instances and the spectra have been found to fit into certain categories related to the overall structure of the complexes. The CD pattern of the d-d transitions together with the CD sign of the ultraviolet tail offers a potentially useful tool in assigning structure in this type of complex.

Introduction

It is well known that the coordination of an optically active ligand to a metal ion induces optical activity into the d-d electronic transitions of the metal ion and circular dichroism (CD) is observed. Coordination of a chelating ligand can contribute to the observed optical activity in two ways: (i) through the conformational effect whereby dissymmetry is conferred about the metal due to puckering of the chelate rings and (ii) through the vicinal effect whereby the dissymmetry of the ligand itself is presented to the metal chromophore and gives rise to optical activity. For square-planar complexes or octahedral molecules with D_{4h} symmetry, only these contributions are possible since there is no net chirality for the complex.

In recent years a number of studies have been carried out on the optical activity of amino acid complexes of copper(II) and nickel(II)[1-3] and a hexadecant rule has been proposed[4,5] as an aid for interpreting the observed CD spectra. For copper(II) the component bands are often masked due to severe overlap of the component d-d transitions but for nickel(II) these transitions are significantly different in energy and a number of CD bands are observed. In order to apply general rules for the CD of these complexes, one must be certain to compare complexes with similar structures and refer to the CD of corresponding absorption bands. Much of the previous work reported for nickel(II) has involved solution CD spectra obtained by mixing simple nickel(II) salts and various amino acids in appropriate ratios. We have carried out studies using freshly prepared solutions of the actual complexes and in some instances have found certain differences in spectra from those reported previously. In this paper we wish to report the results of our studies and a potential means for predicting stereochemistry in these complexes.

Experimental Section

All amino acids were obtained from Nutritional Biochemicals Corp., Cleveland, Ohio, with the exceptions of L-alanine (British Drug Houses) and L-histidine and L-isoleucine (Eastman Organic Chemicals). All were used directly with no further purification.

Three methods were employed in the preparation of the NiL_2 complexes.

Method I (D- and L-Alanine, D-Aspartic Acid, L-Proline, and L-Histidine). This method was adapted from that used by Nakamoto.[6] An aqueous solution of 0.01 mol of amino acid was heated with excess nickel carbonate. (For the aspartic acid complex the pH was adjusted to 8.5 using NaOH.) After sufficient stirring, the mixture was filtered and taken to dryness on a rotatory evaporator. (For alanine, evaporation of the sample was carried

(1) C. J. Hawkins and C. L. Wong, *Aust. J. Chem.*, 23, 2237 (1970).
(2) J. W. Chang and R. B. Martin, *J. Phys. Chem.*, 73, 4277 (1969).
(3) L. I. Katzin and E. Gulyas, *J. Amer. Chem. Soc.*, 91, 6940 (1969).
(4) R. B. Martin, J. M. Tsangaris, and J. W. Chang, *J. Amer. Chem. Soc.*, 90, 821 (1968).
(5) J. M. Tsangaris and R. B. Martin, *J. Amer. Chem. Soc.*, 92, 4255 (1970).
(6) K. Nakamoto, Y. Morimoto, and A. E. Martell, *J. Amer. Chem. Soc.*, 83, 4528 (1961).

out in a vacuum desiccator and yielded well-formed crystals).

Method II (L-Valine and L-Isoleucine). The procedure used is a slight modification of that used by Neuberg, *et al.*[7] Amino acid (0.0114 mol) dissolved in 10 ml of 1 *M* NaOH was added to 26 ml of 0.2 *M* $NiCl_2$. The solution was stirred for several hours and during this time a pale blue solid formed in the case of isoleucine. However, evaporation of the solution to dryness was necessary for the valine complex.

Method III (D-Valine, D-Asparagine, L-Serine, L-Ornithine, and L-Glutamic Acid). Amino acid (0.0114 mol) was added to a warm (40°) solution containing 26 ml of 0.2 *M* nickel ion. ($Ni(ClO_4)_2$ was used for the asparagine and serine complexes while $NiCl_2$ was used for all others.) The solution was neutralized with 10 ml of 1 *M* base (KOH for asparagine and serine and NaOH for all others). The solutions were stirred and evaporated to a low volume, cooled, and filtered. The D-valine complex precipitated immediately, however.

The above complexes were isolated by successive evaporations to a low volume, cooling, and filtering. All CD measurements were obtained on a Durrum-Jasco ORD/UV/5 spectropolarimeter using a 5-cm cell. A Beckman DK-1 spectrophotometer was used for measurements of solution absorption spectra while diffuse reflectance spectra were recorded on a Cary Model 14 spectrophotometer. Infrared spectra were obtained as Nujol mulls using either Beckman IR-10 or Perkin-Elmer 621 instruments. Microanalyses were performed by A. B. Gygli, Toronto, A. Bernhardt, West Germany, or Chemalytics, Inc., Tempe, Ariz.

Results and Discussion

The amino acids used in this study were of two types: (i) simple amino acids capable of forming only one chelate ring and (ii) amino acids with a side chain containing a potential donor atom. The species isolated had the general formula NiL_2 and in the case of simple amino acids compounds of the type of $NiL_2 \cdot 2H_2O$ were isolated. Analytical data are presented in Table I. The literature contains a number of references[6,8,9] to these complexes and they have been shown to be paramagnetic and have a tetragonally distorted octahedral structure with the amino acids in a common plane. The axial H_2O groups are readily lost on heating and recent infrared studies[10] have suggested that in the solid state the uncoordinated carboxyl oxygen can coordinate to form a bridged arrangement. For the polyfunctional acids such bridging does not occur, however.

Simple Amino Acids. Complexes of nickel(II) with the L-amino acids alanine, valine, and isoleucine were prepared and had the general formula $NiL_2 \cdot 2H_2O$. Solids were also obtained for phenylalanine and leucine but these were very insoluble in all common solvents and hence measurements could not be carried out directly. A modified study was performed, however (*vide infra*).

The valine, alanine, and isoleucine species gave CD spectra in methanol as shown in Figure 1 and Table II. The long wavelength region corresponding to the $^3A_{2g} \rightarrow {}^3T_{1g}$ transition showed two negative peaks for the first two compounds while the isoleucine showed one negative band with sufficient broadening to indicate a second component also. The high energy $^3A_{2g} \rightarrow {}^3T_{1g}(P)$ d–d transition has three components with a (+, −, +) arrangement for alanine and valine. The isoleucine is similar but lacks the high energy (+) component. This is possibly due to an overall spectral shift relative to the other compounds, however, with the result that masking of the (+) component occurs. The CD spectrum tails off markedly to negative values in the ultraviolet region for each species.

(7) C. Neuberg, H. Lustig, and I. Mandl, *Arch. Biochem. Biophys.*, 26, 77 (1949).
(8) C. A. McAuliffe, J. V. Quagliano, and L. W. Vallarino, *Inorg. Chem.*, 5, 1996 (1966).
(9) S. E. Livingstone and J. D. Nolan, *Inorg. Chem.*, 7, 1447 (1968).
(10) C. A. McAuliffe and W. D. Perry, *J. Chem. Soc. A*, 634 (1969).

Table I. Analytical Data for the Complexes[a]

Compound	Analyses, % C	H	N
$Ni(D\text{-}Ala)_2 \cdot 2H_2O$	26.40 (26.58)	6.24 (5.91)	9.99 (10.34)
$Ni(L\text{-}Val)_2 \cdot 2H_2O$	36.94 (36.70)	7.18 (7.34)	8.41 (8.58)
$Ni(L\text{-}Ile)_2 \cdot 2H_2O$	40.94 (40.55)	7.72 (7.89)	7.69 (7.89)
$Ni(L\text{-}Pro)_2 \cdot 2H_2O$	37.47 (37.26)	6.27 (6.20)	8.92 (8.70)
$Na_2[Ni(D\text{-}Asp)_2] \cdot 5H_2O$	20.88 (21.02)	4.13 (4.38)	6.31 (6.13)
$Ni(D\text{-}Aspar)_2 \cdot 1.5H_2O$	27.92 (27.59)	4.82 (4.88)	15.61 (16.09)
$Ni(L\text{-}His)_2 \cdot H_2O$	37.58 (37.40)	4.73 (4.67)	22.01 (21.81)
$Ni(L\text{-}Ser)_2 \cdot 3.5H_2O$	21.97 (21.89)	5.35 (5.17)	8.62 (8.51)

[a] Ala, Val, Ile, Pro, Asp, Aspar, His, and Ser are the anions of alanine, valine, isoleucine, proline, aspartic acid, asparagine, histidine, and serine, respectively.

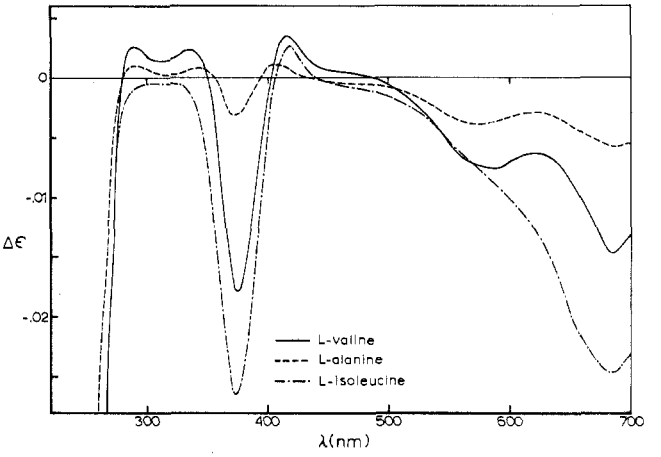

Figure 1. CD curves for nickel(II) complexes of simple amino acids.

For leucine and phenylalanine the CD was determined by adding a solution of nickel(II) chloride slowly to a solution of amino acid until the ratio of nickel(II):amino acid was 1:2. Due to the tendency for precipitation to occur, only a limiting spectrum could be observed but the overall shape resembled those above.

All of the species exhibiting this type of spectrum may be regarded as possessing the trans configuration of ligands about the central metal ion such as has been found for the corresponding glycine complex.[11,12] The negative CD associated with the low-energy absorption band is consistent with predictions from the hexadecant rule but cannot confirm the cis or trans configuration. However, infrared spectra have been obtained and show a simple pattern in the region of the ν_{Ni-N} and ν_{Ni-O} which is quite similar to that of the glycine complex.[13] Only minor shifts occur from compound to compound as would be anticipated on changing the ligand. However, no splitting which would be indicative of the cis isomer is indicated.

The CD spectra reported here are slightly different from those reported previously. In the paper by Katzin and Gulyas[3] the spectra were obtained in solution for various molar ratios and pH values. In no case was a solid sample isolated and the limiting spectrum was not always reported. For alanine their reported spectrum of a 1:2 metal:ligand

(11) A. J. Stosick, *J. Amer. Chem. Soc.*, 67, 365 (1945).
(12) H. C. Freeman, J. M. Guss, and R. L. Sinclair, *Chem. Commun.*, 485 (1968).
(13) R. A. Condrate and K. Nakamoto, *J. Chem. Phys.*, 42, 2590 (1965).

Table II. Spectral Data for Nickel Complexes of Amino Acids

Compound	Absorption λ_{max}, nm	ϵ	Reflectance λ_{max}, nm	CD λ, nm	$\Delta\epsilon$
$[Ni(L\text{-}Ala)_2]\cdot 2H_2O$	1010	8.32	946	673	−0.0053
	622	5.81	608	579	−0.0037
	375	10.0	384	408	+0.0012
				370	−0.0034
				343	+0.0008
				287	+0.0009
				<260	Negative
$[Ni(L\text{-}Val)_2]\cdot 2H_2O$	1012	9.13	1080	682	−0.014
	627	6.34	640	582	−0.0074
	374	11.3	380	416	+0.0034
				376	−0.019
				336	+0.0024
				288	+0.0025
				<270	Negative
$[Ni(L\text{-}Ile)_2]\cdot 2H_2O$	1013	9.74	977	680	−0.025
	620	6.94	618	418	+0.0023
	375	12.2	387	372	−0.027
				<280	Negative
$[Ni(L\text{-}Pro)_2]\cdot 2H_2O$	1001	7.97	1048	586	+0.0096
	620	5.48	645	390	+0.0092
	375	10.9	387	358	−0.0018
				255	+0.0014
				<250	Negative
$Na_2[Ni(D\text{-}Asp)_2]\cdot 5H_2O$	1037	11.3	1048	575	−0.0091
	624	5.63	645	425	+0.0018
	382	10.5	387	385	−0.013
				345	+0.0032
				<280	Negative
$[Ni(D\text{-}Aspar)_2]\cdot 2H_2O$	1005	7.69	1045	605	−0.0038
	611	5.77	625	372	−0.0052
	367	8.92	378	<300	Negative
$[Ni(L\text{-}His)_2]\cdot H_2O$	955	10.1	964	612	+0.050
	554	11.6	544	525	−0.016
	356	14.7	358	386	−0.012
				350	+0.0084
				258	+0.0039
				<250	Negative
$[Ni(L\text{-}Ser)_2]\cdot 3.5H_2O$	1010	7.05	1064	646	+0.0044
	619	5.06	929	564	−0.0053
	371	9.04	602	352	+0.0062
			380	<280	Negative
$[Ni(L\text{-ornithine})_2]\cdot 2HCl$	988	7.49		659	+0.011
	596	8.00		559	−0.0042
	367	13.4		393	−0.010
				363	+0.0078
				<280	Negative

ratio was different from ours and appeared to be a spectrum resulting from a mixture of 1:1 and 1:2 species. Only for 1:3 or 1:4 ratios at pH 9 or greater did the 1:2 spectrum persist. Data for the valine complex were reported only for the 1:1 mixture and no further spectral information was provided. However, it appeared to be similar to alanine. A spectrum reported for valine by other workers[7] would suggest a mixture of species but unfortunately insufficient data were given to confirm this conclusion. Our CD spectra were obtained from dissolved samples of known composition and calculations using published stability constants indicate that the maximum extent of dissociation should be only 3%. Hence, it is felt that our reported CD spectra are quite indicative of the 1:2 species.

L-Proline. This amino acid can form the usual five-membered chelate ring but the coordinated nitrogen also represents an asymmetric center. Great stereoselectivity is possible with this ligand since the nitrogen can coordinate only with the *S* configuration and this requirement also puts restrictions on the overall geometry of the complex. For the L acid (*S* configuration at C*) formation of the NiL_2 complex is only possible for the cis configuration and this has been shown to be the case for the similar palladium(II) complex.[14] Analogous predictions come from the previous structure reported for the copper(II) complex containing both D- and L-proline[15] where a trans structure is necessitated because of the different symmetry requirements of the ligands with two configurations. Data for the proline complex are given in Figure 2 and Table II. Contributions to the observed CD spectrum arise from (i) the vicinal effect of the asymmetric C, (ii) the vicinal effect of the asymmetric nitrogen, and (iii) the conformational effect of the amino acid chelate ring. The last contribution is probably more pronounced than in other simple amino acids but models indicate that the displacement from the plane is still rather small and hence this contribution is not likely to be particularly large. Of the first two effects, the contribution from the asymmetric nitrogen is expected to be much more significant because of the direct attachment to the metal ion. As was observed in the case of copper(II),[1] the d-d absorption bands are of opposite sign from those observed for the simple amino acids. This reversal of sign can be attributed to the vicinal effect of the asymmetric nitrogen. One must, however, be cautious in attributing this reversal entirely to the vicinal effect. For proline, the ML_2 complex has a spiran-type structure and hence a further contribution to the CD is potentially possible. However, for the 1:1 species of both copper(II)[1] and nickel(II)[3] a similar reversal of sign is also apparent and hence if there is a contribution from the spiran arrangement, it only enhances the vicinal effect of the asymmetric nitrogen.

The long CD tail in the ultraviolet region is negative as was observed for the other amino acids with the L configuration. This is consistent with the above arguments since the origins of CD bands in this region lie within the ligand itself and not with d-d transitions of the metal.

Polyfunctional Amino Acids. The amino acids of this type which were studied were histidine, asparagine, aspartic acid, serine, glutamic acid, and ornithine. These acids form complexes which are not easily crystallized (with the exception of histidine) and solutions must be carefully evaporated to dryness in order to obtain a solid. Representative CD spectra for some of the acids are shown in Figure 2 and detailed data are given in Table II. All acids had the L configuration except asparagine and aspartic acid where the D isomer was used. In general, the curves for serine, ornithine, and glutamic acid resembled those shown for L-histidine but were of significantly lower intensity. Detailed quantitative data were not obtained for glutamic acid due to the formation of a glassy product which suggested the formation of polymeric species. However, qualitative CD spectra on solutions of this product indicated similar peaks. At approximately 650 nm a positive peak was observed followed by a negative peak at approximately 560 nm. The high-energy $^3A_{2g} \rightarrow {}^3T_{1g}(P)$ transition showed a predominant positive CD maximum centered at approximately 350 nm and a negative peak at somewhat higher energy was observed for serine and ornithine. Glutamic acid showed a broadening of the 350-nm band. In all cases, for acids with the L configuration, a negative CD tail was observed as was noted earlier for proline and simple amino acids.

The curves for aspartic acid and asparagine are markedly different, however. The D acids were used in this study and would have been expected to give curves which were mirror images of those found for the L acids studied above.

(14) T. Ito, F. Marumo, and Y. Saito, *Acta Crystallogr., Sect. B*, 27, 1062 (1971).

(15) H. C. Freeman, *Advan. Protein Chem.*, 22, 257 (1967).

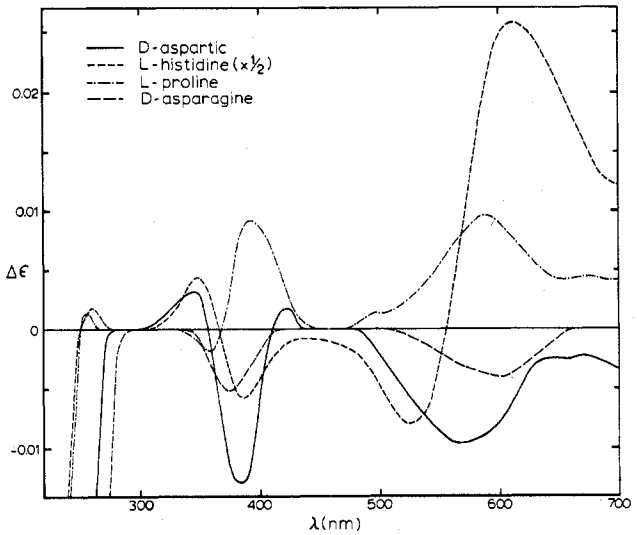

Figure 2. CD curves for nickel(II) complexes of proline and some polyfunctional amino acids.

However, these two D acids gave a markedly different CD spectrum and for the low-energy d-d transition the curves were entirely negative as shown in Figure 2; hence, the corresponding L acids would be entirely positive. Moreover, the ultraviolet tail which was negative for *all* other acids with the L configuration was negative for D-aspartic acid and asparagine.

All of the amino acids in this group have an extra donor group as part of the side chain attached to the α carbon. Because of this, each ligand is potentially tridentate and coordination in the axial sites of the nickel ion is possible. For histidine, an X-ray structure of the NiL_2 species has revealed[15] that the two amino acid rings are arranged in a cis arrangement in a central plane. The two axial sites are occupied by nitrogen atoms from the imidazole nucleus.

In the bis(histidinato)nickel(II) complex contributions to the optical activity arise from (i) the vicinal effect of the asymmetric carbon, (ii) the conformational effect of the chelate rings formed, and (iii) the overall configuration of the complex. The first contribution is similar to those listed for the other amino acids including proline and one would expect similar contributions here. However, there are more chelate rings to be considered in the histidine complex. The steric requirements of the ligand force the λ conformation on the amino acid ring and the chair conformation for the six-membered ring involving nitrogen atoms. These will give some contribution to the CD but should not be particularly large. The third contribution, however, is a major one and arises from the overall configuration imposed on the complex. Using the IUPAC system of nomenclature[16] the configuration "skew chelate pair Δ" is imposed upon the complex. The enhanced circular dichroism observed for this compound is consistent with a contribution from the configurational effect.

The complexes formed with serine, glutamic acid, and ornithine exhibit CD spectra of similar shape to that for histidine but of reduced intensity. For serine and ornithine, the extra donor atoms are unlikely to be coordinated and hence no configurational effect would be observed. The hydroxyl group of serine is not particularly basic and the extra amino group of ornithine would be protonated under the conditions of preparation. An X-ray structure[17] of $Ni(serine)_2 \cdot 2H_2O$ has shown this to be the case and a cis arrangement of the amino acid groups was found. Since glutamic acid has a similar CD spectrum, it would be expected to show a similar arrangement. However, for this compound, polymeric bridging to other nickel atoms is also a possibility but no new chelate rings would be formed. Thus, the CD spectra for all these acids are consistent with a cis arrangement of the chelate rings. Histidine shows enhanced optical activity due to the net chirality imposed on the complex.

However, the CD spectra for asparagine and aspartic acid which are distinctly different need to be explained. The low-energy region of the spectrum exhibits negative CD for the D acid (hence positive for L) and the tail in the ultraviolet region is of opposite sign also. This would suggest the presence of a significantly different species in these two cases. For aspartic acid three geometrical isomers are possible for a given configuration of acid and all three have been separated in the case of cobalt(III).[18] Using their nomenclature these are the trans(N), the cis(N),trans(O_6), and cis(N),trans(O_5) species. Of these the latter two have an arrangement of rings which are completely of opposite chiral sense. For the L acid the cis(N),trans(O_6) has the "skew chelate pair Δ" configuration while the cis(N),-trans(O_5) isomer has the "skew chelate pair Λ" configuration. The trans(N) isomer is symmetrical with respect to a C_2 axis. The L-histidine complex can only form the "skew chelate pair Δ" configuration while such a restriction is not imposed on aspartic acid and asparagine. A reversal of configuration is possible for the cis(N),trans(O_5) isomer and would be manifested in the CD of the d-d transitions. However, since the sign of the ultraviolet CD is also reversed, a different net arrangement for the carboxylate chromophores is suggested. For all isomers the O_5 atoms are cis to both N and O_6. However, for the cis(N),trans(O_5) isomer these atoms are trans to one another and give a different type of chromophore. Hence, it is possible that there is a predominance of this isomer produced in the case of both aspartic acid and asparagine. This particular arrangement is impossible for histidine, due to the steric requirements of the imidazole ring.

Summary

In this study there is the indication of a potentially useful indicator for stereochemistry. For all of the complexes studied spectra were obtained on fresh solutions prepared from solid samples. Under the conditions of the study the extent of dissociation in all cases was quite small and there was no evidence of decomposition or isomerization. Moreover, samples could be recovered from the solutions and posessed identical spectral properties as the initial samples. For the simple amino acids studied a trans arrangement of ligands is produced and the L isomer gives predominantly negative CD throughout the visible region of the absorption spectrum while a negative CD band is present in the uv. For proline where a cis configuration is imposed, a negative band is still observed in the uv. However, the d-d bands show a different CD pattern and a reversal of sign due to the significant vicinal effect of the asymmetric coordinated nitrogen atom. The polyfunctional amino acids also would form cis complexes on the basis of similarity to the CD of histidine. For tridentate coordination the pattern can be directly related to the net chirality of the complex. Thus, by examining the CD of the d-d transitions and the ultra-

(16) IUPAC tentative proposals, *Inorg. Chem.*, 9, 1 (1970).
(17) D. van der Helm and M. B. Hossain, *Acta Crystallogr., Sect. B*, 25, 457 (1969).
(18) S. Yamada, J. Hidaka, and B. E. Douglas, *Inorg. Chem.*, 10, 2187 (1971).

violet region, some insight can be gained concerning the cis-trans isomerism in complexes of this type.

Registry No. $Ni(D\text{-}Ala)_2 \cdot 2H_2O$, 39732-80-4; $Ni(L\text{-}Val)_2 \cdot 2H_2O$, 39732-81-5; $Ni(L\text{-}Ile)_2 \cdot 2H_2O$, 39732-82-6; $Ni(L\text{-}Pro)_2 \cdot 2H_2O$, 39732-83-7; $Na_2[Ni(D\text{-}Asp)_2] \cdot 5H_2O$, 39708-44-6; $Ni(D\text{-}Aspar)_2 \cdot 1.5H_2O$, 37343-98-9; $Ni(L\text{-}His)_2 \cdot H_2O$, 32424-04-7; $Ni(L\text{-}Ser)_2 \cdot 3.5H_2O$, 39732-85-9; $Ni(L\text{-}Ala)_2 \cdot 2H_2O$, 22585-12-2; $[Ni(D\text{-}Aspar)_2] \cdot 2H_2O$, 37343-99-0; $[Ni(L\text{-ornithine})_2] \cdot 2HCl$, 39732-87-1.

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Anomalous Complexation Kinetics of Transition Metal Ions with L-Dopa (3,4-Dihydroxyphenylalanine). Kinetics and Complex Formation with Nickel(II) and Cobalt(II)[1]

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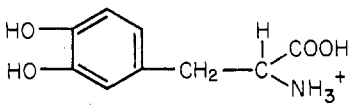
The temperature-jump relaxation method has been used to determine the complexation rate constants for the reactions of L-dopa (amino acid end) with nickel(II) and cobalt(II) at 25° and 0.1 *M* ionic strength. The complexation reactions observed are of the type $M^{2+} + H_2L^- \rightleftarrows MH_2L^+$, where H_2L^- is the anionic form of the ligand, in which both hydroxyl groups are protonated. The rate constants for this reaction are $k_1 = 2.2\ (\pm 0.3) \times 10^3\ M^{-1}\ sec^{-1}$ and $k_{-1} = 3.1\ (\pm 0.8) \times 10^{-2}\ sec^{-1}$ for $M^{2+} = Ni^{2+}$; $k_1 = 4.3\ (\pm 0.3) \times 10^5\ M^{-1}\ sec^{-1}$ and $k_{-1} = 72\ (\pm 7)\ sec^{-1}$ for $M^{2+} = Co^{2+}$. The association rate constants are low compared with normal substitution values. This effect is attributed to misorientation of the ligand in the ion-pair complex by hydrogen bonding. The complex NiH_2L^+ can also undergo reaction according to $NiH_2L^+ \rightleftarrows NiHL + H^+$, for which $k_D = 1\ (\pm 1)\ sec^{-1}$ and $k_H = 6.9\ (\pm 0.4) \times 10^7\ M^{-1}\ sec^{-1}$. The bimolecular protolytic reaction is several orders of magnitude slower than the diffusion-controlled limit. The necessary equilibrium constants were determined by potentiometric pH titration. The measured acid dissociation constants of L-dopa are $pK_{a_2}(-NH_3^+) = 8.76 \pm 0.03$, $pK_{a_3}(-OH) = 9.89 \pm 0.02$; and the stability constants are as follows: Ni^{2+}, $\log K_1 = 4.85 \pm 0.04$, $\log K_2 = 4.28 \pm 0.04$; Co^{2+}, $\log K_1 = 3.75 \pm 0.03$, $\log K_2 = 3.50 \pm 0.04$.

Transition metal ion–α-amino acid complexes are generally formed *via* a mechanism in which the rate-determining step is the loss of a water molecule from the metal ion's inner coordination sphere.[2,3] For normal substitution, ligand penetration into the inner coordination sphere of the metal ion is essentially independent of ligand characteristics.[2]

Recent kinetic investigations into the reactions of Cu^{2+}, Co^{2+}, and Ni^{2+} with hydroxyproline[4] and of Cu^{2+} with L-dopa (3,4-dihydroxyphenylalanine)[5] indicate that the addition of a single hydroxyl group suitably oriented on the parent amino acid (proline[4] and tyrosine,[6] respectively) has a pronounced effect on the rates of metal substitution reactions. Forward substitution rate constants for these metal–ligand systems are from one-third to one-tenth smaller than rate constants observed for normal systems, as in the cases of proline and tyrosine. The distinguishing feature of these anomalously slow complexation reactions is that the effect is comparable for Cu^{2+}, Co^{2+}, and Ni^{2+}, suggesting that the slower reaction rates are not due to a shift to another rate-determining step, such as closure of the chelate ring.[7-9]



dopa, fully protonated = H_4L^+

The present investigation into L-dopa complexation with Ni^{2+} and Co^{2+} was undertaken in the search of more evidence for interaction between the ligand hydroxyl groups and metal ions.

Experimental Section

Reagent grade $Ni(NO_3)_2 \cdot 6H_2O$ and $Co(NO_3)_2 \cdot 6H_2O$ (Fisher), KNO_3 (Baker), L-dopa (Nutritional Biochemicals Corp.), and Chlorophenol Red and Methyl Red (Eastman) were used without further purification.

Stock solutions of KNO_3, metal nitrates, and indicators were prepared by weight. The metal content of the stock solutions was determined by passing aliquots of the solutions through a cation exchanger (Dowex 50) and titrating the liberated acid with standardized sodium hydroxide solution. Solutions to be studied were prepared by mixing the desired volumes of stock solutions with weighed amounts of solid L-dopa in 100-ml volumetric flasks. (Stock solutions of L-dopa were unstable at neutral pH, turning brown after several hours.) The solutions were degassed and then transferred to a double-walled cell of approximately 200-ml capacity. The cell

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(2) (a) M. Eigen and R. G. Wilkins, *Advan. Chem. Ser.*, No. 49, 55 (1965); (b) F. Basolo and R. G. Pearson, "Mechanisms of Inorganic Reactions," 2nd ed, Wiley, New York, N. Y., 1967.

(3) K. Kustin and J. Swinehart, *Progr. Inorg. Chem.*, 13, 107 (1970).

(4) K. Kustin and S. T. Liu, *J. Chem. Soc., Dalton Trans.*, 278 (1973).

(5) R. L. Karpel, K. Kustin, A. Kowalak, and R. F. Pasternack, *J. Amer. Chem. Soc.*, 93, 1085 (1971).

(6) M. L. Barr, E. Baumgartner, and K. Kustin, *J. Coord. Chem.*, in press.

(7) W. B. Makinen, A. F. Pearlmutter, and J. E. Stuehr, *J. Amer. Chem. Soc.*, 91, 4083 (1969).

(8) K. Kustin, R. F. Pasternack, and E. M. Weinstock, *J. Amer. Chem. Soc.*, 88, 4610 (1966).

(9) A. Kowalak, K. Kustin, R. F. Pasternack, and S. Petrucci, *J. Amer. Chem. Soc.*, 89, 3126 (1967).