it is interesting to note that the deviations observed between experiment and theory are qualitatively similar to those seen previously for other self-exchange reactions. Thus it has been found that $\Delta H^* < \Delta H^*_{calcd}$ and $\Delta S^* < \Delta S^*_{calcd}$ for ferrocinium/ferrocene in a number of solvents.[20] and for $Ru(NH_3)_4bpy^{3+/2+}$ in aqueous media.[2] Most likely, these discrepancies reflect a limitation of the dielectric continuum model, possibly arising from changes in short-range reactant-solvent interactions required to form the encounter complex "solvent cage" prior to electron transfer. The requirement of forming a particular encounter geometry, with the two reactants essentially in contact so as to maximize the transmission coefficient, may partly be responsible for the experimental frequency factors being markedly smaller than those calculated that a simple model involving activation of a precursor complex formed in a prior equilibrium step. However, the simple collision model appears to have greater practical utility for outer-sphere processes, at least for the purpose of making numerical calculations.

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Registry No. $(\eta^6\text{-}C_6H_6)_2Cr^I$, 11077-47-7; $(\eta^6\text{-}C_6H_6)_2Cr^0$, 1271-54-1; $(\eta^6\text{-}C_6H_5CH_3)_2Cr^I$, 33505-50-9; $(\eta^6\text{-}C_6H_5CH_3)_2Cr^0$, 12087-58-0; $(\eta^6\text{-}C_6H_5OCH_3)_2Cr^I$, 75170-79-5; $(\eta^6\text{-}C_6H_5OCH_3)_2Cr^0$, 57820-92-5; $(\eta^6\text{-}C_6H_5C_6H_5)_2Cr^I$, 33154-48-2; $(\eta^6\text{-}C_6H_5C_6H_5)_2Cr^0$, 33085-81-3; $(\eta^6\text{-}C_6H_5COOC_2H_5)_2Cr^I$, 57219-88-2; $(\eta^6\text{-}C_6H_5COOC_2H_5)_2Cr^0$, 57219-87-1; $(\eta^6\text{-}C_6H_5Cl)_2Cr^I$, 75170-75-1; $(\eta^6\text{-}C_6H_5Cl)_2Cr^0$, 42087-89-8.

Coordination Modes of Histidine. 3.[1] Stereochemistry of Copper(II) Complexes Related to Pyridoxal Catalysis

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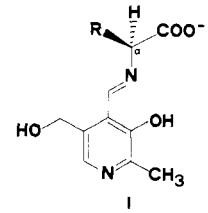
Abstract: Copper(II) complexes of Schiff bases derived from pyridoxal, salicylaldehyde, or pyruvic acid and histidine, histidine methyl ester, and representative amino acids with nonpolar side chains have been prepared by metal ion template synthesis. The mode of coordination to copper(II) of the histidine residues in these complexes has been investigated by circular dichroism spectroscopy. The complexes derived from amino acids with nonpolar side chains provide appropriate references for the glycine-like coordination mode, while the derivatives of histidine methyl ester are appropriate references for the histamine-like mode. The histidine residues exhibit a striking tendency to bind copper(II) through chelate ring types complementary to those of the fused carbonyl residue. Thus, in the complexes derived from pyridoxal and salicylaldehyde the histidine residues bind glycine-like, whereas in those derived from pyruvic acid the histidine residues bind histamine-like. The conformation of the coordinated Schiff base ligands has been deduced from the circular dichroism spectra of the complexes and discussed in relation to vitamin B_6 model reactions. The EPR spectra of the complexes were also investigated in different solvents to establish the donor sets and the ligand field symmetry in solution. The spectra show the pattern typical for tetragonal symmetry ($g_{\|} > g_{\perp}$), and the magnetic parameters were used to compute the molecular orbital coefficients that describe the bonding character in the complexes. The electronic excitation energies required in the calculations were deduced from the circular dichroism spectra.

Most of the transformations that amino acids undergo during metabolism are catalyzed by enzymes requiring pyridoxal phosphate as a cofactor.[2] The mechanisms proposed for pyridoxal catalysis, however, have mostly been derived from studies on model systems utilizing amino acid-pyridoxal and related Schiff bases and their metal complexes.[3,4] The work in this field has focused on mechanistic and spectroscopic properties of the systems, and only recently the enhancement of reactivity of a group to the amino acid α-carbon atom has been related to its correct stereochemical positioning within the molecule.[5] As first suggested by Dunathan,[6] an easy cleavage of a bond to the amino acid α-carbon atom in I can be accomplished by orienting that bond orthogonal to the



I

plane of the extended π system in order to optimize σ-π overlap. This stereoelectronic requirement enables pyridoxal-dependent enzymes to achieve reaction specificity and enhance reaction rates by proper conformational orientation of the bond to be cleaved (or formed). Despite the importance of recognizing the stereochemical factors that control the correct positioning of the groups

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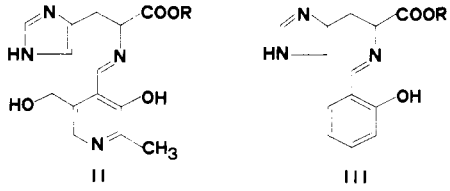
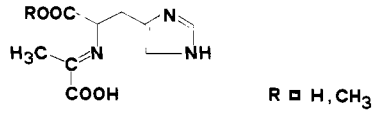
to be labilized, little attention has been paid to the stereochemistry of model systems which mimic the biological reaction types. Detailed conformational studies are currently limited to recent reports on zinc(II) complexes of I[1] and copper(II) complexes of *N*-salicylidene- and *N*-(+)-(hydroxymethylidenecamphorato) amino acids.[7-9]

We describe here the conformational properties of a series of copper(II) complexes with Schiff bases obtained from pyridoxal (II), salicylaldehyde (III), or pyruvic acid (IV) and derivatives



II

III



R ◻ H, CH_3

IV

of histidine. The copper(II) ions were selected because they show the highest overall activity in catalyzing pyridoxal-mediated reactions of amino acids in model systems.[3] The chelates derived from pyruvic acid were also included in this investigation since pyruvate, or other α-keto acids, and metal ions are effective catalysts in promoting reactions of amino acids that are usually related to pyridoxal catalysis.[10-12] The ability of pyruvate to replace pyridoxal as a cofactor has an important precedent in biological systems that seems of relevance to the compounds studied here. Bacterial histidine decarboxylase (E.C. 4.1.1.22), unlike the enzyme from mammalian sources, which requires pyridoxal phosphate,[13] contains a covalently bound pyruvate residue as prosthetic group.[14] As for the more common pyridoxal phosphate coenzyme, this pyruvoyl residue undergoes Schiff-base formation with histidine in a preliminary step of the decarboxylation process. Metal chelates of II–IV, therefore, may well simulate structural features of the enzyme–substrate–cofactor complexes in these biological systems.

Polydentate chiral ligands of the type II–IV provide a useful frame for investigating the effect of the mode of coordination of histidine residues on the optical activity of the metal ion transitions. The histidyl residue is probably the most frequently found metal-binding site in biological systems,[15] and histidine is apparently involved in copper(II) transport in blood.[16] The investigation of structural and spectral properties of metal complexes containing histidine[17] or histidyl residues[18,19] is thus very important for elucidating structure/function relationships in histidine-containing biological systems. However, a main problem usually encountered in these spectra–structure correlations is the apparent tendency by the potentially tridentate histidine ligand to form complexes with mixed chelation modes in solution.[20]

Experimental Section

All reagents were reagent grade and used as received; N^{τ}-methylhistamine was prepared according to a literature method.[21] D-Histidine methyl ester dihydrochloride was prepared by esterification of D-histidine in anhydrous methanol under a stream of dry hydrogen chloride and precipitated by addition of diethyl ether to the methanol solution; $[\alpha]^{25}_{D}$ −9.9° (*c* 2, H_2O) (for L-histidine methyl ester dihydrochloride: $[\alpha]^{25}_{D}$ +9.8° (*c* 2, H_2O)). Elemental analyses were from the microanalytical laboratory of the University of Milano. The electronic, circular dichroism, and infrared spectra were recorded on a Beckman DK-2A, a Jobin-Yvonne Mark III, and a Beckman Acculab 1 instrument, respectively. The EPR spectra were obtained on a Varian E-109 spectrometer operating at X-band frequencies. Conductivity measurements were performed on a Philips conductimeter PR 9500.

Preparation of the Complexes.[22] The complexes Cu(sal-L-his), Cu(sal-D-his), Cu(sal-L-ser), Cu(Hpdx-L-his)Cl, Cu(Hpdx-D-his)Cl, Cu(Hpdx-L-phe)Cl, and Cu(Hpdx-L-val)Cl were prepared according to the following procedure. Equimolar amounts of salicylaldehyde or pyridoxal hydrochloride and the amino acid (2 mmol) were dissolved in water–methanol (1:1, 40 mL). Then copper(II) acetate monohydrate (2 mmol)

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(22) Abbreviations used for the ligands: *N*-pyridoxylideneamino acidato anion = pdx-aa; ring protonated form of pdx-aa = Hpdx-aa; *N*-salicylideneamino acidato anion = sal-aa; *N*-pyruvylideneamino acidato anion = pyv-aa; condensed amino acid anion = aa; histidinate anion = his; alaninate anion = ala; glycinate anion = gly; phenylalaninate anion = phe; valinate anion = val; serinate anion = ser; histidine methyl ester = hisOCH_3; histamine = him; N^{τ}-methylhistamine = himNCH_3. Primed symbols refer to anionic species containing deprotonated imidazole rings: hisOCH_3', and sal-hisOCH_3', pdx-hisOCH_3', etc.

was added to the solution under stirring. After several hours, the green precipitate of the copper(II) complex was collected by filtration, washed with a little water–methanol, and dried under vacuum. The compounds Cu(pyv-L-his), Cu(pyv-D-his), Cu(pyv-L-ala), and Cu(pyv-L-val) were prepared similarly from pyruvic acid. Blue precipitates were obtained in these cases upon concentration under vacuum to a small volume of the reaction solutions. The complexes Cu(pdx-L-his), Cu(pdx-D-his), Cu(pdx-L-val), and Cu(pdx-L-phe) were obtained by reacting equimolar amounts (2 mmol) of free pyridoxal, the amino acid, and freshly prepared cupric hydroxide in water–methanol (1:1, 40 mL). After the reaction mixture was stirred for several hours, the green precipitate was filtered, washed (water–methanol), and dried under vacuum.

To obtain Cu(sal-L-hisOCH$_3$)ClO$_4$, Cu(sal-D-hisOCH$_3$)ClO$_4$, Cu(Hpdx-L-hisOCH$_3$′)ClO$_4$, and Cu(Hpdx-D-hisOCH$_3$′)ClO$_4$, we reacted equimolar amounts of salicylaldehyde or free pyridoxal and free L- or D-histidine methyl ester (2 mmol) in methanol (40 mL). Then copper(II) perchlorate hexahydrate (2 mmol) and sodium hydroxide (2 mmol) were added to the solution under stirring. The green copper(II) complex thus precipitated was filtered, washed with water–methanol, and dried under vacuum. The compounds Cu(Hpdx-L-val)ClO$_4$ and Cu(pdx-himNCH$_3$)ClO$_4$ were prepared similarly from L-valine in water–methanol (1:1) and from free N^{τ}-methylhistamine in water, respectively. The complexes Cu(Hpdx-L-hisOCH$_3$)(ClO$_4$)$_2$ and Cu(Hpdx-D-hisOCH$_3$)(ClO$_4$)$_2$ were obtained by reaction of free pyridoxal, free L- or D-histidine methyl ester, and copper(II) perchlorate hexahydrate (2 mmol) in methanol (40 mL) for several hours, followed by evaporation under vacuum to a small volume and addition of diethyl ether. The green precipitate thus formed was then washed with a little amount of water–methanol and dried under vacuum.

The complexes Cu(Hpdx-L-hisOCH$_3$)Cl$_2$, Cu(Hpdx-D-hisOCH$_3$)Cl$_2$, Cu(pyv-L-hisOCH$_3$)Cl, and Cu(pyv-D-hisOCH$_3$)Cl were prepared by mixing equimolar amounts of free pyridoxal or pyruvic acid, L- or D-histidine methyl ester dihydrochloride, and sodium hydroxide (2 mmol) in methanol (40 mL) under stirring. Then freshly prepared cupric hydroxide (2 mmol) was added in small portions. The solution was concentrated to a small volume and chromatographed on a Sephadex LH-20 column (2.5 × 30 cm, methanol as eluant). A single main fraction was obtained in each case. This was collected and evaporated to dryness under vacuum.

The compound Cu(sal-L-hisOCH$_3$′) was obtained as a green precipitate upon mixing equimolar amounts of salicylaldehyde, free L-histidine methyl ester, and copper(II) acetate monohydrate (2 mmol) in water–methanol (40 mL), while Cu(pyv-L-hisOCH$_3$′) was prepared similarly with use of pyruvic acid, free histidine methyl ester, and freshly prepared cupric hydroxide in water. The green precipitate was filtered, washed with water, and dried under vacuum. The complex Cu(pyv-gly) was prepared according to a published procedure.[23] The elemental analyses of the copper(II) complexes are collected in Table I[24] (supplementary material).

Results

The copper(II) complexes were prepared by metal ion template condensation of the carbonyl compound and the histidine derivative. The free Schiff bases were not isolated due to the easy cyclization reaction to 4,5,6,7-tetrahydropyrido[3,4-*d*]imidazole compounds undergone by histidine Schiff bases, particularly those derived from pyridoxal.[1] A number of complexes containing amino acids with nonpolar side chains were also prepared as appropriate reference compounds, since the conformational preferences of these amino acid residues are known for copper(II) complexes derived from salicylaldehyde and (+)-(hydroxymethylene)camphor.[7] The complexes derived from pyridoxal were prepared with either the pyridine ring protonated or nonprotonated form of pyridoxal in order to ascertain any possible stereochemical change between these forms. However, the attempt to prepare the complexes Cu(pdx-L-hisOCH$_3$)ClO$_4$ and Cu(pdx-D-hisOCH$_3$)ClO$_4$ led to the formation of species containing the deprotonated form of the imidazole nucleus of the histidine residues. These compounds must be formulated as Cu(Hpdx-L-hisOCH$_3$′)ClO$_4$ and Cu(Hpdx-D-hisOCH$_3$′)ClO$_4$, respectively. Complexes containing the imidazole deprotonated form of L-histidine methyl ester were obtained also from salicylaldehyde (Cu(sal-L-hisOCH$_3$′)) and pyruvic acid (Cu(pyv-L-hisOCH$_3$′)). All the other complexes containing histidine residues were prepared by using both L- and D-amino acid derivatives.

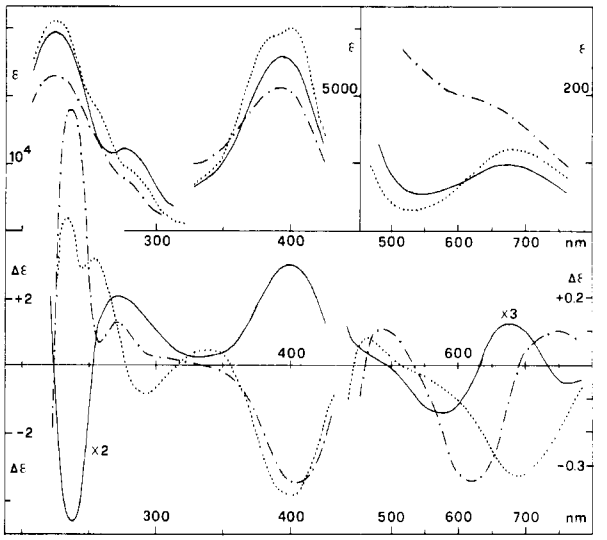

Figure 1. Electronic and circular dichroism spectra of (a) (····) Cu(Hpdx-L-his)Cl in water solution, (b) (···) Cu(Hpdx-L-val)Cl in methanol solution, and (c) (—) Cu(Hpdx-L-hisOCH$_3$)(ClO$_4$)$_2$ in methanol solution.

The Schiff base structure of the ligands in these series of copper(II) chelates is confirmed by the presence of strong imine ν(C=N) bands occurring at 1630–1640 cm^{-1} in the IR spectra of complexes derived from pyridoxal or salicylaldehyde and at 1660–1670 cm^{-1} in those of complexes derived from pyruvate. In addition, the IR spectra of complexes of L- or D-histidine methyl ester show that the carbonyl ester group is noncoordinated (ν(C=O) is at 1730–1740 cm^{-1}).[1,9] The positions of the other main IR bands of the ligands are nearly coincident with those found in the spectra of the corresponding series of zinc(II) complexes.[25] The broad feature of the band near 1100 cm^{-1} in the IR spectra of complexes containing perchlorate anions indicates that these are noncoordinated.[26]

The molar conductivity data in methanol solution at 10^{-3} M concentration obtained for ionic 1:1 complexes are not indicative of anion coordination.[27] The Λ_M value obtained for Cu(Hpdx-L-hisOCH$_3$)Cl$_2$, however, falls in the range for 1:1 electrolytes and suggests that one of the two chloride ions is significantly coordinated in solution.[28] By contrast, the corresponding perchlorate complex, Cu(Hpdx-L-hisOCH$_3$)(ClO$_4$)$_2$, behaves as a 1:2 electrolyte.

Electronic and Circular Dichroism Spectra. The electronic and circular dichroism spectra of the copper(II) complexes described here are summarized in Tables II and III,[24] and representative spectra are given in Figures 1–4. The spectra were recorded in methanol or water solution, depending on the solubility of the compounds, and in pyridine. The complexes Cu(sal-L-his) and Cu(sal-D-his) are completely insoluble in water or methanol, and only spectra in pyridine could be obtained. In general, the copper(II) complexes containing histidine residues possess a low-energy absorption band between 600 and 700 nm (ϵ 100–200) that encompasses the metal d–d transitions. At higher energies the Schiff base chelates derived from pyridoxal (~390 nm) and salicylaldehyde (~375 nm) exhibit an intense absorption band

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(24) Supplementary material.
(25) For detailed assignments of these bands, see ref 1.
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(27) The Λ_M values obtained in methanol at 10^{-3} M concentration are as follows: Cu(Hpdx-L-val)Cl, 62; Cu(Hpdx-L-val)ClO$_4$, 68; Cu(Hpdx-L-hisOCH$_3$′)ClO$_4$, 85; Cu(sal-L-hisOCH$_3$)ClO$_4$, 60; Cu(pyv-L-hisOCH$_3$)Cl, 76; Cu(pyv-D-hisOCH$_3$)Cl, 68; Cu(Hpdx-L-hisOCH$_3$)Cl$_2$, 116; Cu(Hpdx-L-hisOCH$_3$)(ClO$_4$)$_2$, 188. The solubility of Cu(Hpdx-L-his)Cl and Cu(Hpdx-D-his)Cl is too low for reliable measurements.
(28) Geary, W. J. *Coord. Chem. Rev.* **1971**, *7*, 81–122.

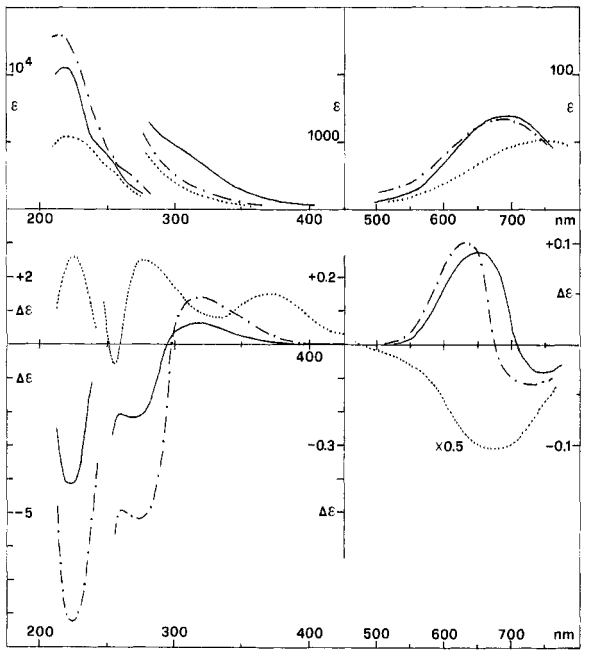

Figure 2. Electronic and circular dichroism spectra of (a) (-···-) Cu(pyv-L-his) in water solution, (b) (···) Cu(pyv-L-val) in water solution, and (c) (—) Cu(pyv-L-hisOCH$_3$)Cl in methanol solution.

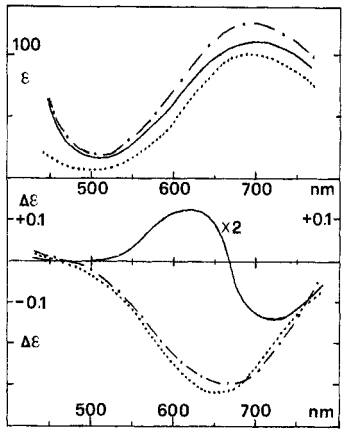

Figure 3. Electronic and circular dichroism spectra in pyridine solution of (a) (-···-) Cu(pyv-L-his), (b) (···) Cu(pyv-L-val), and (c) (—) Cu(pyv-L-hisOCH$_3$)Cl.

that may, by analogy with the related zinc(II) complexes[1] and with corresponding chelates derived from other amino acids,[7,29,30] be attributed to a $\pi \rightarrow \pi^*$ transition originating mainly within the azomethine chromophore. The intense bands occurring at still higher energies (~270 and ~225 nm) are associated with benzene or pyridine ring $\pi \rightarrow \pi^*$ transitions. Shoulders on these bands appear in the electronic spectra of most of the chelates and are often clearly evident in the CD spectra. The UV spectra of the complexes derived from pyruvic acid show only a broad asymmetric band, centered near 220 nm, with badly resolved shoulders on its low-energy side. Also in this case, the CD spectra reveal more detail than the corresponding absorption spectra.

The visible CD spectra of copper(II) complexes derived from pyridoxal or salicylaldehyde recorded in either methanol (water) or pyridine exhibit two or three resolved bands attributable to d–d

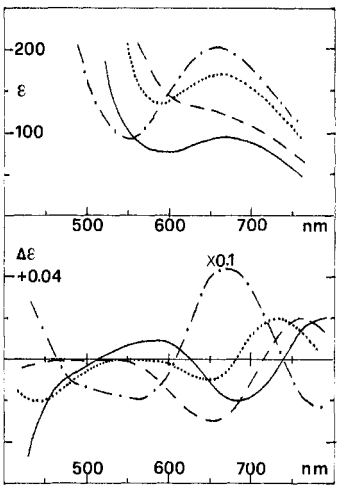

Figure 4. Electronic and circular dichroism spectra of (a) (—) Cu(Hdpx-L-hisOCH$_3$')ClO$_4$ in methanol solution, (b) (···) Cu(sal-L-hisOCH$_3$') in pyridine solution, (c) (---) Cu(pyv-L-hisOCH$_3$') in pyridine solution, and (d) (-···-) Cu(sal-L-hisOCH$_3$)ClO$_4$ in pyridine solution.

transitions. We label the band above 700 nm as band I and the two bands occurring between 600 and 680 nm and below 600 nm as bands II and III, respectively. In several instances band I is not observed; it may occur at lower energy beyond the instrumental range (800 nm), or, more likely, be buried under the more intense and oppositely signed band II. This behavior is similar to that exhibited by the visible CD spectra of simple copper(II) amino acid complexes.[31] The sign pattern of bands I–III is positive (band I), negative (II), and positive (III) for the complexes Cu(pdx-L-his), Cu(Hpdx-L-his)X, Cu(sal-L-his), Cu(Hpdx-D-hisOCH$_3$)X$_2$, and Cu(sal-D-hisOCH$_3$)X (X = Cl, ClO$_4$), although the sign of band III is occasionally reversed in pyridine. This same sign pattern is displayed by the CD spectra of complexes derived from L amino acids with nonpolar side chains, of the type Cu(pdx-L-aa), Cu(Hpdx-L-aa)X, and Cu(sal-L-aa).[7] As expected, the complexes with opposite chirality at the histidine center, namely Cu(pdx-D-his), Cu(Hpdx-D-his)X, Cu(sal-D-his), Cu(Hpdx-L-hisOCH$_3$)X$_2$, and Cu(sal-L-hisOCH$_3$)X, exhibit the pattern negative (I), positive (II), and negative (III) for the CD bands I–III, with band III occasionally inverted in pyridine. In the UV region, the complexes derived from pyridoxal or salicylaldehyde show three or more CD bands. Those corresponding to transitions originating within the ligand chromophores occur near 230, 270, and 400 nm (pyridoxal) or 375 nm (salicylaldehyde). The CD maximum near 230 nm appears bathochromically shifted from the corresponding absorption maximum (near 225 nm) and may therefore be interpreted as the long wavelength lobe of an exciton couplet.[32] In general, the derivatives of L-histidine and D-histidine methyl ester exhibit positive CD activity at 230 nm and negative CD activity within the azomethine band, at 400 (pyridoxal) or 375 nm (salicylaldehyde). These 230-nm and azomethine CD bands have opposite signs in the spectra of derivatives of D-histidine and L-histidine methyl ester. Overlap with other CD bands of similar energy precludes a rationalization of the behavior of the 270-nm band. However, we have the important result that, with no exception, the sign of the Cotton effects associated with the azomethine and the higher energy benzenoid band are related to the sign of visible band II. This is always consignate with the azomethine band and dissignate with the 230-nm CD band.

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Table II. Electronic and Circular Dichroism Spectra of Copper(II) Complexes of Schiff Bases Derived from L-Amino Acids

compound	solvent	UV-vis, λ_{max}, nm[c] (ϵ)	CD, λ_{max}, nm ($\epsilon_l - \epsilon_r$)
Cu(pdx-himNCH$_3$)ClO$_4$	MeOH	226 (20000), 271 (9000), 308 (3300), 386 (6000), 650 (153)	
	py	340 sh (3000), 392 (5300), 625 (197)	
Cu(pdx-L-his)	MeOH	227 (16500), 272 (6000), 397 (3650), 410 sh (3400), 635 (115)	234 (+12.72), 255 (−0.62), 276 (+2.26), 340 (+0.31), 410 (−5.20), 510 (+0.11), 622 (−0.53), 750 (+0.16)
	py	393 (5300), 402 sh (5000), 658 (122)	300[a] (+2.00), 400 (−6.68), 515 (−0.12), 670 (−0.27)
Cu(Hpdx-L-his)Cl	H$_2$O	222 (23000), 271 (7800), 390 (5000), 405 sh (4700), 620 sh (200)	230 (+7.90), 270 (+1.25), 405 (−3.50), 480 (+0.11), 620 (−0.35), 740 (+0.10)
	py	387 (6000), 402 sh (5400), 652 (155)	300[a] (+0.72), 400 (−3.07), 535 (−0.10), 670 (−0.15)
Cu(Hpdx-L-hisOCH$_3$)Cl$_2$	MeOH	222 (40000), 272 (8500), 390 (6400), 665 (85)	228 (−0.65), 276 (+0.40), 400 (+0.85), 590 (−0.05), 675 (+0.03), 800[b] (−0.13)
	py	340 (4300), 398 (2000), 745 (110)	300[a] (+0.40), 350 (−0.10), 410 (+0.20), 570 (−0.03), 670 (+0.03), 800[b] (−0.02)
Cu(Hpdx-L-hisOCH$_3$)(ClO$_4$)$_2$	MeOH	223 (29000), 272 (11000), 388 (6500), 405 sh (6300), 455 sh (985), 670 (95)	230 (−2.30), 275 (+1.10), 400 (+1.50), 590 (−0.05), 670 (+0.04), 760 (−0.02)
	py	398 (5700), 460 sh (800), 655 (175)	410 (+0.35), 580 (−0.04), 670 (+0.06), 760 (−0.03)
Cu(Hpdx-L-hisOCH$_3$')ClO$_4$	MeOH	219 (2500), 271 (8500), 310 sh (5400), 390 (4300), 470 sh (750), 658 (88)	220[d] (−1.30), 250 (+0.30), 330 (−0.22), 380 sh (−0.18), 580 (+0.01), 680 (−0.02), 800[b] (+0.02)
	py	340 sh (4500), 395 (3500), 470 sh (900), 635 (150)	
Cu(pdx-L-val)	MeOH	227 (26500), 272 (10500), 390 (5050), 402 sh (4700), 670 (135)	238 (+5.98), 263 (−1.68), 290 (−0.41), 308 (+0.22), 404 (−3.74), 500 (−0.13), 680 (−0.39)
	py	390 (5150), 406 sh (4700), 660 (160)	330 (+1.12), 405 (−4.58), 500 sh (−0.22), 675 (−0.43), 800[b] (+0.17)
Cu(Hpdx-L-val)Cl	MeOH	225 (31000), 250 sh (19000), 275 sh (9560), 350 sh (2600), 383 (7200), 400 (7500), 683 (122)	230 (+4.49), 250 (+3.33), 290 (−0.93), 340 (+0.52), 400 (−3.88), 460 (+0.08), 682 (−0.33)
	py	350 sh (2600), 391 (3900), 409 sh (3500), 660 (126)	300[a] (−0.25), 330 (+0.73), 410 (−2.93), 500 sh (−0.16), 675 (−0.33), 800[b] (+0.15)
Cu(Hpdx-L-val)ClO$_4$	MeOH	229 (20100), 271 (8800), 388 (5150), 400 sh (4800), 670 (135)	236 (+7.25), 265 (−1.44), 290 (−0.22), 312 (+0.56), 403 (−3.45), 495 (−0.13), 680 (−0.37), 800[b] (+0.05)
	py	391 (5200), 409 sh (4800), 664 (160)	300[a] (−0.40), 325 (+0.98), 410 (−4.28), 490 sh (−0.25), 680 (−0.48), 800[b] (+0.23)
Cu(pdx-L-phe)	MeOH-H$_2$O[e]	223 (16000), 243 sh (10000), 270 sh (4800), 352 (4800), 400 sh (1500), 650 (200)	235 (+2.50), 270 sh (+0.70), 400 (−1.15), 630 (−0.39)
	py	330 (1200), 400 sh (650), 645 (110)	320 (+0.12), 400 (−0.45), 650 (−0.25), 800[b] (+0.06)
Cu(Hpdx-L-phe)Cl	MeOH	224 sh (29000), 240 sh (21000), 275 sh (8700), 325 (3700), 361 (4100), 395 sh (2700), 660 (130)	235 (+4.78), 270 sh (+1.67), 295 (−0.15), 395 (−1.40), 630 (−0.20)
	py	351 (4300), 400 sh (1800), 660 (120)	330 (+0.09), 400 (−1.03), 580 sh (−0.09), 665 (−0.16)
Cu(sal-L-his)	py	376 (7600), 450 sh (150), 655 (195)	375 (−7.36), 455 sh (−0.29), 670 (−0.39)
Cu(sal-L-ser)	py	374 (5150), 450 sh (130), 655 (210)	376 (−4.22), 455 sh (−0.29), 680 (−0.38), 800[b] (+0.07)
Cu(sal-L-hisOCH$_3$)ClO$_4$	MeOH	216 (22700), 240 sh (21300), 270 (14600), 295 sh (2850), 376 (4760), 450 sh (200), 658 (105)	230 (−6.07), 250 sh (−1.97), 275 (+1.75), 376 (+4.35), 450 sh (+0.30), 580 (−0.16), 670 (+0.23), 800[b] (−0.14)
	py	382 (6800), 470 sh (375), 655 (208)	300[a] (+1.70), 382 (+4.16), 560 (−0.28), 670 (+0.43), 800[b] (−0.24)
Cu(sal-L-hisOCH$_3$')	py	330 sh (2100), 387 (1800), 460 sh (600), 660 (170)	300[a] (−0.03), 380 (+0.01), 440 (−0.02), 650 (−0.01), 730 (+0.02)
Cu(pyv-L-his)	H$_2$O	215 (13000), 270 sh (1300), 380 sh (75), 675 (65)	223 (−8.27), 270 (−0.52), 320 (+0.13), 635 (+0.10), 730 (−0.04)
	py	320 sh (1000), 385 (350), 400 sh (330), 680 (125)	300[a] (+0.43), 380 sh (+0.12), 660 (−0.30)
Cu(pyv-L-hisOCH$_3$)Cl	MeOH	220 (10500), 245 sh (4500), 300 sh (800), 688 (68)	220 (−4.20), 270 (−0.22), 315 (+0.06), 645 (+0.09), 740 (−0.03)
	py	685 (110)	300[a] (+0.26), 620 (+0.06), 720 (−0.07)
Cu(pyv-L-hisOCH$_3$')	py	420 sh (550), 650 sh (130)	300[a] (−0.35), 650 (−0.06), 765 (+0.04)

Table II (*Continued*)

compound	solvent	UV-vis, λ_{max}, nm[c] (ϵ)	CD, λ_{max}, nm ($\epsilon_l - \epsilon_r$)
Cu(pyv-L-val)	H_2O	218 (5100), 250 sh (2400), 280 sh (750), 370 sh (30), 740 (51)	224 (+2.61), 253 (−0.07), 280 (+0.25), 368 (+0.15), 670 (−0.21)
	py	325 sh (680), 390 sh (52), 683 (103)	315 sh (+0.25), 395 (+0.10), 650 (−0.32)
Cu(pyv-L-ala)	H_2O	214 (4500), 245 sh (2300), 280 sh (550), 370 sh (30), 745 (45)	225 (+1.63), 250 (−0.10), 272 (+0.21), 365 (+0.12), 700 (−0.14)
	py	325 sh (480), 390 sh (42), 685 (98)	310 sh (+0.35), 395 (+0.08), 645 (−0.21)
Cu(pyv-gly)	H_2O	215 (5500), 240 sh (3000), 745 (80)	
	py	320 sh (850), 690 (125)	

[a] Maximum below solvent cutoff; $\Delta\epsilon$ in parentheses is at 300 nm. [b] Maximum too close or beyond long wavelength limit of instrument to be fully resolved; $\Delta\epsilon$ in parentheses is at 800 nm. [c] Shoulder = sh. [d] Maximum below solvent cutoff; $\Delta\epsilon$ in parentheses is at 220 nm. [e] Ratio 1:1.

The CD spectra of copper(II) complexes derived from pyruvate display only one or two bands in the visible region, above 700 nm (band I) and between 600 and 700 nm (band II). In water (methanol) solution the complexes containing histidine residues of the same chirality, e.g., Cu(pyv-L-his) and Cu(pyv-L-hisOCH$_3$)Cl, exhibit spectra with CD bands of the same sign pattern (negative (I) and positive (II)). In pyridine solution the CD spectra of the derivatives of histidine methyl ester show bands I and II only slightly blue shifted, whereas important changes occur in the spectra of Cu(pyv-L-his) and Cu(pyv-D-his). In these cases CD band II undergoes an inversion of sign and, as a result, a single bathochromically shifted band II is observed. In addition, a rather fast reduction in the optical activity of the solution indicates that Cu(pyv-L-his) and Cu(pyv-D-his) undergo racemization in pyridine, while the spectra of Cu(pyv-L-hisOCH$_3$)Cl and Cu(pyv-D-hisOCH$_3$)Cl are completely stable. The CD spectra of pyruvate complexes containing amino acids with nonpolar side chains show a single band (band II) in either water or pyridine solution, which has negative sign for amino acids with L absolute configuration. In the UV region, the CD spectra of the pyruvate complexes display bands near 220, 270, and between 320 and 370 nm. Of these bands, only that at 220 nm corresponds to a maximum of electronic absorption, while the others can often be observed as poorly resolved shoulders on the low energy tail of the 220-nm electronic band. The sign of the CD bands at 220 and 270 nm appears to be related to that of CD band II. A positive Cotton effect within band II corresponds invariably to negative CD activity at 220 and 270 nm.

Chiral complexes derived from histidine methyl ester and containing deprotonated imidazole rings have been obtained from either pyridoxal, salicylaldehyde, or pyruvic acid. In each case the CD spectra of these compounds, for instance Cu(sal-L-hisOCH$_3$′) and Cu(pyv-L-hisOCH$_3$′), exhibit bands of reversed sign patterns with respect to those of their counterparts containing protonated imidazole nuclei (Cu(sal-L-hisOCH$_3$)ClO$_4$ and Cu(pyv-L-hisOCH$_3$)Cl, respectively). In general, these imidazolate complexes undergo a rather fast racemization in solution. The racemization of Cu(Hpdx-L-hisOCH$_3$′)ClO$_4$ and Cu(Hpdx-D-hisOCH$_3$′)ClO$_4$ in pyridine is so fast that it is practically impossible to observe the optical activity of the solution. Therefore, these complexes may have undergone a partial racemization during their preparation.

EPR Spectra. The EPR spectra of copper(II) complexes were recorded in frozen methanol, or water, and pyridine solutions. The resolution of methanolic or aqueous spectra was often greatly enhanced by addition of very small amounts of ethylene glycol. These added quantities did not affect the features of the electronic and CD spectra of the complexes. The EPR spectra could be fitted for $g_{\parallel} > g_{\perp}$, showing the pattern typical for tetragonal symmetry. The spectral parameters are collected in Tables IV and V,[24] and representative spectra are given in Figures 5 and 6. The methanol (water) spectra of neutral complexes derived from pyridoxal, e.g., Cu(pdx-L-his), Cu(pdx-L-val), and of Cu(Hpdx-L-his)Cl, show the presence of superimposed centers that probably arise from species of different molecular complexity. The clusters are apparently broken in pyridine, since spectra in this solvent are typical for diluted samples. Two species, with rather different $g_{\parallel}$ and $A_{\parallel}$ values, are clearly observed in the EPR spectra of Cu(Hpdx-L-phe)Cl recorded in either methanol or pyridine. We believe these arise from the presence of a Schiff base–carbinolamine equilibrium in solution, since the intensity of the azomethine electronic band and the magnitude of the Cotton effect associated with it (Table II) are rather low in both solvents for Cu(Hpdx-L-phe)Cl compared for instance with those of Cu(Hpdx-L-val)Cl and Cu(Hpdx-L-his)Cl.

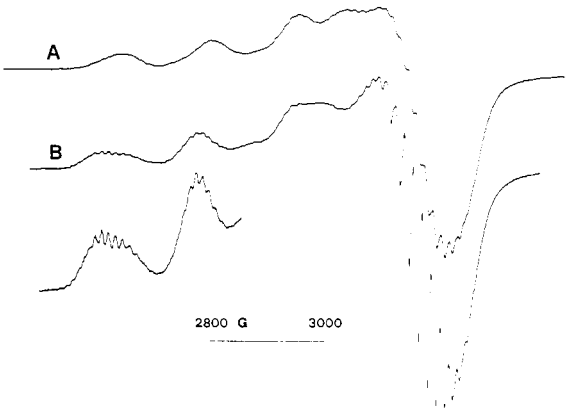

Figure 5. EPR spectra in frozen pyridine solution at −140 °C of (A) Cu(Hpdx-L-val)ClO$_4$ (ν 9.076 GHz) and (B) Cu(Hpdx-L-hisOCH$_3$)Cl$_2$ (ν 9.075 GHz).

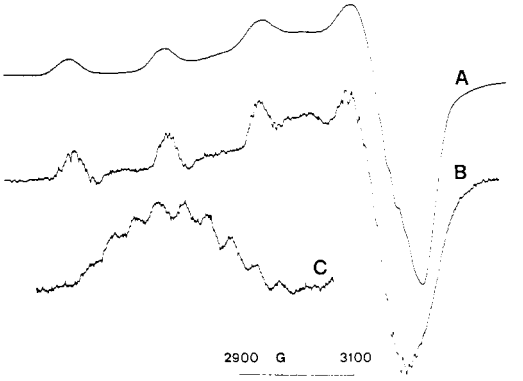

Figure 6. EPR spectra of Cu(pyv-L-his) in frozen aqueous (A) (ν 9.068 GHz) and pyridine (B) (ν 9.074 GHz) solution at −140 °C. Insert C represents the second copper hyperfine line at low-field obtained at increased gain in an expanded scale.

In general the EPR parameters show solvent dependence, indicative of coordination of donor molecules to the metal centers. The $g_{\parallel}$ and $g_{\perp}$ values obtained from pyridine solutions of the complexes are smaller, and the $A_{\parallel}$ values larger, than those obtained from methanol or water solutions. This trend in the $A_{\parallel}$ values is reversed only for Cu(Hpdx-L-val)Cl, Cu(Hpdx-L-val)ClO$_4$, Cu(pyv-L-his), and Cu(pyv-D-his), while the EPR parameters of Cu(Hpdx-L-hisOCH$_3$)Cl$_2$ and Cu(Hpdx-D-hisOCH$_3$)Cl$_2$ are rather solvent independent. In several instances the spectra show superhyperfine interaction with ligand (nitrogen) nuclei,

Table IV. Magnetic Parameters and Molecular Orbital Coefficients for Cu(II) Complexes with Schiff Bases of L-Amino Acids[a]

compound	solvent	$g_\parallel$	$g_\perp$	$10^4\lvert A_\parallel\rvert$, cm^{-1}	$10^4\lvert A_\perp^N\rvert$, cm^{-1} (n)[b]	α^2	α'^2	β_1^2	β^2
Cu(pdx-L-val)	py	2.251	2.061	168		0.78	0.30	0.79	0.97
Cu(Hpdx-L-val)Cl	MeOH	2.274	2.060	180		0.84	0.24	0.78	0.96
	py	2.258	2.057	169	13.9 (3)	0.79	0.29	0.80	0.92
Cu(Hpdx-L-val)ClO_4	MeOH	2.268	2.060	183		0.84	0.24	0.77	0.91
	py	2.258	2.061	164		0.78	0.31	0.81	0.99
Cu(Hpdx-L-phe)Cl[c]	py	2.254		182					
Cu(pdx-L-his)	py	2.252	2.057	179		0.81	0.27	0.77	0.87
Cu(Hpdx-L-his)Cl	py	2.253	2.058	179		0.81	0.27	0.77	0.86
Cu(pdx-himNCH_3)ClO_4[e]	MeOH	2.265	2.079	169		0.81	0.28	0.83	0.96
	py	2.244	2.054	181		0.81	0.28	0.80	0.73
Cu(Hpdx-L-hisOCH_3)Cl_2[f]	MeOH	2.262	2.066	172		0.81	0.28	0.80	0.90
	py	2.263	2.066	174		0.81	0.27	0.80	0.91
Cu(Hpdx-L-hisOCH_3)$(ClO_4)_2$	MeOH	2.278	2.069	162	13.5 (2)	0.80	0.29	0.86	0.94
	py	2.251	2.057	176	13.9 (4)	0.80	0.29	0.78	0.81
Cu(sal-L-his)	py	2.252	2.055	179		0.81	0.27	0.77	0.94
Cu(sal-L-ser)	py	2.250	2.054	176		0.80	0.28	0.76	0.94
Cu(sal-L-hisOCH_3)ClO_4	MeOH	2.265	2.063	169		0.80	0.28	0.82	0.88
	py[d]	2.250	2.063	173	14.0 (4)	0.79	0.29	0.78	0.92
Cu(pyv-L-his)	H_2O	2.271	2.066	175	13.9 (2)	0.82	0.26	0.85	0.82
	py	2.261	2.066	169		0.80	0.29	0.82	0.83
Cu(pyv-L-hisOCH_3)Cl	MeOH	2.276	2.067	170	14.0 (2)	0.81	0.27	0.86	0.83
	py	2.256	2.066	174	14.0 (4)	0.80	0.28	0.85	0.86
Cu(pyv-L-ala)	H_2O	2.297	2.074	155		0.80	0.28	0.87	0.86
	py[d]	2.258	2.065	164		0.78	0.31	0.85	0.84
Cu(pyv-L-val)	H_2O	2.304	2.071	156		0.81	0.27	0.90	0.85
	py[d]	2.254	2.068	166		0.78	0.30	0.83	0.87
Cu(pyv-gly)[e]	H_2O	2.303	2.078	156		0.81	0.27	0.82	0.84
	py	2.263	2.068	159		0.77	0.31	0.82	0.84

[a] The EPR spectra were recorded in frozen solution at −140 °C. [b] Number of nitrogen donors from superhyperfine splitting. [c] Major species. [d] A small amount of heptane was added to increase the spectral resolution. [e] The ΔE_{xy} and ΔE_{xz} excitation energies were assumed equal to the maximum of electronic absorption. [f] The values for the $T(n)$ and S constants of this complex used in the calculations were *0.305* and *0.089*, *respectively*.

which gives a useful indication of the number of nitrogen atoms involved in the donor set. In a few cases a rather complex pattern of lines results from superposition of copper hyperfine and ligand superhyperfine splittings (Figure 5). In order to obtain a qualitative description of the bonding character in the complexes, we have estimated the molecular orbital coefficients α, β_1, and β, which characterize the planar σ and π bonding and the out-of-plane π bonding, respectively, assuming an effective tetragonal site symmetry.[33-35] The molecular orbital coefficients were computed from the spin Hamiltonian parameters according to the usual expressions.[33-35] The values of the ΔE_{xy} and ΔE_{xz} electronic excitation energies required in the calculations were deduced from the circular dichroism spectra. We assumed that coordination by a donor solvent molecule in apical position raises the energy of the d_{z^2} orbital and leads to the following ordering of the copper(II) orbitals: $d_{x^2-y^2} > d_{z^2} > d_{xy} > d_{xz},d_{yz}$. Therefore, CD band I was assigned to the transition $d_{z^2} \rightarrow d_{x^2-y^2}$, CD band II to $d_{xy} \rightarrow d_{x^2-y^2}$, and CD band III to $d_{xz},d_{yz} \rightarrow d_{x^2-y^2}$. The assignment of band I to the transition $d_{xy} \rightarrow d_{x^2-y^2}$ leads to unreasonable values for β_1 and β. Band III is not observed in the CD spectra of pyruvate complexes, and we assumed it occurs under the envelope of CD band II. The computed molecular orbital coefficients are listed in Table IV.

Discussion

In the present series of copper(II) chelates the optical activity of the metal ion chromophore is induced by the chiral Schiff base ligands. If we assume a coordination plane defined by the metal ion, the imine nitrogen donor atom, and the oxygen donor atom of the carbonyl residue (the phenolic oxygen for salicylidene or pyridoxylidene residues, the carboxylate oxygen for pyruvylidene residues), the histidine Schiff base ligands provide three ligating atoms in this plane and a potential fourth donor site in roughly an apical position. A set of two bidentate and two tridentate (facial)[36] binding modes can therefore be used by the histidine residues in these complexes. Although for each bidentate mode the chelate ring conformation chirality can be described by using the symbolism of IUPAC nomenclature (δ, λ),[37] coordination of the histidine residue as a tridentate ligand gives rise to a set of three chelate rings, and it is impossible to designate net conformation chirality.[38] We will use here the δ, λ symbolism to

(33) The forms of the antibonding orbitals in the usual hole formalism are as follows:[34,35]

$$B_{1g} = \alpha d_{x^2-y^2} - (\alpha'/2)\varphi_L(x^2 - y^2)$$

$$B_{2g} = \beta_1 d_{xy} - (1/2)(1 - \beta_1^2)^{1/2}\varphi_L(xy)$$

$$A_{1g} = \alpha_1 d_{z^2} - (1/2)(1 - \alpha_1^2)^{1/2}\varphi_L(z^2)$$

$$E_g = \beta d_{xz} - (1 - \beta^2)^{1/2}\varphi_L(xz)/2^{1/2}$$
$$= \beta d_{yz} - (1 - \beta^2)^{1/2}\varphi_L(yz)/2^{1/2}$$

where the φ_L functions stand for the ligand group orbitals of appropriate symmetry. The odd electron is placed in the B_{1g} orbital in the ground state. The B_{1g} orbital is normalized by the equation $\alpha^2 + \alpha'^2 - 2\alpha\alpha' S = 1$ in which S is the overlap between the copper $d_{x^2-y^2}$ orbital and the ligand orbitals. The spin Hamiltonian parameters are related to the coefficients of the antibonding orbitals through the relationships:[34,35]

$$g_\parallel = 2.0023 - (8\lambda/\Delta E_{xy})[\alpha^2\beta_1^2 - f(\beta_1)]$$

$$g_\perp = 2.0023 - (2\lambda/\Delta E_{xz})[\alpha^2\beta^2 - g(\beta)]$$

$$\alpha^2 = (-A_\parallel/P) + (g_\parallel - 2.0023) + (3/7)(g_\perp - 2.0023) + 0.04$$

$$f(\beta_1) = \alpha\alpha'\beta_1^2 S + \alpha\alpha'\beta_1(1 - \beta_1^2)^{1/2}T(n)/2$$

$$g(\beta) = \alpha\alpha'\beta^2 S + \alpha\alpha'\beta(1 - \beta^2)^{1/2}T(n)/2^{1/2}$$

The typical constants for Cu^{2+} ions, P = 0.036 cm^{-1}, λ = −828 cm^{-1}, and appropriate combinations of the values for the $T(n)$ and S integrals for nitrogen ($T(n)$ = 0.333, S = 0.093) and oxygen ($T(n)$ = 0.220, S = 0.076) were used in the calculations. These values of $T(n)$ and S assume sp^2 hybridization on the ligand bonding atoms.

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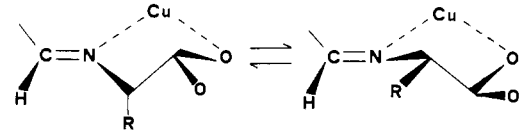
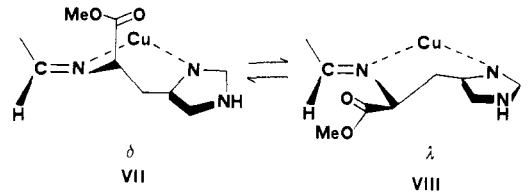
characterize the conformation chirality of the amino acid chelate ring that is fused and coplanar with that of the carbonyl residue, irrespective of whether the branch extending from the amino acid α-carbon atom bears an apical donor atom at its end.

Upon comparison of the CD spectra of copper(II) complexes derived from pyridoxal or salicylaldehyde and L- or D-histidine with their appropriate counterparts in the L- or D-histidine methyl ester series, it can be seen that the spectra in these two series bear a mirror-image relationship when the histidine residues have the same absolute configuration (Table II and III, Figure 1). We have observed similar behavior previously with zinc(II)[1] and copper(II)[9] complexes of Schiff base ligands derived from L-histidine and L-histidine methyl ester. As we originally proposed,[1,9] this result can be explained by assuming that the signs of the Cotton effects associated with the electronic transitions reflect the conformation chirality of the amino acid chelate ring. Thus, ring chiralities of opposite signs must be involved in the coordination of histidine and histidine methyl ester residues of the same absolute configuration. In metal complexes of amino acid Schiff bases derived from pyridoxal or salicylaldehyde, the conformation of the amino acid chelate ring is dictated by the preference for a pseudoaxial disposition of the side chain, both in the solid state[39] and in solution.[1,7] This is probably related to significant steric interaction between the azomethine hydrogen atom and the α-carbon substituent in pseudoequatorial position, as found, for instance, in similar complexes derived from chiral 1,2-diamines.[41] The CD spectra of derivatives of L-histidine, namely Cu(pdx-L-his), Cu(Hpdx-L-his)Cl, and Cu(sal-L-his), display dominant Cotton effects of the same sign pattern as those of complexes derived from L-amino acids with nonpolar side chains. This implies the adoption of a glycine-like chelation mode by the L-histidine residue, with predominant λ conformation (V). Binding to copper(II) of the



λ V ⇌ δ VI



δ VII ⇌ λ VIII

L-histidine methyl ester residues in $Cu(Hpdx\text{-}L\text{-}hisOCH_3)X_2$ and $Cu(sal\text{-}L\text{-}hisOCH_3)X$ (X = Cl, ClO_4) can occur only through the imine and imidazole nitrogen donors (histamine-like), since the ester carbonyl groups are noncoordinated. This involves a disposition of the L-histidine side chain as for D-amino acids and the preference for a δ conformation (VII) by the L-histidine residue bound histamine-like. This simple conformational model does not take into account other contributions to the optical activity of the complexes, e.g., those given by vicinal effects. However, these contributions are of a minor entity when relatively rigid polydentate ligands are used,[40] and the behavior displayed by complexes containing D-histidine residues is in perfect agreement with the above arguments. As expected, the protonation of the pyridine ring nitrogen atom of pyridoxal residues involves no change in the conformation of the ligands. It is quite possible, though, that nonprotonated pyridine nitrogen donors compete with solvent molecules or other groups for binding to the metal center of neighboring molecules, as shown for instance by the structure of Cu(pdx-DL-val).[39b] This seems confirmed by the observation of different species in the EPR spectra of, e.g., Cu(pdx-L-his) and Cu(pdx-L-val) recorded in frozen solutions of nonbasic solvents.

The CD spectra of copper(II) complexes derived from pyruvate show significant dissimilarities to those in the pyridoxylidene and salicylidene series. The spectra of Cu(pyv-L-his) and $Cu(pyv\text{-}L\text{-}hisOCH_3)Cl$ recorded in water (methanol) solution display dominant Cotton effects of the same sign pattern, while this pattern is reversed in the spectra of complexes of the type Cu(pyv-L-aa), where the amino acid side chains carry nonpolar groups (Figure 2). The conformation of the ligand in these Cu(pyv-L-aa) complexes is not expected to vary with respect to that in Cu(sal-L-aa) or Cu(pdx-L-aa) complexes. Therefore, an equilibrium similar to V ⇌ VI rules the chelate ring conformation of the L amino acid residue, with preference for the λ conformer. This is reflected by the dominant Cotton effects of negative sign exhibited by the CD spectra of Cu(pyv-L-aa) complexes within the d–d envelope. When the amino acid is histidine, however, a histamine-like chelation mode is apparently preferred over the glycine-like mode, and the chelate ring conformation adopted by both Cu(pyv-L-his) and $Cu(pyv\text{-}L\text{-}hisOCH_3)Cl$ is that (δ) corresponding to VII. This interpretation is confirmed by the close similarity in the position of the d–d absorption maximum (Tables II and III) and in values of the EPR parameters (Tables IV and V) observed for Cu(pyv-L-his), $Cu(pyv\text{-}L\text{-}hisOCH_3)Cl$, Cu(pyv-D-his), and $Cu(pyv\text{-}D\text{-}hisOCH_3)Cl$ in water (methanol) solution, which imply a common planar N_2O_2 donor set. The corresponding data for Cu(pyv-L-ala), Cu(pyv-L-val), and Cu(pyv-gly) are significantly different from those of the histidine complexes. The preference for a histamine-like chelation mode by the histidine residues in Cu(pyv-L-his) and Cu(pyv-D-his) must be determined by the fused five-membered chelate ring of the pyruvic residue. According to the order of stability of fused chelate ring systems,[10,11d,42] which apparently applies also to the chelate ring types of mixed-ligand ternary complexes,[43] two adjacent five- or six-membered rings are considered less stable than a system consisting of a five- and a six-membered ring. In pyridine solution the CD patterns of Cu(pyv-L-his) and Cu(pyv-D-his) are reversed, whereas those of $Cu(pyv\text{-}L\text{-}hisOCH_3)Cl$, $Cu(pyv\text{-}D\text{-}hisOCH_3)Cl$, and Cu(pyv-L-aa) complexes remain unchanged (Figure 3). The CD spectrum of Cu(pyv-L-his) in pyridine resembles those of Cu(pyv-L-aa) complexes, and we conclude that the conformation of the L-histidine chelate ring has undergone an inversion to the λ conformation (IX) upon coordination of pyridine molecules in apical position. A similar inversion of the Cotton effects in the CD spectrum of Cu(pyv-L-his) can be observed upon addition of piperidine to an aqueous solution of the complex (Figure 7), while ammonia probably coordinates without causing a δ → λ conformational inversion because of its smaller size. The δ → λ inversion could also be accounted for by the apical coordination of deprotonated imidazole nuclei of neighboring molecules rather than the donor base. However, this possibility is ruled out by the lack of inversion of the CD spectrum observed upon addition of triethylamine (a stronger base than either pyridine or piperidine) to a water–

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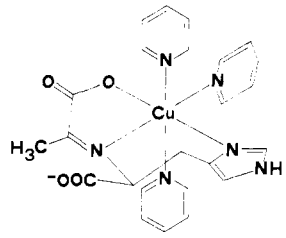
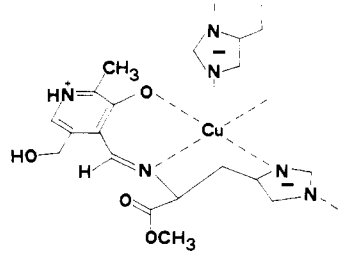


IX

methanol solution of Cu(pyv-L-his). Addition of pyridine to this triethylamine solution gives rise to inversion of the CD spectrum (Figure 7). The access of the donor base is probably sterically hindered by the methyl ester group in the case of Cu(pyv-L-hisOCH$_3$)Cl and Cu(pyv-D-hisOCH$_3$)Cl. Apical coordination by donor bases to copper(II) in Cu(pyv-L-his) and Cu(pyv-D-his) has the important consequence to lead the complex to an easy racemization process.

Somewhat surprising was initially the result that the CD spectra of the complexes we formulated as Cu(pdx-L-hisOCH$_3$)ClO$_4$ and Cu(pdx-D-hisOCH$_3$)ClO$_4$ exhibit mirror-image relationships to the spectra of Cu(Hpdx-L-hisOCH$_3$)X$_2$ and Cu(Hpdx-D-hisOCH$_3$)X$_2$ (X = Cl, ClO$_4$), respectively (Figure 4). The behavior of Cu(sal-L-hisOCH$_3$′) and Cu(pyv-L-hisOCH$_3$′) indicates that the source of inversion of the CD patterns is associated with the presence of deprotonated imidazole rings and that, therefore, the above complexes derived from pyridoxal have structures corresponding to Cu(Hpdx-L-hisOCH$_3$′)ClO$_4$ and Cu(Hpdx-D-hisOCH$_3$′)ClO$_4$. The CD inversion suggests that coordination to copper(II) by the imidazolate anion of a neighboring molecule occurs in an apical position and causes inversion to the conformation with pseudoequatorial side chains of the histidine chelate ring (X). The methyl ester group of these histidine residues is



X

therefore apparently unable to inhibit the apical binding of an imidazolate group. This is confirmed by the observation that addition of a sufficiently strong base (sodium hydroxide) to either Cu(pyv-L-his) or Cu(pyv-L-hisOCH$_3$)Cl produces the imidazolate species and leads to inversion of the CD spectrum, followed by racemization (Figure 7). A considerable number of imidazolate-bridged transition-metal complexes have been recently reported[44] because of their biological importance as models for the active site of superoxide dismutase[45] and, possibly, of cytochrome oxidase[46] and other copper oxidases.[15e,f] The imidazolate-bridged

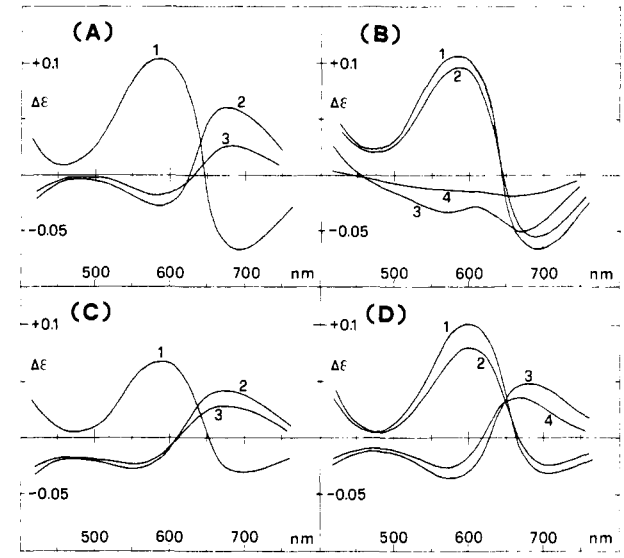


Figure 7. Circular dichroism spectra of (A) Cu(pyv-L-his) in 1:1 water–piperidine (concentration of the complex 4×10^{-3} M) (1) recorded immediately after dissolution, (2) recorded after 3 h, (3) recorded after 6 h; (B) Cu(pyv-L-his) in water–methanol–triethylamine 1:1:1 (concentration 1.5×10^{-2} M) (1) recorded immediately after dissolution, (2) recorded after 18 h, (3) obtained upon addition of 10% (v/v) pyridine to solution 2, (4) same as (3) recorded after 2 h; (C) Cu(pyv-L-his) in aqueous sodium hydroxide solution ([Cu^{2+}]:[NaOH] = 1:2, concentration of the complex 4×10^{-3} M) (1) recorded immediately after dissolution, (2) recorded after 3 h, (3) recorded after 6 h; (D) Cu(pyv-L-hisOCH$_3$)Cl in methanolic sodium hydroxide solution (concentration of the complex 4×10^{-3} M) (1) [Cu^{2+}]:[NaOH] = 1:1, recorded immediately after dissolution, (2) same as (1) recorded after 1.5 h, (3) [Cu^{2+}]:[NaOH] = 1:2, recorded immediately after dissolution, (4) same as (3) recorded after 1 h.

complexes reported here, however, are the first examples in which the bridges between the copper(II) centers belong to histidine residues.[47]

It is possible to refine the description of the stereochemistry of these copper(II) chelates with an attempt to establish the donor set and the bonding character of the complexes. The EPR spectra indicate that in solution the ligand field symmetry of the complexes is essentially tetragonal. Since the Schiff base ligands provide three donor atoms in the copper(II) coordination plane, we expect that the fourth planar position and the axial position on the opposite side to the amino acid side chain can be readily accessible to solvent molecules. The nitrogen superhyperfine splittings observed in several EPR spectra recorded in frozen pyridine solution do, in fact, account for coordination of the expected number of solvent molecules (Tables IV and V). In general, however, the magnetic parameters of the complexes seem more sensitive to changes in the planar covalency than to changes in the axial covalency. Replacement of oxygen donors (methanol or water) by nitrogen donors (pyridine) in planar and axial positions should affect oppositely the EPR parameters, since the g values decrease and $A_{\parallel}$ increases when the planar bonds become more covalent,[48] while the g values increase and $A_{\parallel}$ decreases upon axial coordination of the donor base.[49] For these chelates the g values measured in pyridine are smaller and the $A_{\parallel}$ values generally larger than those in methanol or water solutions, showing that coordination of pyridine in equatorial position has a more marked effect

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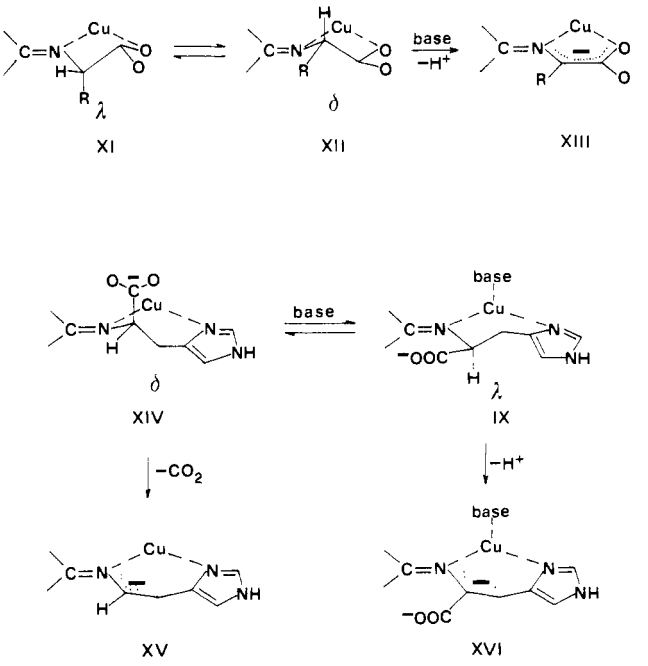
on the g and $A_{\parallel}$ values than additional coordination in axial position. The EPR parameters of Cu(Hpdx-L-hisOCH$_3$)Cl$_2$ and Cu(Hpdx-D-hisOCH$_3$)Cl$_2$ are rather solvent independent, and this suggests that the coordinated chloride ions occupy the fourth equatorial position. Solvent molecules are, however, also involved in the (apical) coordination to these copper(II) centers, since the wavelength of the visible absorption maximum shifts from 665 nm in methanol to 745 nm in pyridine. The $A_{\parallel}$ values of Cu(Hpdx-L-val)X (X = Cl, ClO$_4$), Cu(pyv-L-his), and Cu(pyv-D-his) are larger in methanol (water) than in pyridine solutions. The inversion of the CD spectra undergone by Cu(pyv-L-his) and Cu(pyv-D-his) in pyridine indicates that solvent molecules bind axially the metal center from both sides of the coordination plane (IX), giving rise to a distorted octahedral structure (CuN$_5$O core). This seems confirmed by the observation of the superhyperfine splittings in the pyridine EPR spectra of these histidine complexes. The rather complex pattern of lines probably arises from the presence of nonequivalent (equatorial and axial) nitrogen atoms (Figure 6). However, the resolved structure of the copper hyperfine lines in the $g_{\parallel}$ region seems in agreement with coupling to five nitrogen donors. The decrease of $A_{\parallel}$ in pyridine reflects, therefore, a stronger interaction by the axial donor molecules. In the case of the Cu(Hpdx-L-val)X complexes, six-coordination is unlikely to occur and the nitrogen superhyperfine splitting observed in the pyridine EPR spectrum of Cu(Hpdx-L-val)Cl accounts for the presence of only two solvent molecules coordinated. The decrease of $A_{\parallel}$ in pyridine can be explained by considering that steric repulsion between the bulky isopropyl groups and the coordinated pyridine molecules may result in a slight lowering of the symmetry of the metal complex.[50] The above qualitative description of the solvent effects on the variation of EPR parameters is confirmed by the trends in the calculated molecular orbital parameters (Table IV). The limits of this approach have been discussed;[51] however, the results can often be meaningful when a series of closely related compounds is compared. The bonding parameters of the complexes indicate moderately covalent σ and in-plane π bondings, with α^2 and β_1^2 values of about 0.8, and weakly covalent out-of-plane π bonding, with β^2 values of about 0.9. In general, both the α^2 and β_1^2 values are smaller in pyridine than in water or methanol solution. Therefore, coordination of pyridine in the plane gives rise to stronger planar covalency while additional coordination in the axial position has apparently only a minor effect. It is worth noting that only for the pyridoxylidenevaline complexes is β_1^2 slightly larger in pyridine than in methanol. Since this parameter is related to the overlap of in-plane orbitals of π type, a lowering of the symmetry of the complex upon coordination of the larger pyridine molecules is in agreement with a reduction in the in-plane π overlap (β_1^2 increases). This is apparently compensated by an increase in σ covalency (α^2 decreases). The decrease in α^2 from methanol to pyridine for these valine complexes is, in fact, the largest within the series. The accuracy of the β^2 parameters is rather low, and their variation within the series of these copper(II) complexes is probably not significant.

The information about the stereochemistry of these complexes of amino acid Schiff bases can be used for a qualitative interpretation of pyridoxal model reactions.[52] A dynamic conformational XI $\rightleftharpoons$ XII equilibrium rules the chelate ring conformation of L-amino acid residues in Cu(pdx-L-aa), Cu(Hpdx-L-aa)X, and Cu(sal-L-aa) complexes (Scheme I). The relationship

Scheme I



XI XII XIII XIV IX XV XVI

between these two possibilities is diastereomeric, and one (λ, XI) predominates in solution. According to Dunathan,[6] a bond to the amino acid α-carbon can be easily cleaved when it is oriented orthogonal to the plane of the π system. If we take into account the cleavage of the C$_\alpha$–H bond, the first step in a number of enzymic reactions reproduced by model systems (racemization, transamination, β-elimination, γ-elimination, retroaldolization), only the minor (δ, XII) conformer contains this bond in a favorable (axial) position for an easy breaking process. This feature has been found also in the corresponding zinc(II) complexes[1] and is probably common to every related metal system, thus accounting for the rather low reactivity attained by model systems. The complexes derived from pyruvate, Cu(pyv-L-aa), are subjected to the same stereochemical preferences as their pyridoxal analogues, with the important exception of the complexes derived from histidine. In this case the amino acid residue chelates histamine-like, and the presence of a coordinating base of suitable size can influence the $\lambda \rightleftharpoons \delta$ equilibrium to the extent of stabilizing the conformer (IX) containing the carboxyl group equatorial and the C$_\alpha$–H bond axial (Scheme I). This leads the complex to an easy racemization process, in full agreement with Dunathan's prediction. It is worth emphasizing that the occurrence of racemization is related to the size of the added base rather than its basicity. Since the donor base binds copper(II) in planar and axial positions, an exceedingly large size of the coordinated base in planar position hinders the axial approach of additional molecules and prevents the inversion to the ring conformation with equatorial side chain. Decarboxylation of an amino acid can occur if the C$_\alpha$–COO$^-$ bond is oriented perpendicular to the azomethine π system. This condition is never fulfilled in systems derived from pyridoxal or salicylaldehyde and explains why decarboxylation is not usually observed in model systems. The pyruvate complexes behave similarly unless, again, the amino acid is histidine. The preferred conformer of the pyruvylidenehistidine complexes (XIV) carries the carboxyl group axial and is expected to decarboxylate easily (Scheme I). Preliminary experiments seem to confirm this prediction, but the decarboxylation is probably flanked by side reactions involving oxidation steps.[53] Both these reactions (de-

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(52) Besides the stereochemistry of the groups involved, a number of factors are important in determining the reactivity of model systems. For instance, carbanion stabilization must be taken into account as well as α-C–H bond orientation in those processes that involve the cleavage of this bond as a preliminary step. The stereochemical factors, however, have generally been underestimated so far.

(53) Upon warming of an aqueous solution of Cu(pyv-L-his) in a water bath, a brown precipitate separates slowly. The elemental analysis of this product (Found: C, 31.78; H, 3.45; N, 13.64) agrees with the loss of one carbon atom by the starting Cu(pyv-L-his) complex. The product of simple decarboxylation, however, should correspond to Cu(pyv-him'), and the rather low value found for hydrogen in the elemental analysis of the brown material indicates that the ligand has probably undergone some oxidation reaction.

carboxylation and oxidation) have been recently observed in peptide complexes containing histidine residues bound histamine-like.[54]

Conclusions

The mode of coordination to copper(II) of histidine residues has been investigated in a series of Schiff base chelates derived from pyridoxal, salicylaldehyde, and pyruvic acid. The corresponding complexes derived from amino acids with nonpolar side chains provide appropriate references for the glycine-like coordination mode, while the derivatives of histidine methyl ester are appropriate references for the histamine-like mode. The preference for either mode is apparently ruled by the chelate ring type of the fused carbonyl residue, and histidine exhibits a striking tendency to bind copper(II) through chelate ring types complementary rather than similar to those of the carbonyl residues. Thus, copper(II) complexes derived from pyridoxal, salicylaldehyde, or (+)-(hydroxymethylene)camphor[9] contain histidine residues bound glycine-like, while in those derived from pyruvic acid or 2-pyridinecarboxaldehyde[55] the histidine residues are bound histamine-like. These results can be of some importance to infer the coordination mode of histidine residues in complexes with small peptides, where the deprotonation of amide nitrogen atoms often leads to chelate ring systems similar to those of the complexes reported here.[31d,e,56] Circular dichroism can easily distinguish the glycine-like and histamine-like binding modes in these complexes of histidine Schiff bases, since the preference for a pseudoaxial disposition of the side chain involves opposite conformation chiralities for the histidine chelate rings in the two binding modes. The investigation of solvent effects on the variations of the EPR parameters enables one to refine the stereochemical description of copper(II) complexes of amino acid Schiff bases in terms of donor sets, ligand field symmetry, and bonding character. A simple conformational model accounts for the observed trends in the circular dichroism spectra and provides a key to the interpretation of vitamin B_6 model reactions on a stereochemical basis. Although different theoretical approaches to the circular dichroism of chiral transition-metal complexes have been developed, particularly for copper(II) complexes,[57,58] they have not produced a model capable of widely applicable spectra–structure correlations. These largely rely upon simpler approaches applied to series of chiral complexes of closely related structures, even though they may give no account for the mechanisms leading to the CD. The intuitive conformational model employed here is particularly useful for correlating the overall CD features of the complexes to the stereochemistry of the chiral polydentate ligands.

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Registry No. Cu(pdx-himNCH$_3$)ClO$_4$, 80864-78-4; Cu(pdx-L-his), 80864-79-5; Cu(Hpdx-L-his)Cl, 80864-80-8; Cu(Hpdx-L-hisOCH$_3$)Cl$_2$, 80864-81-9; Cu(Hpdx-L-hisOCH$_3$)(ClO$_4$)$_2$, 80878-13-3; Cu(Hpdx-L-hisOCH$_3$')ClO$_4$, 80864-83-1; Cu(pdx-L-val), 63569-28-8; Cu(Hpdx-L-val)Cl, 80864-84-2; Cu(Hpdx-L-val)ClO$_4$, 80864-85-3; Cu(pdx-L-phe), 63569-29-9; Cu(Hpdx-L-phe)Cl, 80864-86-4; Cu(sal-L-his), 64254-72-4; Cu(sal-L-ser), 80864-87-5; Cu(sal-L-hisOCH$_3$)ClO$_4$, 80864-89-7; Cu(sal-L-hisOCH$_3$'), 80878-97-3; Cu(pyv-L-his), 80864-90-0; Cu(pyv-L-hisOCH$_3$)Cl, 80864-91-1; Cu(pyv-L-hisOCH$_3$'), 80878-96-2; Cu(pyv-L-val), 80864-92-2; Cu(pyv-L-ala), 80864-93-3; Cu(pyv-gly), 75441-94-0.

Supplementary Material Available: Listings of elemental analysis (Table I), electronic and CD spectra of copper(II) complexes derived from D-amino acids (Table III), and EPR data of copper(II) complexes derived from D-amino acids (Table V) (5 pages). Ordering information is given on any current masthead page.

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Organophosphazenes. 15. Reactions of Hexafluorocyclotriphosphazene with *tert*- and *n*-Butyllithium Reagents[1]

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Abstract: The reactions of *tert*- and *n*-butyllithium reagents with hexafluorocyclotriphosphazene ($N_3P_3F_6$) have been examined. In contrast to the behavior of *n*-butyllithium, the reaction of *tert*-butyllithium with $N_3P_3F_6$ gives good yields of $N_3P_3F_5C_4H_9$. While the *n*-butyllithium reaction follows a geminal pathway at the stage of disubstitution, the *tert*-butyllithium reaction gives exclusively the trans nongeminal isomer for the compounds $N_3P_3F_{6-n}(t\text{-}C_4H_9)_n$ (n = 2, 3). This is the first example of a regio- and stereospecific reaction in phosphazene chemistry. At the stage of trisubstitution, solvent (diethyl ether) cleavage by *tert*-butyllithium is competitive with phosphazene substitution, resulting in the concomitant formation of *trans*-2,4,6-$N_3P_3F_3(OC_2H_5)(t\text{-}C_4H_9)_2$. These results are discussed in terms of competing steric and electronic effects. The butylphosphazenes are characterized by mass spectrometry and infrared and NMR (^{1}H, ^{13}C, ^{19}F, ^{31}P) spectroscopy.

One of the most active fields of investigation in cyclophosphazene chemistry is the study of substitution reactions.[2-4] Aminolysis and alcoholysis reactions of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, have received a great deal of attention,

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