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Transition Metal Complexes of Ligands Containing Azomethine Group. V.* Stereochemistry and Reactivity of Four-Coordinate Nickel(II) Complexes Derived from (S)-(+)-Cysteine Derivatives

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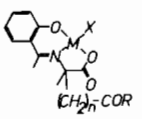
By the condensation of salicylaldehyde (acetylacetone) with (S)-(+)-cysteine ester in the presence of Ni^{2+} ions, diamagnetic, binuclear, square-planar Schiff base complexes were prepared. Their circular dichroism spectra show negative Cotton effect due to the stereospecific coordination of the chiral ligand. From the PMR spectra it follows that complexes in solution exist in preferred δ conformation with the axial –COOR group. From the ligand field spectra and magnetic moments it was deduced that in donor solvents complexes exist as monomeric hexa-coordinate ones. In addition, alkoxycarbonyl group undergo ester exchange which is facilitated by the inductive effect of –CH=N group. Although complexes were prepared in the presence of base, they did not undergo racemisation. Increased optical stability was ascribed to unfavourable conformation of the complex.

Introduction

It is well known that many reactions of α-amino acids catalysed by pyridoxal containing enzymes can be simulated *in vitro* by the Schiff base metal complexes[1,2]. Special interest is paid to the metal complexes of polyfunctional amino acids, both for their biological importance and for their stereochemical properties. The latter becomes evident in synthesis (equilibrium displacement[3]) of type Ia complexes, the



Ia R=OH or ONa, M = Cu^{2+}

b R=OCH_3, M = Ni^{2+}

result of which depends on the distance of the two carboxyl groups as well as on the amino acid (n = 1) being optically active or racemic[4]. Although complexes Ib contain both –CH=N and –COOR groups, the presence of which facilitates racemisation[5], were prepared optically active[6]. This fact was ascribed to the unfavourable conformation at the α-carbon atom[6,7]. Similarly, the ester group in these complexes does not undergo transesterification. Because the stereochemistry of metal complexes is of principal importance in coordinated ligands reactivity, we describe here the synthesis and stereochemistry of nickel(II) complexes with structure Ib (n = 0), but with different donor sets atoms, including further information concerning their optical stability and reactivity on carbonyl groups.

Results and Discussion

Stereochemistry

Condensation of (S)-(+)-cysteine esters with salicylaldehyde (acetylacetone) similarly as with pyridoxal[8] proceeds with the formation of a yellow solution containing both Schiff base and thiazolidine. Only if Ni^{2+} ions are present, thiazolidine transforms with the formation of a nickel(II) Schiff base complex as the only reaction product. The formation of the nickel(II) complex is accompanied by a colour change from yellow to red-brown which is typical for nickel(II) complexes containing sulfur bridges (*vide infra*). Quite different is the behaviour of methionine ester, which forms a complex with methionine acting as monodentate ligand[9]. This behaviour is a consequence of the lowered donor ability of the thioether group of methionine in comparison with the mercapto group of cysteine.

The complexes prepared are derived from tridentate ligands. In the case of nickel(II) complexes, in which Ni^{2+} ion can generally reach coordination number four, five or six, the remaining coordination sites can be occupied by the solvent molecules. At the same time it must be taken into account that the tendency to reach a coordination number higher than four is influenced both by electronic and steric factors[10]. As follows from the experimental part, complexes were isolated from the solvent with low coordinating ability

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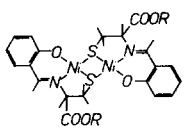
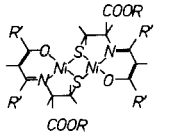
and thus strong ligand field will favour four-coordinate low-spin, square-planar configuration of Ni(II). From the elemental analysis it follows that the Ni^{2+}: ligand ratio is equal to one. Therefore, the coordination number of four is realized through the formation of a sulfur bridge (II, III). This was demonstrated by molecular



IIa $R=C_2H_5$
b $R=CH_3$
c $R=H$
d $R=Na$



IIIa $R=C_2H_5$, $R'=CH_3$
b $R=CH_3$, $R'=CH_3$

weight measurements. The determination of molecular weights, which show the binuclear character of complexes prepared, estimates also square-planar arrangements of donor atoms around Ni^{2+} ion (C_S symmetry).

For square-planar nickel(II) complexes in dependence of chromophore symmetry, theory predicts 3–4 transitions within the *d*-orbitals[11,12]. The electronic spectra correspond to the transitions expected for nickel(II) complexes with C_S symmetry. From these transitions the broad low-energy band located at 600 and 525 nm which is magnetic dipole allowed band[13] can be assigned according to their values of ε as *d–d* transitions. The remaining intense bands (see Table I) are assigned as electric dipole allowed transitions[14].

Although the electronic absorption spectra correspond to square-planar nickel(II) complexes with a singlet ground state (the absence of absorption maxima at about 700 nm excludes complexes with coordination number 5[15,16]), the geometry of complexes can be definitively determined by the measurements of magnetic susceptibilities. These data (see Table I) show that both complexes are diamagnetic with the b_{2g}^2 e_g^4 a_{1g}^2 configuration corresponding to the singlet ground state[17]. The remaining small residual paramagnetism observed may be attributed to temperature-independent contributions[18].

Both II and III can exist in δ and λ conformations[19] in which the –COOR group can be axially or equatorially arranged (see Figure 1). Both in II and III the ligand is stereospecifically coordinated with δ conformation of the gauche chelate ring, in which the –COOR group adopts axial position. This arrangement which is sterically favoured, decreases the possible in plane "1,3-interactions" between the methyl group (or hydrogen atom) located at the azomethine carbon atom and the –COOR group. Inspection of molecular models (see Figure 2) suggests that this interpretation is reasonable, because for λ conformation serious steric interactions are possible. Further evidence for the preferred δ conformations can be obtained from the

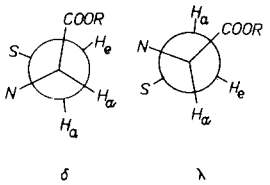


Figure 1. Conformation of Nisal((S)-CysOR) and Niacac((S)-cysOR). Projection along the C–C cysteine bond.

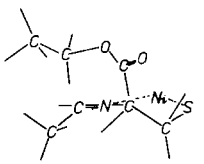


Figure 2. Structure of Nisal((S)-CysOR) and Niacac((S)-CysOR) with minimum of steric interactions.

TABLE I. Spectral and Magnetic Properties of Nickel(II) Complexes.

Compound	Solvent	λ, nm (ε_{max})	
IIa $Ni_2sal_2((S)\text{-}CysOEt)_2$[a]	$CHCl_3$	600 (220), 525 (301), 295[b] (4150), 260 (8030)	
	Pyridine	610 (77), 445 (2565)	
IIIa $Ni_2acac_2((S)\text{-}CysOEt)_2$[c]	$CHCl_3$	525 (110), 360[b] (1210), 320[b] (2010), 290 (2640)	
	Pyridine	640 (120), 425 (745)	
	T, °K	$10^{-6}\chi_M$/Ni	μ/Ni[d]
IIa $Ni_2sal_2((S)\text{-}CysOEt)_2$	296	0.15	0.87
IIIa $Ni_2acac_2((S)\text{-}CysOEt)_2$	296	0.66	0.63
IIc Nisal((S)-CysOH)·$2H_2O$	296	10.99	3.11
IId Nisal((S)-CysONa)·$3H_2O$	296	8.16	2.52

[a] sal = salicylaldehyde. [b] Shoulder. [c] acac = acetylacetone. [d] $\mu = 2.84\ (\chi_M T)^{1/2}$.

TABLE II. ^{1}H NMR Data of Nickel(II) Complexes.

Compound	δ, ppm (assignments)
IIb Ni_2sal_2((S)-CysOMe)$_2$[a]	2.00–2.14d (cysteine methylene), 2.60–2.80m (cysteine methylene), 3.70s (–OCH_3 methyl), 5.00d (α-methine), 6.56m, 7.25m (aromatic protons), 8.02–8.22d (azomethine)
IIIa Ni_2acac_2((S)-CysOEt)$_2$[b]	1.28t (–C_2H_5 methyl), 1.90s (acetylacetone methyl), 2.02–2.16d (cysteine methylene), 2.56–2.80m (cysteine methylene), 4.22m (–C_2H_5 methylene), 4.50d (α-methine), 5.00s (γ-methine)

[a] In DMSO-d_6. [b] In $CDCl_3$. s = singlet, d = doublet, t = triplet, m = multiplet.

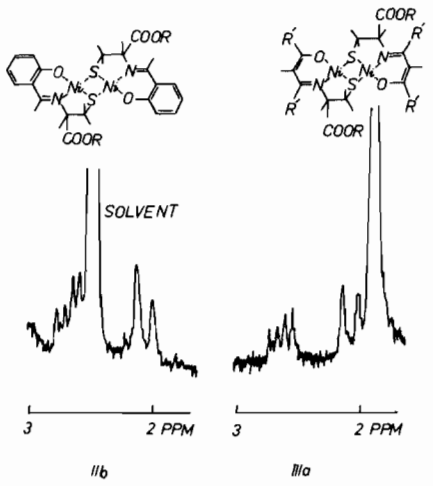


Figure 3. Proton magnetic resonance spectrum of methylene part of nickel(II) complexes. Ni_2sal_2((S)-CysOMe)$_2$ (IIb), Ni_2acac_2((S)-CysOEt)$_2$ (IIIa).

proton magnetic resonance spectra (see Table II and Figure 3). From the ^{1}H NMR spectra follows the large chemical shift between equatorial (H_e) and axial (H_a) protons of the –CH_2 group which indicates a difference in their magnetic environments. Complexes are derived from the d^8 square-planar system which exhibits magnetic anisotropy owing to the plane of the metal ion and donor atoms[20]. This allows to discriminate between the axial and equatorial protons according to their low- or high-field shift. Therefore, the high-field doublet observed at 2.14–2.00 ppm (IIb) or at 2.16–2.02 ppm (IIIa) with a spacing of 14.0 Hz characteristic for geminal coupling constant corresponds to the equatorial proton of the –CH_2 group. The absence of further splitting shows that the α-CH–CH_e vicinal coupling constant is nearly zero. From this it follows that the dihedral angle for α-CH–CH_e calculated from the Karplus equation[21] is 90°.

On the other hand the low-field multiplet at 2.8–2.6 ppm (IIb) or at 2.80–2.56 ppm (IIIa) belonging to axial proton gives spacings of 7 and 14 Hz characteristic both for vicinal and geminal coupling constants. Using these data and applying the Karplus equation it follows that the dihedral angle for α-CH–CH_a is 40°. The observed chemical shift difference between the axial and equatorial protons demonstrates the presence of only one conformation corresponding both to the ligand configuration and structure with the absence of steric interactions.

The complexes studied display optical activity. Because they are square-planar, their optical activity may arise only from the vicinal effects due to the chiral ligand and from the chelate ring conformation. From Table III it can be seen that the signs of the ligand field circular dichroism bands of both complexes are the same, both showing a negative Cotton effect. At the same time the course of circular dichroism of the two complexes somewhat differ from each other. The complex derived from salicylaldehyde (IIb) show through the whole spectrum only a negative Cotton effect. This behaviour, which is characteristic for binuclear salicylaldimine complexes[6] is related to the presence of a planar aromatic ring.

TABLE III. Circular Dichroism Spectra of Nickel(II) Complexes.

Compound	Solvent	λ, nm (Δε)
IIb Ni_2sal_2((S)-CysOMe)$_2$	$CHCl_3$	620 (–2.47), 535 (–10.07), 445 (–8.93), 385 (–10.92), 330 (–17.50)
	Pyridine	640 (–0.50), 450 (+4.40), 365 (–1.91), 325 (+6.89)
IIIa Ni_2acac_2((S)-CysOEt)$_2$	$CHCl_3$	515 (–15.58), 390 (+22.57), 320[a] (+12.90), 295 (+37.32)
	Pyridine	620 (–1.32), 470 (–1.70), 375 (+5.72), 330 (+6.31)

[a] Shoulder.

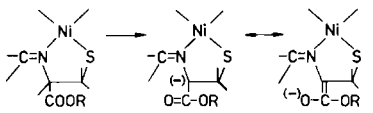
As was mentioned above, the complexes prepared are binuclear, diamagnetic and square-planar when prepared from non-donor solvents. However, when dissolved in pyridine or prepared from water (IIc, d), there occurs a λ_{max} shift (see Table I) together with the formation of a new absorption maxima in the spectral region of the high-spin nickel(II) transitions (IIb = 830 nm, $\varepsilon = 5$; 870 nm, $\varepsilon = 5$. IIIb = 925 nm, $\varepsilon = 2$, measured in pyridine). These derivatives can be formulated on the basis of their ligand field spectra[10] and magnetic moments[22] as six-coordinate high-spin complexes, because the formation of an absorption maximum at about 1000 nm as well as the value of magnetic moment about 3.0 B.M. are diagnostic for them.

Pyridine also markedly affects the circular dichroism spectrum of IIb and this behaviour, which reflects the change from binuclear to mononuclear species[6], suggests the monomeric nature of this six-coordinate complexes (see Table III).

Reactivity

It was established[5] that the presence of both azomethine and ester groups enormously enhances the reactivity of coordinated ligands. This activation manifests itself in the reduction of electron density at the α-carbon atom causing the rapid racemization of optically active amino acid ester. Recently[6] it was found that the mere presence of these mentioned groups is insufficient for racemization. Also other factors, such as preffered conformation[6,7] and formation of carbanion[5] must be taken into consideration. Only in those cases when all these conditions are met does racemization proceed easy.

The study of molecular models shows that bidentate coordination of condensed (S)-(+)-cysteine ester also leads to an unfavourable conformation as far as the loss of the α-proton is concerned. At the same time the stabilization of the reactive carbanion by enolate resonance is achieved:



Despite the fact that the complexes described were prepared under optimal conditions for the racemization of amino acid esters, *i.e.* in the presence of base (CH_3COO^- ion), they display induced optical activity (*vide supra*). From this it would appear that labilization of α-proton together with simultaneous formation of carbanion does not take place. On the other hand in Schiff base metal complexes, where the amino acid ester is coordinated as a monodentate through the nitrogen atom, rapid loss of optical activity occurs depending on the kind of metal ions[23]. The difference between these two types of complexes consists in the bond conformation at the α-carbon atom. Therefore results obtained here unambiguously support the importance of conformation on the facile racemization of optically active amino acid esters.

The electron-withdrawing azomethine group provides also the reactivity of the alkoxycarbonyl group in that the latter undergoes transesterification. Therefore chelates IIa and IIIa were converted into methyl esters on refluxing in methanol. Although many mechanisms concerning transesterification were suggested, it appears that increased nucleophillicity of the acyl carbon atom induced by the azomethine group is of first importance. This assumption can be supported by the fact that Ib, where n = 1 or 2 did not readily undergo transesterification, while IIa and IIIa with the alkoxycarbonyl group immediately attached to the α-carbon atom were transesterified.

Experimental

Physical Measurements

Electronic absorption spectra were obtained using an Optica–Milano CF-4 spectrophotometer. Circular dichroism spectra were recorded on a Juan Dichrograph. Proton magnetic resonance data were obtained using a Varian Model XL-100-15 spectrometer (with tetramethylsilane or hexamethyldisilane as an standard). Magnetic susceptibilities of solids were determined by the Gouy method. Diamagnetic corrections were calculated from a table of Pascal's constants. Molecular weights of the complexes in benzene or nitrobenzene were determined cryoscopically.

Synthesis of Complexes IIa, IIIa

To a solution of 20 mmol of (S)-(+)-cysteine hydrochloride ethylester (obtained by passage of dry HCl gas through a suspension of (S)-(+)-cysteine (Fluka) in absolute ethanol) in anhydrous ethanol, 60 mmol of anhydrous sodium acetate dissolved in ethanol were added. The NaCl separated was removed by filtration and 20 mmol of salicylaldehyde (acetylacetone) (both produced by Fluka) was added to the filtrate. The reaction mixture was heated for 10 min at 50° C and then 20 mmol of nickel(II) acetate tetrahydrate dissolved in ethanol were added. After cooling the red-brown reaction mixture the crystals of the desired product were filtered off, washed with a small portion of ethanol and dried *in vacuo* (20 Torr). *Anal.* Calcd. for IIa, $C_{12}H_{13}O_3NSNi$ (310.0): C, 46.49; H, 4.23; N, 4.52. Found (611.0): C, 45.97; H, 4.48; N, 4.51. Calcd. for IIIa, $C_{10}H_{15}O_3NSNi$ (288.0): C, 41.75; H 5.25; N, 4.86. Found (566.0): C, 41.23; H, 5.40; N, 4.64.

Complexes IIb and IIIb were prepared using the same procedure as described for IIa and IIIa starting

from (S)-(+)-cysteine hydrochloride methylester and absolute methanol. *Anal.* Calcd. for IIb, $C_{11}H_{11}O_3NSNi$ (297.0): C, 44.48; H, 3.73; N, 4.71. Found (599.0): C, 44.35; H, 3.65; N, 4.32. Calcd. for IIIb, $C_9H_{13}O_3NSNi$ (274.0): C, 39.45; H, 4.78; N, 5.11. Found (512.0): C, 39.30; H, 4.97; N, 4.83. IIc: A water solution containing 20 mmol of (S)-(+)-cysteine was mixed with 20 mmol of salicylaldehyde dissolved in methanol. The reaction mixture was heated for 10 min to 50° C and then poured into a water solution containing 20 mmol of nickel(II) acetate tetrahydrate. The solid separated was filtered off, washed with water and dried *in vacuo* (10 Torr). *Anal.* Calcd. for $C_{10}H_{13}O_5NSNi$: C, 37.77; H, 4.12; N, 4.41. Found: C, 37.73; H, 4.18; N, 4.86. IId: For preparation of IId the same procedure as described for IIc was used. Instead of (S)-(+)-cysteine, the sodium salt of this ligand was used. *Anal.* Calcd. for $C_{10}H_{14}O_6NaNSNi$: C, 33.55; H, 3.94; N, 3.91. Found: C, 33.97; H, 4.00; N, 3.84.

Transesterification

0.1 g of IIa (IIIa) was dissolved in 30 ml of dry methanol and refluxed for 5 hr. The solid product was obtained by evaporating the reaction mixture to dryness. *Anal.* Found (IIb): C, 44.01; H, 3.80; N, 4.50. For IIIb, found: C, 38.44; H, 4.81; N, 5.02.

Acknowledgements

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