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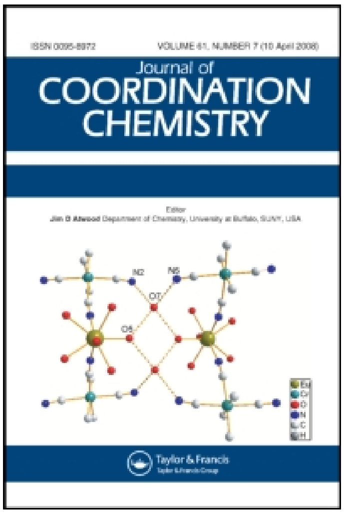

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PREPARATION AND CHARACTERIZATION OF NEW SUPROFEN COMPLEXES OF Fe(III), Co(II) AND Ni(II)

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The preparation and properties of new complexes containing the biometals Fe(III), Co(II) and Ni(II) coordinated to the anti-inflammatory drug Suprofen are reported. The elemental analyses, together with the magnetic and thermal behavior and electronic, IR and Raman spectra, indicated the following stoichiometries for the latter two complexes: $[M(Sup)_2(H_2O)_4]$. For the Fe(III) complex, the generation of a dinuclear species may be proposed on the basis of ^{57}Fe Mössbauer measurements.

Keywords: Cobalt(II); nickel(II); iron(III); Suprofen; solid complexes; spectroscopy; magnetic and thermal behavior

INTRODUCTION

We have initiated studies on the coordination chemistry of anti-inflammatory, analgesic and antipyretic drugs with transition-metal ions of biological interest in order to examine their binding modes and to attain an insight into their general physicochemical properties.

The ligand selected in the present study is Suprofen (HSup), α-methyl-4-(2-thienyl-carbonyl)phenylacetic acid (Figure 1). Recently, we investigated the crystal structure and the fundamental physicochemical properties of the dinuclear $[Cu(Sup)_2H_2O]_2$ complex[1] and the interaction of the vanadyl(IV) cation with Suprofen in solution.[2]

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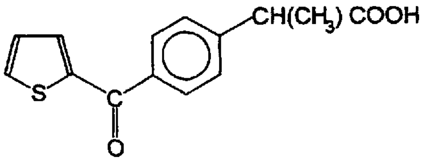

FIGURE 1 Structure of Suprofen (HSup).

This article reports the synthesis and characterization of new Co(II), Ni(II) and Fe(III) suprofenate complexes.

EXPERIMENTAL

Reagents

HSup (Sigma) and $COCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$ (Riedel de Häen) and $Fe(NH_4)(SO_4)_2 \cdot 6H_2O$ (Merck) were used as supplied.

Preparation of the Solid Complexes

The solid complexes were prepared according to the procedure used for the synthesis of the Cu(II)-Suprofen complex.[1,3] A solution of 3.84 mmol of HSup in 40 mL of 0.1 M NaOH was prepared at 60°C, filtered and solutions of $CoCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$ and $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$ were added (1.92 mmol in 7 mL of H_2O, for the first two cations and 0.64 mmol in 2 mL of H_2O, for the Fe(II) salt). Violet, green and brown solids precipitated immediately. They were washed several times with cold water and dried in an oven, at 60°C. The absence of sodium ions in the complexes has been confirmed. The chemical analysis of the obtained solids support the following formulas: $[Co(Sup)_2(H_2O)_4]$, $[Ni(Sup)_2(H_2O)_4]$ and $[FeSup(OH)_2\text{-}(H_2O)_2]_2$.

Anal. Calc. for $C_{28}H_{30}O_{10}S_2Co$ (%): C, 51.8; H, 4.6; S, 9.9. Found: C, 51.7; H, 4.3; S, 9.8.

Anal. Calc. for $C_{28}H_{30}O_{10}S_2Ni$ (%): C, 51.8; H, 4.6; S, 9.9. Found: C, 51.6; H, 4.3; S, 9.7.

Anal. Calc. for $C_{28}H_{32}O_{13}S_2Fe_2$ (%): C, 44.7; H, 4.2; S, 8.5. Found: C, 44.3; H, 4.1; S, 8.4.

Physical Measurements

Infrared spectra were recorded on a Perkin Elmer 580B spectrophotometer, using KBr pellets. Raman spectra were measured with the FRA 106 Raman

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unit of a Bruker FTIR IFS 66 instrument, using the 1064 nm line of a Nd : YAG laser for excitation.

Electronic UV–Vis and diffuse reflectance spectra were recorded on a Shimadzu UV-300 spectrophotometer (UV–Vis range); the NIR region of the electronic spectrum was measured on the Bruker IFS 66 FT-IR instrument.

Room temperature magnetic susceptibilities were determined at a magnetic field strength of 6 kG with a Cahn-2000 balance, calibrated with $Hg[Co(SCN)_4]$.

Thermogravimetric (TG) and differential thermal analyses (DTA) were performed on a Shimadzu thermoanalytical system (models TG 50 and DTA 50). Alumina was used as a DTA standard. Measurements were performed under an oxygen flow (60 mL min^{-1}) using Pt-crucibles at a heating rate of 10°C min^{-1}.

Mössbauer spectra of the Fe(III) complex were obtained at room temperature in a constant acceleration mode with transmission geometry and simultaneous accumulation in two halves of 256 channels, each of a conventional multiscaler. The two halves of the spectra were independently fitted with Lorentzian curves on a parabolic base line with a non-linear least-squares program with constraints. A ^{57}Co/Rh source of *ca.* 10 mCi activity was employed. The reported isomer shifts are relative to α-Fe.

RESULTS AND DISCUSSION

Synthesis of the Complexes

The preparation of the complexes is straightforward and occurs by direct interaction of aqueous solutions of the metal cations and the ligand. In the case of the iron complex, the process is more complicated because Fe(II) is oxidized to Fe(III) during the synthesis. In this case, also a complex with different stoichiometry is precipitated.

Mössbauer Spectrum and Magnetic Moments of the Solid Complexes

The oxidation state of the iron complex was confirmed by its Mössbauer spectrum, shown in Figure 2, which clearly demonstrates the presence of a species containing two Fe(III) centers. This spectrum presents two doublets with isomeric shifts of 0.38 ± 0.01 and 0.37 ± 0.02 mm s^{-1} and quadrupolar

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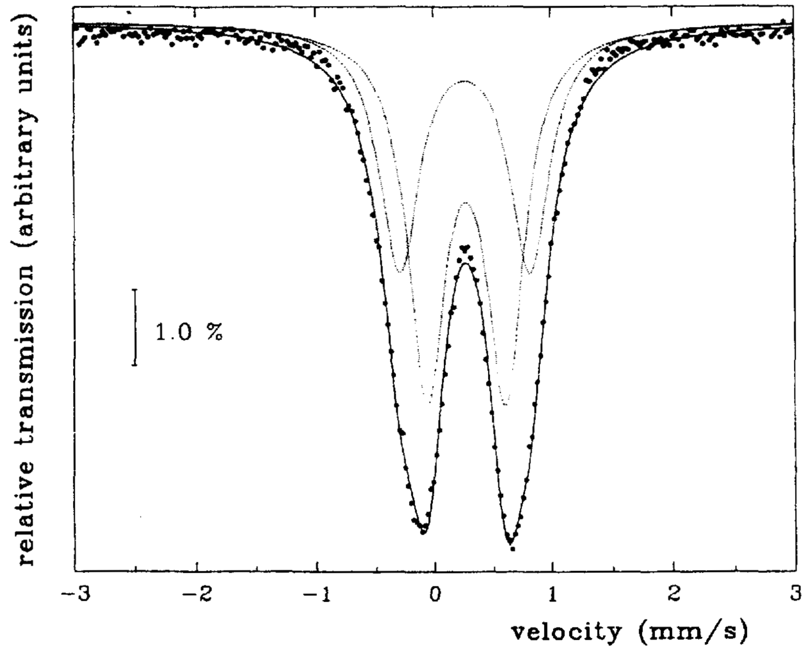

FIGURE 2 ^{57}Mössbauer spectrum of $[Fe(Sup)(OH)_2(H_2O)_2]_2$.

interactions of 0.66 ± 0.01 and 1.09 ± 0.01 mm s^{-1}, respectively. These values are typical for Fe(III) in octahedral environments.[4]

As the percentage of each component is about 50%, it may be concluded that this complex presents a bimetallic complex with two metallic centers in slightly different environments. According to the stoichiometry proposed from the chemical analysis one can speculate, that a non-equivalent distribution of the H_2O molecules and OH^- groups takes place over the two Fe(III) centers.

The magnetic moments were measured at room temperature. The value of 5.3 BM for the cobalt complex indicates a Co(II) ion with a d^7 high-spin configuration with an important orbital contribution and distorted octahedral geometry.[5]

For Ni the magnetic moment of 3.6 BM is within the range for octahedral d^8 ions with high orbital contribution.[5]

In the case of the Fe(III) complex a magnetic moment of 4.0 BM were determined for each metal ion, which shows important coupling between the two centers.

Electronic Spectrum

In Table I the position of the electronic absorption bands of acetonitrile solutions of the complexes are shown, along with those of the reflectance spectra of the solids. The extinction coefficients are high because of the deformation of the octahedral environment in Co/Sup and Ni/Sup and because of charge transfer in Fe/Sup.

In Co/Sup the ν_3 band is structured and multiple due to the inclusion of spin forbidden transitions to ^2G and ^2H; ν_2 is weak because it involves a two electron transition,[6] 10 Dq is calculated as $\nu_2 - \nu_1$ and $C = 4031\ cm^{-1}$.

For Ni/Sup three transitions and a forbidden transition to ^1E_g are expected.[6] This transition is joined with the ν_2 band, and a doubly structured band is observed in this region; ν_2 is chosen as the most intense band and 10 Dq can be calculated directly from the $^3A_{2g} \rightarrow {}^3T_{2g}$ transition. $C = 4339\ cm^{-1}$.

The bands observed in the Fe(III) complex have higher molar absorptivity values and are attributed to charge transfer processes; the $^6A_{1g} \rightarrow {}^4E_g(D)$ transition is masked and the B and C Racah's parameters cannot be calculated. Assuming $C = 4.477B$, for an octahedral field, 10 Dq and B can be estimated as: 8366 and 760.5 cm^{-1}, respectively.

Infrared and Raman Spectra

The most characteristic vibrational bands are summarized in Table II. The spectra are similar to those of the dinuclear $[Cu(Sup)_2(H_2O)]_2$ system.[1]

HSup presents a strong band in 1727 cm^{-1} due to vibration of the C=O carboxylic acid group; this band disappears upon complexation. In the Co/Sup and Ni/Sup complexes the antisymmetric and symmetric stretchings

TABLE I UV–Vis–NIR electronic (CH_3CN solution) and diffuse reflectance data (parentheses: $\varepsilon = M^{-1} \cdot cm^{-1}$)

Complex	ν (cm^{-1})	*Assignment*	10 Dq (cm^{-1})	B (cm^{-1})	*Reflectance* (cm^{-1})
Co/Sup	7903 (10)	$^4T_{1g} \rightarrow {}^4T_{2g}$	9878		1600 (sh)
	17781 (sh, 48)	$^4T_{1g} \rightarrow {}^4A_{2g}$		870	17301
	18975 (49)	$^4T_{1g} \rightarrow {}^4T_{1g}(P)$			18692
Ni/Sup	8807 (10)	$^3A_{2g} \rightarrow {}^3T_{2g}$			
	13698 (20.5)	$^3A_{2g} \rightarrow {}^3T_{1g}$	8807	921	13514
	15037 (18)	$^3A_{2g} \rightarrow {}^3E_g$			14925
	24390 (43)	$^3A_{2g} \rightarrow {}^3T_{1g}(P)$			25000
	10417 (100)	CT			
Fe/Sup	18181 (151)	CT	8366	760.5	18868
	21505 (313)	CT			21793

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TABLE II Infrared and Raman spectra (values in cm^{-1})

Suprofen	*IR*		*Raman*		*Assignments*
	Co/Sup = Ni/Sup	*Fe/Sup*	*Co/Sup = Ni/Sup*	*Fe/Sup*	
1727 (s)					ν(C=O) carbox
1592 (s)	1629 (s)	1629 (s)	1638 (m)	1632 (m)	ν(C=O) ketone
	1603 (s)	1600 (s)	1608 (s)	1607 (s)	$\nu_{as}(COO^-)$
1562 (m)	1568 (s)	1557 (sh)	1564 (m)	1569 (w)	Benzenic ring
1506 (s)	1513 (m)	1514 (m)	1503 (w)	1503 (w)	ν(C–C/C–S) thiophene
1452 (m)	1457 (m)	1457 (m)	1450 (w)		Benzenic ring
	1411 (s)	1412 (s)	1412 (s)	1411 (s)	Thiophene ring
	1396 (sh)		1374 (w)		$\nu_s(COO^-)$
	1357 (m)	1355 (s)	1347 (w)	1355 (m)	Thiophene vibration
1308 (s)	1303 (sh)		1304 (m)		
1297 (sh)					
1289 (sh)	1288 (s)		1277 (s)	1287 (m)	ν(C–C) Thiophene
1224 (s)	1232 (m)		1230 (m)		
1193 (w)	1186 (m)		1192 (m)	1187 (m)	

vs: very strong; s: strong; m: medium; w: weak; sh: shoulder.

of the carboxylate group appear centered at 1603 cm^{-1} (s) and 1396 cm^{-1} (sh), respectively. The difference between the frequencies (207 cm^{-1}) demonstrates that the carboxylate is monodentate.[7]

In Fe/Sup the band located at 1568 cm^{-1} (s) in the other two complexes becomes a weak shoulder, as observed for the Cu/Sup binuclear complex; $\nu_{as}(COO^-)$ appears at 1600 cm^{-1} (s) and ν_s is probably overlapped with the stretching of the thiophene ring at 1412 cm^{-1}; the smaller difference among these bands suggests that the carboxylate group acts as a bridge.[7] The absorptions at 1513, 1411 and 1357 cm^{-1} are related to the C–C and C–S stretches of the thiophene.[8,9] The bands located at 1568 and 1457 cm^{-1} are assigned to benzenic stretching modes[8] (see Table II).

Thermal Behavior

The thermal behavior of the three complexes was investigated by means of TG and DTA measurements, under an oxygen flow. The analysis of the three thermograms is briefly discussed in the following paragraphs.

For the Co(II) complex pyrolysis starts at 115°C, with a mass loss of 2.8% that corresponds to the removal of one bound water molecule;

$$[Co(Sup)_2(H_2O)_4] \xrightarrow{\phi,O_2} Co(Sup)_2(H_2O)_3 + H_2O \qquad (1)$$

this process is accompanied by a very weak endothermic DTA signal centered at 98°C.

Between 250°C and 500°C two further TG steps can be observed, indicating at least two other chemical events, related with exothermic DTA signals at 312°C (weak) and 463°C (strong). The total mass loss observed up to 500°C was about 75%, confirming the final generation of $CoSO_4$:

$$[Co(Sup)_2(H_2O)_4] \xrightarrow{\phi, O_2} Co(SO_4) + \text{volatile products} \qquad (2)$$

The presence of the sulfate could be confirmed unambiguously from IR spectroscopic analysis[10] of the residue collected at the mentioned temperature. Further heating, up to 900°C, generates a mixture of $Co(SO_4)$ and Co_2O_3.

The Ni(II) complex behaves in a similar manner, but the first loss, which in this case starts at 108°C, involving a weak endothermic DTA signal at 84°C, implies a mass loss of 5.8% which corresponds to the release of two water molecules:

$$[Ni(Sup)_2(H_2O)_4] \xrightarrow{\phi, O_2} Ni(Sup)_2(H_2O)_2 + 2H_2O \qquad (3)$$

The decomposition continues in three successive TG steps, between 260°C and 500°C with DTA signals at 286°C (strong, endo), 356°C (weak, exo) and 500°C (strong, exo). The total mass loss of 75.6% corresponds, also in this case, to formation of the sulfate,

$$[Ni(Sup)_2(H_2O)_4] \xrightarrow{\phi, O_2} NiSO_4 + \text{volatile products} \qquad (4)$$

which was confirmed by IR spectroscopy.[10] At higher temperatures decomposition of the sulfate takes place and at 900°C a mixture of $NiSO_4$ and Ni_2O_3 is observed.

The thermogram of the dimeric Fe(III) complex shows a first mass loss of 4.5%, starting at 92°C, corresponding to the release of two water molecules:

$$[Fe(Sup)(OH)_2(H_2O)_2]_2 \xrightarrow{\phi, O_2} [Fe(Sup)(OH)_2(H_2O)]_2 + 2H_2O \qquad (5)$$

The pyrolysis continues in three successive TG steps between 160°C and 400°C, with one strong exothermic DTA signal at 240°C. The total mass loss of 61% coincides with the formation of $FeSO_4$, also confirmed by IR:[10]

$$[Fe(Sup)(OH)_2(H_2O)_2]_2 \xrightarrow{\phi, O_2} 2FeSO_4 + \text{volatile products} \qquad (6)$$

Interestingly, this implies reduction of Fe(III) during thermolysis of the complex.

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Further heating up to 900°C, shows two additional TG steps and one very strong exothermic DTA signal at 548°C. The final residue (30.3%) and its red color are consistent with partial decomposition of the sulfate:

$$4FeSO_4 \xrightarrow{\phi,O_2} 2FeSO_4 + Fe_2O_3 + \text{volatile products} \tag{7}$$

The presence of this mixture was also supported by the IR spectroscopic analysis of the residue.[10,11]

To conclude, during thermal degradation of the three complexes the sulfates of the respective divalent cations are generated between 500° and 550°C. The stabilization of these metal sulfates is supported by the similar thermal behavior of other sulfur containing complexes of iron, cobalt and nickel.[12]

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CONCLUSIONS

The interaction of the anti-inflammatory drug Suprofen with Co(II) and Ni(II) in solution generates *pseudo*-octahedral complexes of stoichiometry $[M(Sup)_2(H_2O)_2]$ in which the drug acts as a monodentate ligand through one oxygen atom of the deprotonated carboxylate moiety. The electronic and vibrational spectra and magnetic behavior clearly support this proposal. Due to steric effects it is probable that the two suprofenate ligands are in *trans* positions.

In the case of iron, oxidation of Fe(II) to Fe(III) takes place during synthesis of the complex. In this case a dimeric structure of stoichiometry $[Fe(Sup)(OH)_2(H_2O)_2]_2$ is generated. The Mössbauer spectrum of this complex clearly confirmed the oxidation state of the metal centers and shows the presence of slightly different octahedral environments around them, probably from a non-symmetric distribution of the OH^- and H_2O ligands. The vibrational spectra show that in this case the carboxylate group of the drug acts as a bridging ligand; *i.e.*, the two Fe(III) ions are linked by a pair of deprotonated suprofenate anions. On the other hand, the magnetic behavior suggests important coupling between the two iron centers.

The thermal behavior of the three complexes confirmed the proposed stoichiometries. Interestingly, in all cases the $M(II)SO_4$ sulfates are generated as the primary pyrolysis products. At higher temperatures a partial degradation of the sulfates takes place, generating mixures with the corresponding sesquioxides.

Acknowledgments

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