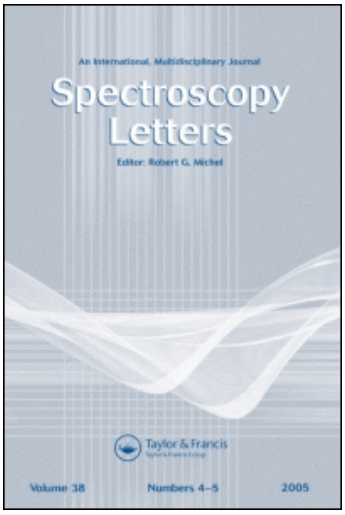

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Zinc (II) and Nickel (II) Complexes of Cysteinyl-Cysteine

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ZINC (II) and NICKEL (II) COMPLEXES OF CYSTEINYL-CYSTEINE

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ABSTRACT

Complexes of transition metals with cysteinyl-cysteine: cys-cys are of interest as models for metalloproteins such as metallothionein. Infrared and Raman Spectra of cys-cys, Ni (II)- $(cys\text{-}cys)_2$ and Zn (II)-$(cys\text{-}cys)_2$ complexes are reported.

The results show that the dipeptide is bound to transition metals through sulfur only.

INTRODUCTION

Reports on the synthesis and pharmacological properties of sulfhydryl containing aminoacids and

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related molecules have been studied for their varied biological activities[1-4]. On the other hand, sulfhydryl groups are known to have a strong affinity for transition and heavy metals[5-12].

Because of this important affinity and their excellent properties as antidotes, we have studied the coordination of the dipeptide cysteinyl-cysteine with Ni(II) and Zn(II). Zinc occurs, in several metalloproteins, such as alcohol deshydrogenase and metallothionein where it bound to the protein through different cysteine residues[13-15].

In metallothionein, an extremely cysteine rich low molecular weight protein, the cysteines occur seven times in alternating cys-X-cys sequences and three times each cys-cys and cys-X-X-cys sequences, where X is an aminoacid other than cysteine[16-17].

The ligand studied is a synthetic product obtained from the coupling method. The solid complexes have been studied by Infrared and Raman Spectroscopy on well defined phases.

EXPERIMENTAL

- REAGENTS AND APPARATUS :

BOC-S-Benzyl cysteine and Dicyclohexylcarbodiimide (DCCI) are Fluka Puriss grade used without further purification. Dimethyl chloride is used after distillation from K_2CO_3. All stages of preparation were carried under an atmosphere of nitrogen purified through Oxysorb Catalyst ($O_2 < 0.02$ ppm). I.R. Spectra were recorded between 4000 and 200 cm^{-1} on a 225 Perkin Elmer Spectrometer using KI pressed disks. Raman Spectra were recorded on a Jobin

Yvon Ramanor HG 2S Spectrometer with Argon ion laser source (5145 Å).

Preparation of Cys-Cysteine

BOC-S-Benzyl cysteine methyl ester (10^{-2} M) - prepared from BOC-S-Benzyl cysteine in MeOH - was dissolved in CH_2Cl_2. BOC-S-Benzyl cysteine (10^{-2}M) with DCCI (10^{-2}M) was added and the mixture stirred overnight at 0°C, then at room temperature.
Dicyclohexylurea was filtered off and washed with ethylacetate. yield : 85%.

To a solution of 0.008 Mole of BOC-(S-Bzl) cysteine-OMe in 20 ml of methanol was added 10 ml of 1M sodium hydroxide. The solution was neutralized by the addition of 1M HCl and evaporated to dryness.
The residue was dissolved in methanol. After removing the insoluble material, the solution was allowed to stand. The crystals of BOC-(S-Bzl)cysteinyl-(S-Bzl)cysteine were collected.yield : 72%.

Cleavage by HBr, TFA procedure[18] for 90 minutes was used for removal off the protective groups. The solvent and acidic excess were removed in vacuo. Ethyl acetate and ether were added. The ester phase was washed by $NaHCO_3$, H_2O, HCl 0.5N and dried. The residue was triturated with ether, the solid filtered, washed with ether and dried in vacuo yield 56%. The cysteine analysis on a Beckman 120 Amino Acid Analyser give : first cysteine residue : 1.01
Second cysteine residue : 0.99

$Zn(II)-(Cys-Cysteine)_2$

Dropwise and very slow addition of degased 5M sodium hydroxide solution into a 1:2 mole ratio

aqueous methanolic solution containing zinc sulfate and cysteinyl-cysteinate yield a white precipitate when the pH stabilizes at 6-8. The solid phase is then isolated, thoroughly washed with water and MeOH and dried (P_2O_5) under vacuum.

Ni(II)-(cys-cysteine)$_2$

This green compound was prepared by essentially the same procedure, the nickel salt been $NiCl_2$.

Analysis - Nickel and Zinc Analysis on an Instrumentation Laboratory 251 Spectrophotometer gives:
Zinc : found 12.50, calculated 12.83
Nickel : found 11:40 calculated 11.72.

RESULTS AND DISCUSSION

The position and attribution of the main vibration bands of the ligand and the metal complexes are given in table I. Examination of the Raman spectrum of the Ni(II) and Zn(II) complexes shows principally the absence of sulfhydryl group which would give strong diffusion lines around 2570 cm^{-1} [19-21].

Absorption between 1750-1700 cm^{-1} were not detected in the I.R. Spectra excluding the presence of ester group[21] which has been hydrolised. Consequently one finds two characteristics absorptions of the carboxylate groups : a strong IR band at 1575 cm^{-1} (ν_{as} COO^-) and a medium IR band which corresponds to a strong Raman line round 1435 cm^{-1} (ν_s COO^-)[21-22].

TABLEAU 1

CYS-CYSTEINE : L				Zn L_2	N_i L_2	Attribution
IR		Raman		IR	IR	
3320	vs			3320 s	3322 s	νNH(amide) + $\nu\nu NH_2$
300	sh				3300 sh	
2925	s	2925	s	2923 s	2921 s	νCH_2
2850	m	2850	m	2850 m	2847 m	
2575	vs	2575	vs	-	-	νSH
1627	vs	1620	w	1624 s	1624 s	ν C=O (amide I)
1610	sh	1600	w	1608 sh	1610 sh	δ NH_2
1575	s	-		1568 s	1565 s	νas COO^-
1550	vs	1545	w	1549 s	1548 s	δNH + νCN (amide II)
1503	s	1500	w	1500 m	1498 m	-
1450	m			1445 m	1445 m	
1437	m	1435	s	1435 m	1433 m	νs COO^-
1252	m	1250	s	1240 m	1242 m	νCN + NH (amide III)

vs = very strong s = strong m = medium w = weak
sh = shoulder

The peptide group is characterised by very strong IR bands situated at 3320 cm^{-1} (ν_{NH}), 1627 cm^{-1} (ν C= O, amides I), 1550 cm^{-1} (νCN + δNH, amide II) and by an IR medium peak corresponding to a strong Raman line at 1250 cm^{-1} (νCN + δNH, amide III).

Around 3300 cm^{-1} one observes, as well as the strong absorption at 3320 cm^{-1}, a shoulder at 3300 cm^{-1}. These two absorptions superposed on the νNH band must be attributed to νNH_2 oscillations. The Raman spectrum shows around 1600 cm^{-1}, two weak, but distinct bands at 1620 cm^{-1} and 1600 cm^{-1}. The first having been connected to the νC= O (amide I) vibration, the second is tentativly assigned to δNH_2 vibration. The very strong IR absorption centred at 1627 cm^{-1} also shows a shoulder at 1670 cm^{-1} indicating the superposition of the superposition of the two vibrations (amide I and δNH_2). All the assignments are assembled in table I.

The IR spectra of the ligand and the complexes show an important analogy. No significant spectral perturbation of the vibrations associated with peptidic NH, amine and carboxylate group was observed. These results are consistent with the cys-cysteine being coordinated to the metal through the sulfur. No alterations being observed between the ligand and their complexes at the level of the characteristic absorptions of the amino and carboxylic group, allowed us to specify the coordination modes through the thiol function.

CONCLUSION

Cysteine has a chelation mode susceptible of appearing in a proteinic sequence.

Within the whole of a study, this work specifies :

- the nature of the complexes : Ni(II)-$(cys\text{-}cys)_2$ and Zn(II)-$(cys\text{-}cys)_2$ formed in a delimited pH range $6.5 < pH < 7.2$.
- The infrared and Raman Analysis give that thiol is the only preferential complexing group implicated in the coordination with Ni^{2+} and Zn^{2+}. While for cysteine[19] and dipeptides containing sulfhydryl groups suchas mercaptopropionylglycine[7-20], also carboxylate or, and amino group occur in the coordination.
- The type of chelation lead to be bidentate for the ligand. Consequently, the Zn(II) and Ni(II) complexes have a tetragonal structure.

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