

- [10] L.D. PETTIT, *Pure Appl. Chem.*, **56**, 247-292 (1984).
- [11] A. ODANI, O. YAMAUCHI, *Inorg. Chim. Acta*, **93**, 13-18 (1984).
- [12] H. MUHONEN, R. HÄMÄLÄINEN, *Finn. Chem. Lett.*, 120-124 (1983).
- [13] D. VAN DER HELM, M.B. LAWSON, E.L. ENWALL, *Acta Crystallogr.*, **B27**, 2411-2418 (1971).
- [14] S.-H. KIM, R.B. MARTIN, *J. Am. Chem. Soc.*, **106**, 1707-1712 (1984).
- [15] J.L. MEYER, J.E. BAUMAN JR., *J. Chem. Eng. Data*, **15**, 404-407 (1970).
- [16] a) I. SÓVÁGÓ, R.B. MARTIN, *FEBS Lett.*, **106**, 132-134 (1979);
b) G. ARENA, R. CALI, V. CUCINOTTA, S. MUSUMECI, E. RIZZARELLI, S. SAMMARTANO, *Thermochim. Acta*, **74**, 77-86 (1984).



PS5.3 — TH

J.P. LAUSSAC

A. ROBERT

R. HARAN

Laboratoire de Chimie de Coordination du CNRS

Unité n.° 8241 liée par convention à l'Université Paul Sabatier

205, route de Narbonne, 31 400 Toulouse

France

B. SARKAR

The Research Institute of the Hospital for Sick Children

Toronto

Canada

and

Department of Biochemistry

University of Toronto

Canada

MODELS FOR METAL-PROTEIN

INTERACTION:

COPPER(II) COMPLEXES WITH A CYCLIC PEPTIDE HAVING SIDE-CHAIN IMIDAZOLYL AND CARBOXYL GROUPS

Considerable effort has been devoted to the study of macrocyclic ligands and their metal complexes. Thus, introduction of a metal ion into functionalized cyclic peptides may be an appropriate model for the studies of binding by metalloenzymes. Such cyclic peptides can be designed to incorporate amino acid side chains that are important for the function of various enzymes. For example, the imidazolyl and the carboxyl groups of histidine

and glutamic acid seem to play an important role in the coordination of proteins or naturally occurring peptides to metal ions. The investigation of simple cyclic peptides having side-chain imidazolyl and carboxyl groups as model might be of significant value in elucidating the details of enzyme mechanisms, particularly in aqueous solution.

We chose to synthesize cyclo-(Gly-L-Glu-Gly-L-His-Gly-Gly-L-His-Gly) (hereinafter denoted G5H2Gu). Complexation of G5H2Gu with the transition metal ion Cu(II) in aqueous solution over a wide pH range and with different peptide/metal ratios, has been studied by using carbon-13 and proton NMR, ESR and Visible Spectroscopy.

The results obtained are discussed in terms of different complexes depending on the pH and are compared with a cyclic peptide having different side-chains and a different cavity size.



PS5.4 — MO

L. ANTOLINI

L. MENABUE

G.C. PELLACANI

M. SALADINI

Istituto di Chimica Generale e Inorganica

University of Modena

Italy

L.P. BATTAGLIA

A. BONAMARTINI CORRADI

Istituto di Chimica Generale e Inorganica

Centro di Studio per la Strutturistica Diffattometrica del C.N.R.

University of Parma

Italy

THE ROLE OF THE TOSYL GROUP ON THE COORDINATION ABILITY OF N-PROTECTED AMINOACIDS. SOLID STATE BEHAVIOR OF N-TOSYLVALINATE COPPER(II) COMPLEXES

Among N-protected aminoacids, as N-acetyl-, N-benzoyl-, N-benzyloxycarbonyl and N-toluenesulfonyl-aminoacids, only the latter class of deri-

vatives has been proved to coordinate in aqueous and alcoholic solution to the copper(II) ion, acting as carboxylate ligand, or, undergoing amide nitrogen deprotonation at $\text{pH} > 5$, as naturally occurring L- α -aminoacids.

In this communication we report the results of an investigation concerning the interactions between *N*-tosylvaline and copper(II) ion. At pH lower than 5 two solid simple complexes, one green and one blue, having formula $\text{CuL}_2 \cdot 3\text{H}_2\text{O}$ and $\text{CuL}_2 \cdot 2\text{H}_2\text{O} \cdot 2\text{MeOH}$, respectively, have been separated. For the blue complex the crystal structure was determined. It consists (Fig. 1) of monomeric units in which the copper atom, lying on the symmetry centre, is surrounded by two carboxylic oxygens ($\text{Cu-O1} = 1.954(4) \text{ \AA}$) and two water molecules ($\text{Cu-O2} = 1.989(3) \text{ \AA}$) in a square planar arrangement. Two long contacts with two methanol molecules ($\text{Cu-O3} = 2.492(4) \text{ \AA}$) complete the coordination to elongated tetragonal bipyramid. The second carboxylic oxygen is not involved in the coordination ($\text{Cu} \cdots \text{O4} = 3.137(4) \text{ \AA}$). These data reinforce the assignment of this type of geometry, based on spectroscopic results, for the $\text{Cu}(\text{tsgly})_2 \cdot 4\text{H}_2\text{O}$ ($\text{tsgly} = N$ -toluensulfonyl-glycine monoanion) [1].

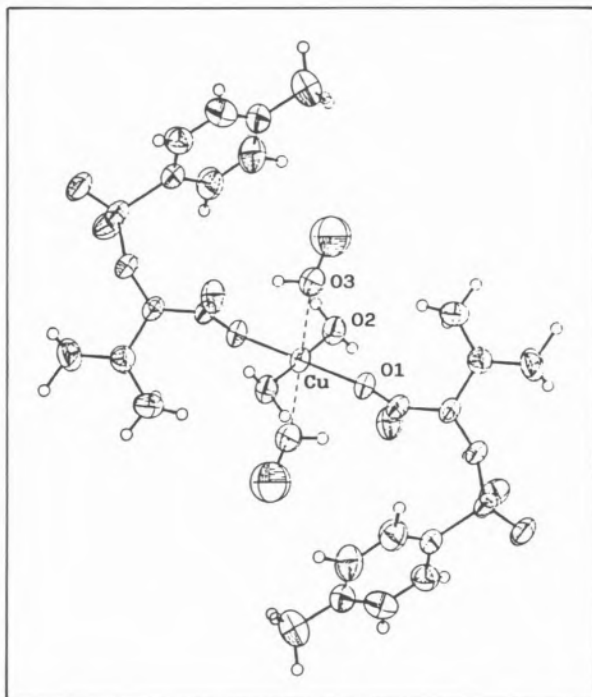


Fig. 1

ORTEP view of the $[\text{Cu}(\text{tsval})_2 \cdot 2\text{H}_2\text{O} \cdot 2\text{MeOH}]$

The green compound shows physical properties indicating a dimeric structure with strong antiferromagnetic interactions between the copper(II) within the pairs.

By treating these two complexes in aqueous or alcoholic solution with an equimolar amount of 2,2'-bipyridine, a deep blue compound of formula $\text{Cu}(\text{tsval})_2 \text{bipy}$ ($\text{tsval} = N$ -toluensulfonylvalinate monoanion; $\text{bipy} = 2,2'$ -bipyridine) was separated. Since it presents unusual spectroscopic properties, the crystal structure was determined. In the unit cell, two crystallographically independent and chemically inequivalent copper(II) ions are present. Each copper atom is surrounded by two carboxylic oxygen atoms, belonging to two different aminoacids, and two bipyridine nitrogen atoms, $[(\text{Cu-O})_{\text{mean}} = 1.938(4) \text{ \AA}, (\text{Cu-N})_{\text{mean}} = 2.001(4) \text{ \AA}]$. The five coordination positions are occupied for one copper atom by a carboxylic oxygen of an adjacent aminoacid ($\text{Cu-O} = 2.457(3) \text{ \AA}$) giving rise to a dimeric unit with a monoatomic bridge, and for the other copper atom by a sulphonic oxygen ($\text{Cu-O} = 2.407(3) \text{ \AA}$) of one of the two aminoacids coordinated through one carboxylic oxygen to the same copper atom giving rise to a discrete molecule.

REFERENCES

- [1] L. ANTOLINI, L.P. BATTAGLIA, G. BATTISTUZZI GAVIOLI, A. BONAMARTINI CORRADI, G. GRANDI, G. MARCOTRIGIANO, L. MENABUE, G.C. PELLACANI, *J. Am. Chem. Soc.*, **105**, 4327-33 (1983).



PS5.5 — TU

GRAZYNA FORMICKA-KOZŁOWSKA

Institute of Chemistry
University of Wrocław
Joliot-Curie 14, 50-383 Wrocław
Poland

LESLIE D. PETTIT

School of Chemistry
The University of Leeds
Leeds LS2 9JT
U.K.

THE CUPRIC INTERACTION WITH OPIOID PEPTIDES

The role of peptides as classical hormones has long been known. More recently it has been appreciated a different role of some peptides acting in the central nervous system (*e.g.* thyroliberin, somatostatin, opiate related peptides, etc.). It is thought that they act as local tissue regulators and in some instances also as neurotransmitters [1]. Control of sleep, memory, perception are possible functions for these peptides.

All these peptides may serve as special chelate agents for trace elements, widely distributed in the body, especially for copper present in brain. It has been proved that some of the neuropeptides retain their biological activity in the form complexed by transition metal ions [2].

Since a few years we have been interested in metal (especially Cu(II)) interaction with some neuropeptides [3,4] and their chemical analogs [5]. All these peptides proved to be very specific ligands for metal ions.

Recently we have been studying the cupric complexation by some opiate related peptides *i.e.* β -casomorphin-5 and its di-, tri- and tetra-peptide fragments and enkephalin analogs.

β -casomorphin-5 is the opioid isolated from β -casein with the following sequence: Tyr-Pro-Phe-Pro-Gly. For our studies besides the β -casomorphin-5 itself, we have used a series of peptides: Tyr-Pro-Phe-Pro, Tyr-Pro-Phe, Tyr-Pro, Pro-Phe-Pro-Gly, Pro-Phe-Pro. Spectroscopic

(CD, EPR) and potentiometric studies have shown that the Cu(II) interaction with the β -casomorphin fragments depends strongly on the *N*-terminal amino acid. With Pro in this position typical peptide complexes containing the Cu-N⁽⁻⁾ bond are formed. With Tyr in this position a dimeric species, Cu₂L₂, becomes a major complex at physiological pH values, with the copper(II) bound to the -NH₂, CO groups of one ligand and to the phenolic oxygen of a second ligand.

The proline residue in the second and fourth positions in β -casomorphin-5 acts as a «break-point» to Cu(II) coordination and destroys completely the coordination ability of amino acid residues after the first Pro. In other systems with a proline residue inside the peptide chain the *N* and *C* terminals either interact separately [6] or form a macro-chelate with the peptide bent in a β -conformation [7].

Similar to the β -casomorphin, the enkephalin peptides with opiate activity contain the L-tyrosine residue on the *N*-terminus. This position of Tyr residue is a common feature to most endorphins and it is an important factor for their biological activity. Only the 2nd and 5th positions of enkephalin analogs can be safely manipulated to give a peptide with potent activity. Enkephalins and their structural analogs are of great interest to physicians and pharmacologists, because their properties might give the information on the mechanism of the development of drug addiction. Besides the pharmacologists are looking for enkephalin analogs which elicit analgesia but are less addicting with the hope to find the addiction-free pain relievers.

The following peptides have been studied: Tyr-Gly-Gly-Phe-Met (Met-enkephalin), Tyr-D-Ala-Gly-Phe-Met-NH-CH₂-CH₂-NH₂, Tyr-D-Ala-Gly-Phe-Met-N-(CH₃)₂, Tyr-D-Ala-Gly-Phe-Leu-ol. Spectroscopic and potentiometric data have indicated that all peptides mentioned above form similar four nitrogen complexes with cupric ions. Only in some cases a weak interaction of the phenolic oxygen with Cu(II) has been observed.

It is interesting to compare the role of a Tyr residue placed in a different position of a peptide chain. In β -casomorphin-5 the Tyr residue plays an important role in the formation of a major dimeric complex, while in enkephalin analogs the