of mercapto and imidazole groups to Cu(II) ion in reversed micelles is also studied by ESR and NMR. Results obtained will be discussed with particular attention to the properties of copper metalloenzymes.

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Interaction of the Transition Metal Ions with Natural Peptides

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NMR, CD, EPR and absorption spectra studies as well as polarographic and potentiometric studies on metal ion interaction with two natural peptide *i.e.* glutathione (GSH) and thyrotropin releasing factor (TRF, L-pyroglutamyl-L-histydyl-L-prolinamide) have revealed quite unusual features of both tripeptides as the chelating agents [1–4].

In the case of Cu(II), Co(II) and Ni(II)–TRF systems, the tripeptide acts as the tridentate ligand with formation of the metal ion bonds with N3 imidazol, N^- of the peptide linkage between Pyr and His and the amide nitrogen of pyroglutamic acid. CD spectra studies have shown that the conformation of the chelate rings is very sensitive on the deprotonation process of N1 imidazole nitrogen (see also [4]).

GSH and its oxidized form GSSG with Cu(II) and Co(II) forms very interesting redox system [2]. Both forms of the glutathione are extremely sensitive on the presence of cupric ions in the solution, especially at higher pH region. All studies have shown that the cysteine residue is the most specific coordination site for all studied metal ions *i.e.* Cu(II), Co(II) and Ni(II).

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The Structure and Action of Eseroline: a New Antinociceptive Drug

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The synthesis of eseroline and its salts has been performed in an attempt to clarify the relationship between structure and activity of physostigmine and eseroline.

Eseroline as a free base is quite unstable and is easily oxidized [1], whereas its salts with acids like salicylic, fumaric, tartaric *etc.* are stable even in solution in presence of antioxidant agents. The structure, conformation and electronic properties of eseroline have been investigated through ^1H and ^{13}C NMR, mass spectrometry, UV and IR spectroscopies. All of these measurements show that the structure is similar to that of physostigmine. The ^{13}C NMR spectrum is closely related to that of physostigmine, thus allowing to safely establish the same spatial arrangement of the dipirrolic moiety in both molecules.

Eseroline has antinociceptive activity comparable in potency to that of morphine. At variance with physostigmine, eseroline shows high affinity for the opioid receptor sites as demonstrated by its ability in inhibiting stereospecific [^3H]-naloxone binding in homogenates of rat brain [2]. The groups interacting with the opioid receptor sites are the phenolic ring and the pyrrolidine nitrogen which show the same distance between the phenolic ring and the piperidine nitrogen of the morphine molecule. Eseroline, although derived from physostigmine by hydrolysis

of N-methylcarbamoil group, is also structurally related to morphine. The methylcarbamate group present in physostigmine differentiates this drug from eseroline and is responsible in determining the well known indirect cholinomimetic activity.

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Synthesis and Chemical Properties of Copper(I) and Copper(II) Complexes of N,N'-Bis(3-(2-Thenylidene)-iminopropyl)piperazine (TIPP) and N,N'-Bis(3-(2-Thenyl)aminopropyl)piperazine (TAPP)

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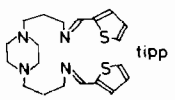
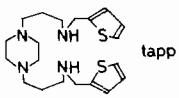
Despite much current interest in the unusual physical properties of a variety of copper containing proteins [1], the chemistry and reactivity of Cu(II) and especially Cu(I) ions in non-classical N_xS_y coordination environments remains rather undeveloped. We have studied the chemical properties of Cu(I) and Cu(II) complexes of the polyfunctional ligands tipp and tapp, which contain four nitrogen and two sulfur atoms as potential donor sites. Preliminary results of the X-ray structural determination of a member of





this series of complexes, $[Cu(tapp)][ClO_4]_2$, indicate a distorted square-planar geometry of the Cu(II) ion, with a CuN_4 coordination. In solution, electronic and EPR spectra of $[Cu(tapp)]^{2+}$ show solvent dependence (Table I). In particular, the intensity of absorption bands (at ~300 and ~600 nm) decreases with time in donor solvents (CH_3CN, CH_3NO_2). We are currently investigating in more detail the nature of these effects.

A similar behavior is exhibited by the complex $[Cu(tipp)]^{2+}$. However, in this case the changes observed in the electronic spectra are mainly related to the hydrolysis of the coordinate Schiff base undergone by the complex in the presence of traces of water. This reaction is known to occur in other metal coordinated Schiff bases derived from 2-thiophenecarboxaldehyde [2].

TABLE I. EPR Parameters in Frozen Solutions at 77 K.

Compound	Solvent	$g_{\|\|}$	$A_{\|\|}.10^4$ (cm^{-1})
$[Cu(tipp)][ClO_4]_2$	acetone	2.210	155
	nitromethane	2.235	185
$[Cu(tapp)][ClO_4]_2$	acetone	2.204	180
	nitromethane	2.243	209

The Cu(I) complexes of tapp and tipp are stable in the solid state. In solution, $[Cu(tapp)]^+$ undergoes rapid aerobic oxidation, while $[Cu(tipp)]^+$ shows a remarkable stability toward oxidation. In Fig. 1 the rate of hydrolysis of $[Cu(tipp)]^{2+}$ and $[Cu(tipp)]^+$ in undried acetonitrile are compared. The faster hydrolysis of the Cu(II) complex is explained in terms of: (*i*) the higher charge of the ion, which produces a higher degree of polarization of the coordinated imine linkage, and (*ii*) a partial displacement of coordinated Schiff base by solvent molecules occurring in the case of $[Cu(tipp)]^+$. An intermediate with intense blue color is formed if $[Cu(tipp)]^{2+}$ is prepared from $Cu(OSO_2CF_3)_2$ in pre-dried CH_2Cl_2. This evolves to the product actually isolated in the standard preparation, but its reaction with traces of water is extremely fast (Fig. 2), and also leads to products formed through a transamination process preceding the hydrolysis step.

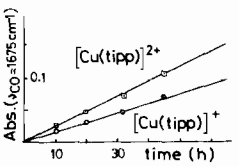


Fig. 1.

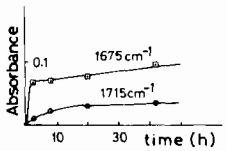


Fig. 2.

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Interaction of Lanthanide Ions with Glutamic Acid and γ-Carboxyglutamic Acid

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Interactions of lanthanide ions with glutamic acid and γ-carboxyglutamic acid has been studied by the