INTRODUCTION

1.1 Biochemical activity of copper

The general involvement of copper in biological systems is well documented. Role of copper(II) ions in the biological systems was recognized in an early stage because of the isolation of copper proteins. The function of copper in biological systems is primarily associated with the reduction of oxygen to water with the transfer of oxygen to a substrate. More positive Cu(II)/Cu(I) redox potentials at neutral pH indicating a more effective stabilization of Cu(I) vs. Cu(II), characteristic visible absorption spectra and ESR behaviour differentiate biological copper species from the copper(II) complexes of synthetic origin. The challenge to develop model systems has generated much activity in this field and these studies have yielded copper(II) complexes with very interesting properties.
it has been found that the spectral properties of the complexes are reflected in their redox behaviour, i.e. the spectral and redox properties are interrelated.\textsuperscript{15}

The low molecular weight Cu(II)-\(\alpha\)-amino acidato complexes are considered to be biologically active since they have been found to involve in the transport of Cu(II) ions between blood and tissues\textsuperscript{16}. Several ternary histidine Cu(II) complexes have been detected in human serum along with Cu(L-his)\textsubscript{2}.\textsuperscript{17} These observations acted as catalysts for the investigation of the properties of Cu(II)-\(\alpha\)-amino acids and their derivatives. The chemistry of Cu(II) complexes of \(\alpha\)-amino acids has developed not only from the inorganic point of view but also because of possible biological interest.

1.2 Copper(II)-\(\alpha\)-amino acid complexes

Bidentate \(\alpha\)-amino acids coordinate to Cu(II) through the amino nitrogen and the carboxylic oxygen donor atoms. Depending upon the pH of the medium, they form mainly two types of complexes, [CuL]\textsuperscript{+} in the pH range 4.5-5.8 and CuL\textsubscript{2} in the pH range 6.2-7.5.\textsuperscript{18-20} At neutral pH the complexes have square-planar arrangement of the donor atoms around the metal ion with the metal ion slightly disposed towards the axial positions. Few complexes have two water molecules occupying the axial coordination sites (I) and few have one water molecule and one carboxylic oxygen of neighbouring complex molecule at their axial positions (II). The nature of the donor oxygen atoms at the apical positions has been found to have little effect on the properties of the complexes.\textsuperscript{21}
1.2.1 Spectral properties

Bis(α-amino acidato)copper(II) complexes exhibit the d-d transition in their electronic spectra at ca. 620 nm in aqueous media at neutral pH. The absorption band is weak with $\varepsilon_{\text{max}}$ value in the range 50-100 $\text{M}^{-1}\text{cm}^{-1}$. On lowering pH, the d-d band shifts to higher wavelengths (ca. 720 nm) and has been ascribed to formation of protonated species such as $[\text{CuL}_2\text{H}]^+$, $[\text{CuL}]^+$, $[\text{CuLH}]^{2+}$ etc., where LH = α-amino acid. The Cu(II)-α-amino acid complexes have also been studied by CD spectroscopy and are shown to exhibit two CD extrema, one in the 590-620 nm region and another at ca. 700 nm. Many Cu(II)-L-amino acidato complexes exhibit positive CD band at 700 nm (I) and a negative CD band in the 620-590 nm region (II); the Cu(II) complexes of imino acids L-proline and L-hydroxy proline exhibit opposite Cotton effect i.e. negative sign for the band I and positive sign for the band II. This has been attributed to the second asymmetric centre, imino nitrogen, produced in the ligand as a result of chelation. In addition to these two CD extrema, another extrema has also been observed at ca. 730 nm. The assignment of the three possible transitions is in the following order of increasing energy:

$$B_{1g} \rightarrow A_{1g} < B_{1g} \rightarrow B_{2g} < B_{1g} \rightarrow E_g$$
A great deal of literature is available on the ESR data of the Cu(II)-α-amino acid complexes.\textsuperscript{19,25-32} Many workers have studied the ESR spectra as dilute powders,\textsuperscript{28} glasses, and frozen solutions.\textsuperscript{25-27} The nitrogen superhyperfine splitting is useful to establish the number of nitrogen atoms coordinated to the Cu(II) ion. Recently, it has also been shown that mono and bis-(α-amino acidato)copper(II) complexes can be readily distinguished on the basis of their g and hyperfine A values.\textsuperscript{19} The X-band and K-band ESR spectra of the trans-planar Cu(II) complexes of α-amino acids, in polycrystalline state at room temperature, found to exhibit a variety of ESR line-shapes. However, the frozen glassy spectra are similar and represent typical axial spectra and have been fitted with $d_{x^2-y^2}$ ground state. The ESR parameters indicate a normal tetragonal geometry for the complexes.\textsuperscript{25} ESR spectroscopy has also been used to investigate the change in copper-ligand bond strength; for example, decrease of g values characterizes elongation of axial band and shortening of the planar Cu-O bond.\textsuperscript{32} Correlation among the g values, the d-d band energies, bonding parameter and geometrical configuration of the coordinating atoms for several Cu(II)-α-amino acid complexes has been obtained.\textsuperscript{25-32}

1.2.2 Electrochemical properties

In comparison to the bulk of spectral investigations reported so far, the Cu(II) complexes of α-amino acids have received only less attention with respect to their redox properties.\textsuperscript{33} Electrochemical reduction of these complexes leads to the formation of the corresponding Cu(I) species. A fraction of the Cu(I) species
could be reoxidized to Cu(II)-complex electrochemically while another fraction undergoes chemical decomposition/disproportionation generating Cu(0) at the hanging mercury drop electrode. The Cu(0) species produced undergoes two-electron oxidation to Cu(II)(aq) during the reverse scan which subsequently gets reduced at a less negative potential during the second scan. Thus the CV profile is constituted of two redox couples, one corresponding to the close to reversible Cu(II)/Cu(I) process at ca. -0.25 V vs. SCE and another at -0.01 V corresponding to Cu(II)(aq)/Cu(0)(Hg) process. Controlled potential coulometry (CPC) experiments over mercury pool towards the determination of number of electrons involved in the redox process have been unsuccessful. The CPC experiments yield coulombs which correspond to n = 2. This value does not agree with the other experimental evidences given for the involvement of Cu(I) species in the redox process. The apparent discrepancy arises because of the reason that under the continuous influence of cathodic potential the Cu(I) species generated by the first electron-transfer undergoes chemical decomposition/disproportionation to Cu(0)(Hg). Hence the overall process involves two electrons.

1.3 Condensation reactions of Cu(II)-amino acid complexes

Coordination of α-amino acids to metal ions increases the nucleophilic reactivity at the α-carbon atom through bond polarization by the metal ion.\(^{34,35}\) The most obvious illustration of this effect is that, most (not all) metal ions increase the rate of racemization of α-amino acids. For example,
with Co(III) complexes, it has been demonstrated by NMR spectroscopy that the rate of racemization is similar to H-D exchange rate at the α-carbon atom (equation 1.1).

\[
\text{Co(III), Cr(III), Cu(II), Pd(II) and Pt(II) ions accelerate the racemization rates of α-amino acids. The mechanism is not always as simple as that outlined above (equation 1.1). This effect could also be considered as a simple model of the action of metal ions in some biological transformations of amino acids.}^{36}
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During the last three decades a great deal of literature has appeared concerning the reactions of metal coordinated α-amino acids\(^ {37-49}\) or small peptides\(^ {50,51}\) with various aldehydes. In these reactions generally the simple bis(α-amino acidato)metal complexes are used. Reactions of chiral cobalt(III) complexes such as \(\Lambda- (+)[\text{Co(en)}_2(\text{gly})]^2+\) have been found to yield high asymmetric products with low overall yield.\(^ {52,53}\) The use of an α-amino acid-Schiff base metal complex instead of bis(α-amino acidato)metal complexes seems to increase the nucleophilicity at the amino acid α-carbon atom and prevents N-alkylation.\(^ {45,54-56}\)

The metal assisted synthesis of DL-threonine from glycine was one of the first such reactions reported three decades ago.\(^ {37}\) The reaction which is base catalyzed, proceeds under far milder conditions than for free glycine. Similar metal assisted reac-
tions are also known for ligands such as amino alcohols and amino thioethers. A few metal-assisted condensation reactions of α-amino acids are discussed below.

The reaction of Cu(gly)$_2$ with acetaldehyde under basic conditions (sodium bicarbonate, pH 11) yields, bis(2,5-dimethyloxazolidine-4-carboxylato)copper(II) dihydrate, 1 (equation 1.2).

\[
\text{Cu(gly)$_2$} + \text{MeCHO, NaHCO}_3, \text{pH 11} \rightarrow \text{bis(2,5-dimethyloxazolidine-4-carboxylato)copper(II) dihydrate, 1}
\]

The complex on decomposition in an acid medium by H$_2$S releases DL-threonine in the aqueous solution, copper being recovered in the form of insoluble CuS. Comparative studies show that formaldehyde is unable to form serine from its reaction with Cu(gly)$_2$, in the conditions in which acetaldehyde gives DL-threonine, in ca. 40% yield. The reaction is similar to aldol condensation and has been explained by the mechanism shown in Scheme 1.1.
Condensation of Cu(gly)$_2$ with formaldehyde in presence of sodium bicarbonate at pH 8.5 yields bis(dihydro-1H,3H,5H-oxazolo[3,4-c]-oxazole-7a-carboxylato)copper(II), 2. The reaction has been suggested to follow the same mechanism (Scheme 1.1). However, after the formation of the expected product, bis(oxazolidine-4-carboxylato)copper(II) (equation 1.3) further condensation takes place (which is absent in the case of acetaldehyde condensation probably due to steric hindrance) resulting the formation of complex 2 (equation 1.3).

Condensation between aldehydes and α-amino acids in the absence of metal ions, with the acid and amino groups protected is known to occur very slowly, since the beginning of this century. The coordination not only protects the groups but also activates the α-methylene group that, in basic conditions, most easily forms carbanions as is seen in equations 1.2 and 1.3. This activation has been related to the charge of the complex species. For example, the condensation between the metal coordinated glycine and acetaldehyde has been shown to follow the decreasing order of reactivity:

\[
\text{[Co(en)$_2$(gly)]}^{2+} > \text{Co(gly)$_3$} > \text{[Co(gly)$_2$(C$_2$O$_4$)]}^{-}
\]

The reactivity order also changes with various metal ions as shown below:

\[
\text{Cu(gly)$_2$} > \text{Co(gly)$_3$} > \text{Ni(gly)$_2$} > \text{Zn(gly)$_2$}
\]
Activation of the amino protons more than the α-methylene group of metal coordinated glycine has been established recently. Condensation of Cu(gly)$_2$ with formaldehyde at acidic pH (4.5) has been reported to yield, [bis(N-1,3-dioxo-5-azacyclo-hexyl)acetato]zinc(II). Co(II), Ni(II) and Cu(II) complexes of glycine also undergo similar condensation reaction with formaldehyde at pH 4.5 yielding the corresponding metal complexes (equation 1.4).

Another reaction of Ni(gly)$_2$ is also known, where the amino group alone reacts with formaldehyde even at a basic condition (pH 8.5) in presence of ammonia. The product has been identified to be [3N,7N-(1,3,5,7-tetraazabicyclo[3.3.1]-nonyl diacetato])nickel(II). It has also been shown that under the same experimental conditions Cu(gly)$_2$ also undergoes similar condensation reaction forming the corresponding Cu(II) complex, as shown in equation 1.5.
This reaction is interesting due to two important factors: (i) the non-involvement of α-methylene group in the condensation, though the reaction was carried out at pH 8.5 (ii) the two glycine units in the resultant complex (as explained for the nickel complex) are cis to each other implying that they must have undergone conversion from the initial trans Ni(gly)$_2$.

It is clear from the foregoing discussion that most of these reactions involve various transition metal complexes of glycine. This is due to the fact that mostly these reactions have been carried out in order to develop simple methods to synthesize substituted α-amino acids preferably in an optically active form, from glycine. The investigations on similar condensation reactions of Cu(II) complexes of the other α-amino acids are also significant, for these reactions seem to exhibit stereospecificity. So far, only α-alanine has been investigated in this respect. It has been reported that, Cu(L-ala)$_2$ undergoes condensation reaction with formaldehyde at pH 8.5 in presence of ammonia, to yield [3N,7N-(1,3,5,7-tetraazabicyclo-[3.3.1]nonyl)-dipropionato]copper(II), 5, while Cu(DL-ala)$_2$ under the same experimental conditions yields, bis(4-methyloxazo-lidine-4’-carboxylato)-copper(II) dihydrate, 6.

\[
\begin{align*}
\text{5} & \\
\text{6}
\end{align*}
\]
It may be noted that formation of 5 is similar to the condensation reaction of Cu(gly)$_2$ with formaldehyde and ammonia at pH 8.5 (equation 1.5). Very little is known about the condensation reactions of most of the remaining α-amino acidato metal complexes. A few of the condensation products have been characterized by X-ray crystallography and their geometry established. However, no further investigations such as electronic spectra, ESR and electrochemical data in aqueous solution are reported.

1.4 Copper(II) alicyclic-α-amino acid complexes

Copper(II) complexes of alicyclic-α-amino acids such as, 1-aminocyclopropane-1-carboxylic acid, 1-aminocyclobutane-1-carboxylic acid etc. have been found to be complexes of uniformly varying geometry;$^{66}$ the change in geometry from complex to complex arising from the increasing ring size at the α-carbon of the amino acid units. Recent investigations$^{27,32}$ on bis(l-aminocyclopentane-1-carboxylato)copper(II) and a few other trans bis (α-amino acidato) complexes reveal that the substitutions at the α-carbon have definite effect on the geometry and hence the properties of the complexes. These complexes are shown to be aquated in solution with two water molecules in the axial sites. Electronic spectral and ESR data are comparable to the Cu(II)-α-amino acid complexes.

1.5 Copper(II) complexes of amino acid Schiff bases

1.5.1 Reactivity

Condensation of glycine has been recognized to be the best way to synthesize β-hydroxy-α-amino acids. However, this reaction
is not facile due to the low acidity of the methylene group. The use of transition metal complexes of Schiff bases derived from glycine and salicylaldehyde or pyruvic acid\textsuperscript{42,53,54} instead of free glycine or bis(glycinato)metal complexes improves the yields and widens the scope of the reaction. The Schiff base complexes in many instances\textsuperscript{67,68} undergo condensation reactions yielding optically active products with high enantiomeric excess (ee). For example, threonylglycine\textsuperscript{68} and threonine\textsuperscript{69-72} could be synthesized with an ee of 95\% by condensation of Cu(II) complexes of chiral Schiff bases of glycylglycine and glycine respectively with acetaldehyde. Optically pure $\alpha$-alkyl-$\alpha$-amino acids could also be prepared via alkylation of Ni(II) complexes of Schiff bases derived from DL-alanine and (S)-2-N-$\$\$-benzylprolyl)$amino benzaldehyde.\textsuperscript{72} The transition metal complexes of Schiff bases of $\alpha$-amino acids and salicylaldehyde (III), pyridoxal (IV), pyruvic acid (V), and (1R)-3-(hydroxymethylene)camphor (VI) are important from the bioinorganic point of view, since the complexes have been shown to be good model systems for the catalytic intermediates in the reactions of pyridoxal phosphate with $\alpha$-amino acids.\textsuperscript{73-77}
The Schiff base complex IV exhibits tautomerism as shown by the equation 1.6.

\[
\begin{align*}
&\text{HOCH}_2 \quad \text{R} \quad \text{HOCH}_2 \\
&\text{M} \quad \text{N} \quad \text{M} \\
&\text{CH}_3 \quad \text{R} \quad \text{CH}_3
\end{align*}
\]

Both transamination and racemization require loss of a proton attached to the \(\alpha\)-carbon of the amino acid, which must be very reactive in these structures. In fact, this property has been exploited to synthesize various \(\beta\)-hydroxy-\(\alpha\)-amino acids. 67-72

1.5.2 Spectral and redox properties

Several Cu(II) complexes of \(\alpha\)-amino acid Schiff bases have been characterized by X-ray crystallography. 78-82 The X-ray analysis revealed that the complexes coordinate via phenolic oxygen, one carboxylic oxygen and the imino nitrogen with a water molecule completing near square-planar geometry of Cu(II) ion.

Many of the model studies of the metal complexes of \(\alpha\)-amino acid Schiff bases have been upon the spectroscopic and mechanistic properties of the complexes. Recently, enhancement of reactivity of \(\alpha\)-methylene group has been related to its correct stereochemical positioning within the molecule. 83-86 Due to the importance of stereochemical factors that control the correct positioning of the groups to be labilized, considerable attention has been paid to the stereochemistry of the model
systems, which mimic the biological reaction types.\textsuperscript{82,86-89} Detailed conformational studies on the Cu(II) complexes are available in literature and are briefly discussed here along with the UV-Vis and ESR spectral data.

The UV absorption spectra of Cu(sal-aa)(H\textsubscript{2}O) complexes, where sal-aa = N-salicylidene-\(\alpha\)-amino acidato anion, exhibit an intense band at ca. 375 nm and has been attributed to \(\pi \rightarrow \pi^*\) transition originating mainly within the azomethine chromophore. The intense bands occurring at still higher energies, viz., 270 and 225 nm, have been assigned to be associated with benzene ring \(\pi \rightarrow \pi^*\) transitions. Shoulders were observed in the spectra of most of the chelates.\textsuperscript{86} The UV spectra of Cu(pyv-aa)(H\textsubscript{2}O) complexes, where pyv-aa = N-pyruvylidene-\(\alpha\)-amino acidato anion, are found to exhibit only a broad band centered near 220 nm, with badly resolved shoulders on its low energy side. The UV spectral data are available for few other Cu(II)-Schiff base complexes also.\textsuperscript{86-89}

For Cu(sal-aa)(H\textsubscript{2}O) complexes the d-d transitions were observed in the wavelength region 680-600 nm in solution, which has been ascribed to the square-planar or weakly distorted tetragonal geometry.\textsuperscript{89-96} The d-d band was shifted significantly to higher energy regions whenever the \(\alpha\)-amino acid unit had a third donor group (e.g., histidine), which can interact axially.\textsuperscript{89,96}

CD spectra are more informative than the electronic spectra. Several Cu(II) and Zn(II) complexes of Schiff bases of aldehydes
such as salicylaldehyde, pyridoxal, pyruvic acid etc. and α-amino acids have been investigated by CD spectroscopy recently.\textsuperscript{86,89,97}

In general the complexes derived from salicylaldehyde and pyridoxal in methanol exhibit three CD extrema at 360, 270 and 230 nm corresponding to the maxima of the electronic absorption. Similarity in the CD spectra of various Schiff base complexes has been interpreted to be due to common conformation adopted by the coordinated ligands.\textsuperscript{98} The Cotton effect associated with the azomethine and the high energy benzenoid band are related to the sign of visible band observed between 680 and 600 nm. This is always consignate with the azomethine band and dissignate with the 230 nm band. The visible CD spectra of Cu(II) complexes of L-amino acid Schiff bases in methanol or pyridine exhibit two or three resolved bands attributable to d-d transitions, similar to the simple Cu(II)-α-amino acidato complexes,\textsuperscript{20,98-102} at a wavelength higher than 700 nm (positive), 680-600 nm (negative) and at a wavelength lower than 600 nm (positive). In several instances the band at the lower energy side of 700 nm was absent and has been explained to occur at lower energy beyond the instrumental range (800 nm), or more likely, be buried under the more intense oppositely signed band in the 680-600 nm region.\textsuperscript{86}

The Cu(II) complexes derived from pyruvylidene Schiff bases show significant dissimilarities to those of the salicylidene and pyridoxylidene series. CD spectral data available in literature\textsuperscript{89,98} reveal that histidine containing complexes exhibit a striking tendency to bind Cu(II). For example, the CD spectra of Cu(pyv-L-his) in water displays dominant Cotton effects of opposite sign pattern of that of Cu(pyv-L-aa)
complexes, where the amino acid is with non polar side chain. The unique behaviour of Cu(pyv-L-his) has been inferred to be due to the interaction of the imidazole group with the central Cu(II) ion, leading to change in conformation.\textsuperscript{89}

ESR data of the Cu(II) complexes of these Schiff bases are also available in literature.\textsuperscript{86,88,89,94,96,103,104} The frozen glassy ESR spectra in aqueous methanol for most of these complexes could be fitted for $g_\parallel > g_\perp > 2.0$, showing the pattern typical for tetragonal symmetry.\textsuperscript{86,89,96} The general characteristics of the spectra are as follows: (i) the frozen glassy ESR spectra of the complexes in methanol or water are axial with an extra high field absorption (ii) the ESR parameters show solvent dependence, indicative of coordination of donor molecules to the metal centres; the $g_\parallel$ and $g_\perp$ values obtained from pyridine solutions are smaller and $A_\parallel$ values larger (iii) in several instances the spectra exhibit superhyperfine interaction with the ligand (nitrogen) nuclei, which gives useful information of the number of nitrogen atoms involved in the donor set (iv) in some cases complex pattern of lines results from superposition of copper hyperfine and ligand superhyperfine splittings.

Using the ESR and CD data, molecular orbital coefficients, $\alpha$, $\beta_1$ and $\beta$, which characterize the planar $\sigma$ and $\pi$ bonding and the out-of-plane $\pi$-bonding, respectively have been calculated for these Cu(II) complexes. The magnitudes of molecular orbital coefficients enable one to refine the stereochemical description of these Cu(II) complexes in terms of donor sets, ligand field symmetry and bonding character.
The (N-salicylidene-amino acidato)copper(II) complexes have a water molecule at the fourth equatorial site as has been mentioned already. Recently\textsuperscript{105} it has been shown that, the change in ESR parameters $g_{iso}$, $A_{iso}$, $g_{||}$ and $A_{||}$ observed for the Cu(sal-aa)(H$_2$O) complexes in presence of pyridine is due to the formation of pyridine adducts. Though the metal complexes of amino acid-Schiff bases have been extensively studied, no detailed work on their redox properties is reported so far.

1.6 Scope of the present investigation

Electrochemical investigations on Cu(II)-amino acidato complexes have shown that electroreduction of these complexes proceeds via Cu(I) intermediate complex species. In general, reversibility of the Cu(II)/Cu(I) process depends on the stability of the intermediate Cu(I) species. The Cu(I) species is stable only in tetrahedral or pseudo-tetrahedral environments. To investigate the effect of structural variation on the reversibility of the Cu(II)/Cu(I) redox process, it was planned to synthesize Cu(II) complexes of varying geometry. It is known that Cu(gly)$_2$ undergoes condensation reactions with formaldehyde and acetaldehyde under various experimental conditions yielding products with the same CuN$_2$O$_2$ chromophore. However the products possess different degrees of tetragonal distortion. Towards synthesizing more number of such complexes similar condensation reactions of Cu(II) complexes of a few other amino acids are carried out. In this way it became possible to synthesize a variety of structurally different complexes. They are characterized and their electrochemical behaviour examined.
During the course of our investigation on the condensation reactions, it has been observed that some of these reactions are stereospecific. Similar behaviour has been reported only for Cu(II) complexes of L-alanine and DL-alanine previously. In the present investigation condensation reactions of Cu(II) complexes of L-serine, DL-serine, L-threonine and DL-threonine with formaldehyde and acetaldehyde are included. CD spectroscopy has been used to follow the reactions.

While the Cu(II) complexes of \( \alpha \)-amino acids such as glycine, alanine etc., have been investigated extensively only limited data is available on the Cu(II) complexes of alicyclic-\( \alpha \)-amino acids. As a part of our investigation on the redox properties of Cu(II) complexes of \( \alpha \)-amino acids and related systems it became a natural extension to study the spectral and electrochemical properties of the Cu(II) complexes of some alicyclic-\( \alpha \)-amino acids.

The Cu(II) complexes of N-salicylidene-\( \alpha \)-amino acids have been the subject of various spectral investigations because of their usefulness as model systems to study the enzymatic reactions of pyridoxal phosphate and their ability to catalyze transamination and racemization. However, their redox behaviour has not yet been reported. In conformity with our research plan, it appeared logical to investigate the redox behaviour of these complexes. For this purpose, Cu(II) complexes of Schiff bases of number of amino acids have been prepared and their redox characteristics examined. It is known that these complexes form
adducts with N-donor bases such as imidazole, pyrazole and pyridine.\textsuperscript{105,106} The adducts show differences in their electronic and ESR parameters revealing change in geometry, nature of coordination \textit{etc.} from their parent complexes. We also planned to investigate the adducts electrochemically in order to elucidate their redox mechanism and more fully understand the structural changes accompanying adduct formation.
1.7 References


