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# Structures and stabilities of metal(II) (Co(II), Ni(II), Cu(II), Zn(II), Pd(II), Cd(II)) compounds of N-protected amino acids

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CONTENTS

## A. INTRODUCTION

Our understanding of the nature of metal binding sites in proteins owes much to the study of models involving metal complexes with amino acids and small peptides. The coordinating power of $\alpha$-amino acids toward a large number of transition metal ions was the object of a great deal of investigation during the years 1960–1975 and the results are collected in some detailed and exhaustive reviews [1–3]. In particular, copper(II) complexes of amino acids have been studied in considerable detail; if there are no complicating donor side chains, the amino acids coordinate solely through the amino and carboxylato groups, forming stable five-membered chelate rings with the metal ion, as has been found for each of the 20 or so naturally occurring L-$\alpha$-amino acids [1–4]. In these complexes, the five coordination of the copper(II) ion is favoured since the strong ligand field of the four in-plane donor atoms weakens the axial interactions. The introduction of a substituent directly on the amino group gives rise to a series of compounds, known as N-protected amino acids. These exhibit diminished affinity of the amino group for the metal ions and reduce the ligand field of the in-plane donors. This permits a variety of coordination types to arise.

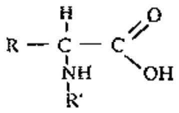
The study of the metal ion complexes of these N-protected amino acids has expanded rapidly in the last ten years. The results are so abundant that they need to be collected and rationalized in a critical summary to allow lines for future work in this area to be developed.

Most of this article will describe the stability, structure, optical and magnetic properties of the copper(II) compounds of N-protected amino acids. A second part will report what is known about cobalt(II), nickel(II), zinc(II), palladium(II) and cadmium(II) complexes of the same ligands. Furthermore, the biological connections of these studies will be emphasized in the discussion of the various sections.

## B. THE INVESTIGATED N-PROTECTED AMINO ACIDS

Figure 1 reports the list of the N-protected amino acids considered in this review. In the case of *N*-acetyl-, *N*-benzoyl- and *N*-tosyl-alanines, both the $\alpha$ and $\beta$ forms have been investigated.

The N-protected amino acids find special practical application in peptide syntheses. The benzyloxycarbonyl and tosyl groups in particular represent the most suitable groups for temporary protection of the $\alpha$-amino group. These markedly reduce racemization, give high yields and are easily and quantitatively removed from the products [5,6]. The dansyl group, in turn, is widely used as a fluorescent probe



N-protected-amino-acid

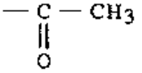
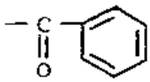
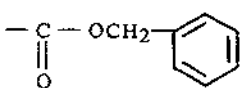
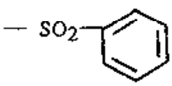
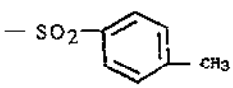
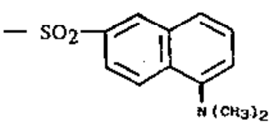
| R' | N-protected-group (abbreviation) |
|---|---|
|  $-C(=O)-CH_3$ | acetyl (ac) |
|  | benzoyl (bz) |
|  | benzyloxycarbonyl (z) |
|  | phenylsulphonyl (bs) |
|  | 4-toluenesulphonyl (tosyl) (ts) |
|  | 5-dimethylaminonaphthalene-1-sulphonyl (dansyl) (ds) |

Fig. 1. List of N-protected amino acids considered in this review, with abbreviations in parentheses.

to study protein conformational changes [7,8] and to identify N-terminal residues of peptides [9,10].

N-protected amino acids are also biologically important, with their direct involvement in biological processes having been demonstrated in many cases. From this point of view, *N*-acetyl derivatives are the most important. They are present in some natural proteins and peptides and are postulated to be the starting unit in the biosynthesis of some peptide chains [11]. Other examples of direct involvement of *N*-acetyl- and *N*-benzyloxycarbonyl amino acids in natural processes are reported in refs. 12–16 and 17, respectively.

Crystal structures are also known for some of the N-protected amino acids considered in this paper. These include *N*-benzoyl-glycine (hippuric acid) [18], *N*-acetyl-glycine (aceturic acid) [19], *N*-acetyl-L-tryptophan [20], *N*-dansyl-glycine [21] and *N*-benzenesulfonyl-DL-alanine [22].

For a clear understanding of the coordinative behaviour of the N-protected amino acids, the paper will be divided into sections: in particular, Sects. C and D will deal with interactions of the copper(II) ion with *N*-acetyl-, *N*-benzoyl- and *N*-benzyloxycarbonyl amino acids and with *N*-tosyl-, *N*-dansyl- and *N*-phenylsulphonyl amino acids, respectively, while Sect. E will describe the interactions of cobalt(II), nickel(II), zinc(II), cadmium(II) and palladium(II) ions with all the investigated N-protected amino acids.

## C. COORDINATIVE BEHAVIOUR OF N-PROTECTED AMINO ACIDS CONTAINING A PEPTIDE GROUP TOWARD COPPER(II) IONS

The peptide group is abundant in nature and there is a wide interest in its metal ion binding capabilities, which are generally found to be very low, even though it presents two potential binding atoms for complexation of protons and metal ions. However, the amide oxygen atom is weakly basic and metal ion coordination will not occur at this site (in aqueous solution, it bonds preferentially to water molecules (mass effect) rather than to the metal ions) and the amide nitrogen atom (hybridized $sp^2$) can coordinate only if deprotonated. The coordination of the peptide group is therefore favoured in neutral or basic solution, in which, however, it suffers competition from metal ion hydrolysis and precipitation [2,23].

All the N-protected amino acids considered in this section, which includes the *N*-benzoyl-, *N*-acetyl- and *N*-benzyloxycarbonyl amino acids, present identical binding sites and, in particular, contain one peptide bond. The importance of the N-protected amino acids with respect to simple amino acids derives from the fact that the presence of a primary ligating site (anchor), such as a carboxylic group in the $\alpha$ or $\beta$ position with respect to the amide group, may favour the chelation of the amide group. This reduces the importance of metal ion hydrolysis and permits attainment of pH regions where substitution of a metal ion for an amide hydrogen may occur [23]. Therefore N-protected amino acids are very appropriate ligands since they provide simple model compounds for understanding metal–protein interactions. A detailed knowledge of the acid–base behaviour of the N-protected amino acids, and of the metal ion is very relevant in order to understand the metal complex formation.

### *(i) Binary complexes in aqueous solution*

The N-protected amino acids do not present zwitterionic character in aqueous solution, since the two pK dissociation values generally range from 3 to 4 ($pK_{A1}$) and 12 to 14 ($pK_{A2}$), arising from the equilibria [24,25]

$$\mathrm{R'CONHCHRCOOH} \underset{}{\overset{\mathrm{pK_{A1}}}{\rightleftharpoons}} \mathrm{R'CONHCHRCOO^{-} + H^{+}}$$

$$\mathrm{R'CONHCHRCOO^{-}} \underset{}{\overset{\mathrm{pK_{A2}}}{\rightleftharpoons}} \mathrm{R'CONCHRCOO^{-} + H^{+}}$$

In aqueous solution, *N*-acetyl-glycinate forms a complex of low stability (log $K^{\mathrm{Cu}}_{\mathrm{CuL}} = 1.3$) [24,25] in which it acts as a unidentate ligand binding through the carboxylate group [24–26] and a similar behaviour can be predicted for all the *N*-acetyl- and *N*-benzoyl amino acids on the basis of their strictly comparable $\mathrm{pK_{A1}}$ values. In any case, no hint of amide hydrogen deprotonation is ever found to occur in the investigated systems before metal(II) hydroxide precipitation [24,26].

Neither have potentiometric pH titrations of the ternary $\mathrm{Cu^{2+}}$/2,2'-bipyridine/*N*-acetyl-glycinate system revealed any evidence of amide hydrogen deprotonation [23].

### (ii) *Solid state behaviour*

The N-protected amino acids considered in this section generally interact with copper(II) in strongly concentrated solutions, separating as two types of compound: blue compounds from aqueous solution, and therefore only observed for water-soluble N-protected amino acids such as *N*-benzoyl-glycine and the *N*-acetyl amino acids, and green compounds for all the N-protected amino acids from alcoholic solution.

#### (a) *Blue complexes*

A listing of the blue complexes separated from aqueous solution, and of their spectroscopic and magnetic characteristics, are collected in Table 1. Variations in these properties between the complexes reflect their structural differences.

The compound $[\mathrm{Cu(bzglyO)_2(H_2O)_2}]_2 \cdot 4\mathrm{H_2O}$ exists as a dimer in which each copper atom, in a distorted [4+1] square-based pyramid (Fig. 2), is coordinated to one *N*-benzoyl-glycinate ion and two water molecules and shares coordination to two other *N*-benzoyl-glycinate ions. These latter act as bridges in the dimer. *N*-Benzoyl-glycinate anions coordinate only through the terminal carboxylic oxygen [27,28]. The results of a magnetic investigation on the dimer [29] indicate a small antiferromagnetic value of the singlet–triplet splitting, $2J$. The structural arrangement is such that each bridging oxygen atom occupies an in-plane coordination site of one copper(II) ion and an apical site of the other copper(II) ion. Thus the magnetic orbitals which lie in the $xy$ plane and contain the unpaired spins interact very little at the bridging oxygen atoms [29]. Its room temperature EPR data [30] are reported in Table 1.

The structures of the bis(*N*-acetyl-glycinato)diaquacopper(II) dihydrate [31–33] (Fig. 3) and bis(*N*-acetyl-*β*-alaninato)diaquacopper(II) [34] complexes consist of very

TABLE 1

Physical data for blue binary copper(II) complexes obtained from aqueous solutions

| Compound | Colour | d–d band ($10^3$ cm$^{-1}$) | | $g_{\parallel}$ | $g_{\perp}$ | Chromophore | Ref. |
|---|---|---|---|---|---|---|---|
| $[Cu(bzglyO)_2(H_2O)_2]_2 \cdot 4H_2O$ | Blue | 11.3 sh | 14.6 | 2.356 | 2.068 | $O_5$ | 27,30 |
| $[Cu(acglyO)_2(H_2O)_2] \cdot 2H_2O$ | Blue | 12.8 sh | 16.1 | 2.369 | 2.069 | $O_4$ | 30,31,32 |
| $[Cu(ac\text{-}\beta\text{-}alaO)_2(H_2O)_2]$ | Blue | 12.7 sh | 15.9 | 2.322 | 2.067 | $O_4$ | 34 |
| $[Cu(acvalO)_2]_n$ | Blue | 13.0 | 16.9 | 2.304 | 2.066 | $O_4$ | 35,40 |
| $[Cu(acleuO)_2]_n$ | Blue | 13.0 | 17.0 | 2.297 | 2.051 | $O_4$(?) | 39 |

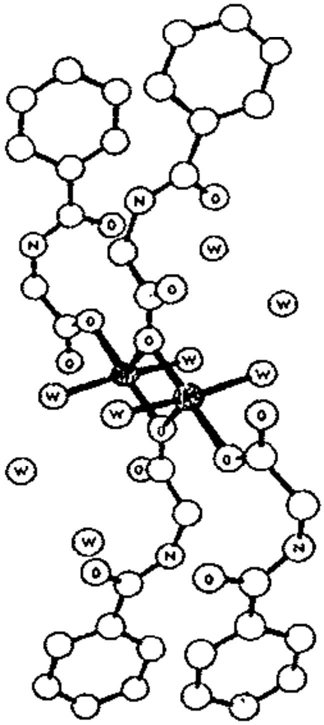


Fig. 2. Projectional view of Cu(II) hippurate dimer (W = water oxygen; N = amide nitrogen; O = oxygen) [27,28].

simple monomeric units, in which the copper(II) atom is coordinated by two centrosymmetrically related carboxyl oxygens and two water molecules in an essentially square-planar arrangement. For these compounds, considerations based only on the shortness of the Cu···O(2) distances (2.614(3) and 2.580(2) Å for $[Cu(acglyO)_2(H_2O)_2]\cdot 2H_2O$ [32] and $[Cu(ac\text{-}\beta\text{-}alaO)_2(H_2O)_2]$ [34], respectively) involving the second carboxylic oxygen are not sufficient to assign a tetragonal geometry. It seems more correct to consider those distances as non-bonding interactions, since the angle between the Cu–O(2) vector and the normal to the O(1)O(4)O(1′)O(4′) plane of 36.4° [33] and 33.8° [34], respectively, prevents overlap of the metal–ligand orbitals. This agrees with their d–d band maximum values (15 000–16 100 $cm^{-1}$ [31,34]), representative of an isolated $CuO_4$ chromophore (Table 1).

It is interesting to note that, upon increasing the hydrophobic character of the *N*-acetyl amino acid, the hydration of the complex decreases quite smoothly and its coordinative ability is sharply modified. In fact, in anhydrous $[Cu(acvalO)_2]_n$ [35] the ligand bridges two different copper(II) ions via one carboxylic oxygen and the carbonylic oxygen atom. This gives rise to a monodimensional polymeric network in which each copper atom, surrounded by four oxygen atoms, is essentially square

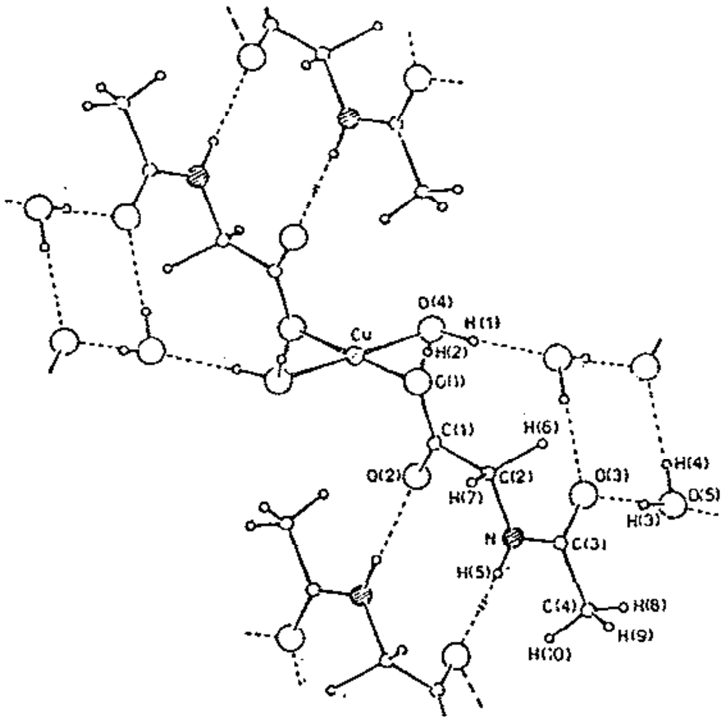


Fig. 3. Perspective view of [Cu(acglyO)$_2$(H$_2$O)$_2$] [32,33].

planar (Fig. 4). Similarly to the complexes mentioned above, the angle between the Cu–O(2) vector and the normal to the O(1)O(4)O(1′)O(4′) plane of 40.3° and the Cu–O(2) distance of 2.904(4) Å exclude O(2) involvement in metal ion coordination [35]. In this complex, it is worth noting not only the non-chelating mode for the coordination of the peptide oxygen, till now observed in only very few cases such as in Cu(glycyl-L-alanina)·H$_2$O [36], Cu(glycyl-L-methionine) [37] and [Cu(L-methionylglycine)(H$_2$O)]·2H$_2$O [38], but also the non-chelating equatorial coordination, of which no examples are known.

The anhydrous Cu(acleuO)$_2$ compound [39] seems very similar to the [Cu(acvalO)$_2$]$_n$ compound on the basis of its spectroscopic and magnetic properties [40] (Table 1).

Thermal analyses performed on the hydrated blue monomeric complexes demonstrate that the dehydration is accompanied by dimerization [30,34,41].

### (b) Green complexes

The green complexes obtained for all the investigated *N*-acetyl-, *N*-benzoyl- and *N*-benzyloxycarbonyl amino acids from alcoholic solution and their optical and magnetic properties (taken from refs. 30, 31, 34, 40 and 42–53) are reported in Table 2.

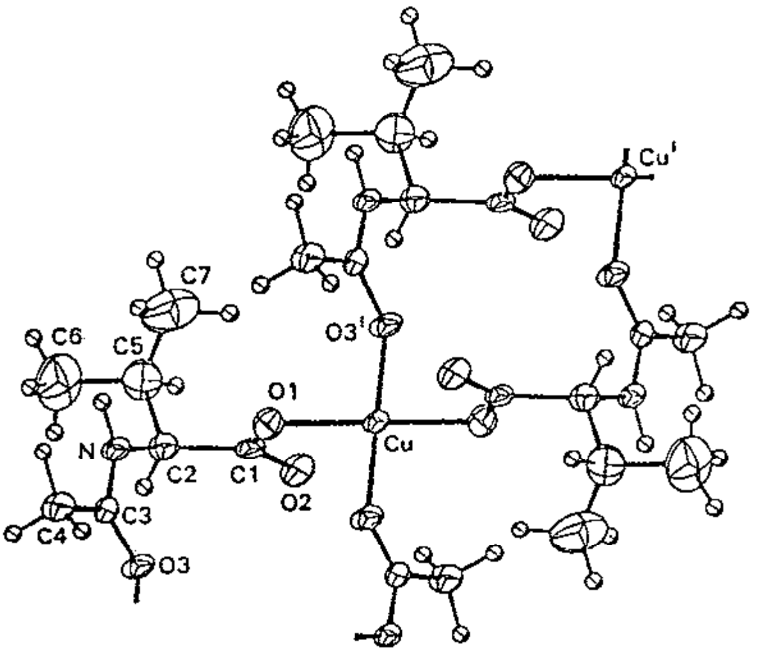


Fig. 4. ORTEP view of $[Cu(acvalO)_2]_n$ [35].

For three of them, $[Cu(acglyO)_2(H_2O)]_2$ [54], $[Cu(ac\text{-}\beta\text{-}alaO)_2(H_2O)]_2 \cdot 2H_2O$ [34] and $[Cu(bz\text{-}\alpha\text{-}alaO)_2(H_2O)]_2$ [55], the crystal and molecular structures have also been determined. They consist of dimeric units, closely resembling dimeric copper acetate monohydrate and other similar copper(II) carboxylato complexes [56,57].

In particular, magnetic susceptibilities of all these complexes, satisfactorily described by the usual Bleaney–Bowers equation for exchange coupled dimers [58], show very similar $2J$ values in the range from $-272$ to $-350\ \text{cm}^{-1}$, typical of antiferromagnetically coupled binuclear carboxylate complexes [57] (Table 2). For the anhydrous complexes, the broadening of the ESR signals suggests that relevant interdimeric exchange is present [51].

The spectroscopic results, showing two bands at 13 900–14 900 $\text{cm}^{-1}$ (the "ordinary copper(II) band (d–d)" [57]) and 25 600–27 800 $\text{cm}^{-1}$ (charge transfer band, considered as diagnostic of a dimeric structure [56]), unambiguously confirm the presence of this structural type for all the complexes reported in Table 2. In refs. 31, 34, 39, 40, 43 and 45–52, the IR band shifts of the most significant ligand functions in the complexes with respect to the free ligands are also discussed, confirming that the amino acids, coordinating through both the carboxylic oxygen atoms, act as bidentate ligands toward two different copper(II) ions.

The $[Cu(bzleuO)_2(H_2O)]_2 \cdot 2H_2O$ compound [50] displays physical and spectroscopic characteristics similar to those of the complexes reported in Table 2. How-

TABLE 2

Physical data for green binary copper(II) complexes recovered from alcoholic solutions

| Compound | Band I ($10^3$ cm$^{-1}$) | Band II ($10^3$ cm$^{-1}$) | $\mu_{eff}$ (B.M.) | $g_{\parallel}$ | $g_{\perp}$ | $\lvert 2J \rvert$ (cm$^{-1}$) | Ref. |
|---|---|---|---|---|---|---|---|
| $[Cu(acglyO)_2(H_2O)_2]$ | 13.9 | 27.8 sh | 1.49 | 2.44 | 2.07 | 272 | 31,53 |
| $[Cu(ac\text{-}\alpha\text{-}alaO)_2(H_2O)]_2$ | 14.2 | 27.0 sh | | 2.375 | 2.080 | 316 | 45,46 |
| $[Cu(ac\text{-}\beta\text{-}alaO)_2(H_2O)]_2 \cdot 2H_2O$ | 14.0 | 27.0 sh | | 2.429 | 2.106 | 324 | 34 |
| $[Cu(acvalO)_2(H_2O)]_2$ | 13.9 | 26.3 sh | 1.34 | 2.397 | 2.106 | 351 | 40 |
| $[Cu(actrpO)_2(H_2O)]_2$ | 14.1 | 26.0 sh | 1.36 | 2.427 | 2.190 | 351 | 47 |
| $[Cu(bzglyO)_2(H_2O)]_2$ | 14.3 | 25.7 sh | 1.66 | | | | 43 |
| $[Cu(bz\text{-}\alpha\text{-}alaO)_2(H_2O)]_2$ | 14.1 | 27.0 sh | 1.44 | 2.395 | 2.087 | 313 | 46,48 |
| $[Cu(bz\text{-}\beta\text{-}alaO)_2]_n$ | 14.9 | 27.0 | 1.41 | 2.374 | 2.074 | 303 | 46,49 |
| $[Cu(bzvalO)_2(H_2O)]_2$ | 14.1 | 25.6 sh | 1.46 | 2.393 | 2.089 | 302 | 51 |
| $[Cu(bzleuO)_2(H_2O)]_2$ | 14.1 | | 1.68 | 2.40 | 2.12 | 284 | 50 |
| $[Cu(zglyO)_2(H_2O)]_2$ | 14.6 | 27.0 sh | 1.41 | 2.371 | 2.065 | 295 | 52 |
| $[Cu(z\text{-}\alpha\text{-}alaO)_2]_n$ | 14.7 | 26.3 sh | 1.35 | 2.344 | 2.071 | 343 | 52 |
| $[Cu(zvalO)_2(H_2O)]_2$ | 14.8 | 26.3 sh | 1.33 | 2.384 | 2.083 | 350 | 52 |
| $[Cu(zleuO)_2(H_2O)]_2$ | 14.3 | 26.7 sh | 1.37 | 2.337 | 2.074 | 335 | 52 |
| $[Cu(acglyO)_2]_n$[a] | | | 1.46 | 2.29 | 2.07 | 292 | 53 |
| $[Cu(bzglyO)_2]_n$[a] | | | 1.43 | 2.363 | 2.071 | 327 | 30,42,44 |
| | | | 1.47 | 2.348 | 2.06 | | 53 |
| $[Cu(bzvalO)_2]_n$[a] | 15.2 | 24.4 sh | 1.39 | 2.362 | 2.119 | 342 | 51 |

[a] Obtained by dehydrating the green or blue hydrated compounds.

ever, its complicated magnetic properties reveal the presence of a great amount (36%) of monomeric copper(II) impurity, even though the complex was shown to be analytically pure. These studies on the ESR and magnetic properties of the copper(II) complexes of N-protected amino acids can be considered of particular interest [59] in order to deepen our knowledge of metal–protein interactions.

The lack of a sufficient number of structural data does not allow any correlation among structural and magnetic results to be made. It may indicate a rational direction for further experiments, which could help to explain the factors determining the magnetic behaviour of copper(II) acetate-type compounds (which is an open problem), because of the unusually large series of homologous compounds that are available.

### *(iii) Solid ternary complexes*

Easy formation of adducts is observed when the binary blue or green complexes are reacted with amines. This is considered to be a confirmation of the coordinative behaviour of the N-protected amino acids through the carboxylate group [31,39,40,43–45,47–51].

From apolar solvents, a series of $CuL_2A$ (A = monodentate amine; L = N-protected amino acidate anion) compounds are separated [44,48,51]. Their magnetic behaviour (Table 3) provides examples of strong antiferromagnetic exchange interactions, unambiguously indicating that they adopt the typical carboxylate cage structure. The importance of these studies on simple complexes, as models of very complicated systems, is demonstrated by the possibility of applying these results for a reasonable explanation of the mechanism which might account for the observed antiferromagnetic behaviour of type-3 copper enzymes, which were suggested to involve a similar exchange coupling type through the appropriate carboxylate groups of the peptide chain [44].

In alcoholic solutions, compounds of formula $CuL_2A_2$ or $CuL_2B$ (A = monodentate amine; B = bidentate amine; L = N-protected amino acidate anion), in some cases containing water molecules, are invariably separated [31,39,40,43–45,47–50]. Most probable configurations are suggested on the basis of spectroscopic and magnetic measurements.

Systematic investigations on the imidazole, *N*-methyl-imidazole and 2,2′-bipyridine adducts of *N*-acetyl-, *N*-benzoyl- and *N*-benzyloxycarbonyl amino acidate– copper(II) systems ($CuL_2A_2$ or $CuL_2B$ compounds) are discussed in refs. 60–64. These studies are relevant from a biological point of view since it is well documented that low-molecular-weight ternary complexes of copper(II), in which mixed N,O-atom donor set is the preferred chromophore [65,66], are abundant in living systems, being involved in the transport of the metal ion through biological fluids and living tissues. Comparative studies on small synthetic systems duplicating this metal ion arrangements have indicated that their relatively high stability is primarily responsi-

TABLE 3

Magnetic and spectroscopic results for green dimeric copper(II) adducts at room temperature

| Compound | Band I ($10^3$ cm$^{-1}$) | Band II ($10^3$ cm$^{-1}$) | $\mu_{eff}$ (B.M.) | $g_{\parallel}$ | $g_{\perp}$ | $\|2J\|$ (cm$^{-1}$) | Ref. |
|---|---|---|---|---|---|---|---|
| $[Cu(bzglyO)_2(DMF)]_2$ | | | | 2.353 | 2.065 | 313 | 44 |
| $[Cu(bzglyO)_2(Me_2SO_2)]_2$ | | | | 2.363 | 2.075 | 292 | 44 |
| $[Cu(bz\text{-}\alpha\text{-}alaO)_2(3\text{-}mepy)]_2$ | 13.7 | 25.6 sh | 1.53 | | | | 48 |
| $[Cu(bz\text{-}\alpha\text{-}alaO)_2(4\text{-}mepy)]_2$ | 13.7 | 25.6 sh | 1.54 | | | | 48 |
| $[Cu(bzvalO)_2(py)]_2$ | 13.9 | 25.6 sh | 1.49 | 2.393 | 2.093 | 308 | 51 |
| $[Cu(bzvalO)_2(3\text{-}mepy)]_2$ | 13.7 | 26.0 sh | 1.37 | 2.389 | 2.098 | 350 | 51 |
| $[Cu(bzvalO)_2(4\text{-}mepy)]_2$ | 13.8 | 25.6 sh | 1.38 | 2.403 | 2.081 | 335 | 51 |

ble for the large range of natural occurrence of mixed complexes. The major contribution to their stability is derived from the presence of an imidazole moiety in the metal coordination sphere, enabling $\pi$-back-donation from metal to unsaturated ligand $\pi$-orbitals lowering the electron concentration near the central ion [23].

In this area, the modelistic approach on ternary copper(II) *N*-protected amino acidate complexes provides many closely related structural and spectroscopic data, which reproduce realistic model systems of many naturally occurring mixed ligand complexes. This also allows the rationalization of the coordination behaviour of aromatic monodentate and bidentate amines, such as imidazoles, pyridines and 2,2′-bipyridine. For imidazoles, the resultant effect of their basic properties ($pK_A$ about 7.0) and $\pi$-back-donation power invariably leads to separate complexes in which the copper(II) ion geometry is essentially and invariably square-planar with a *trans*-$CuN_2O_2$ chromophore (see the structural results performed on $[Cu(bzglyO)_2(im)_2]$ [60], $[Cu(ac\text{-}\alpha\text{-}alaO)_2(meim)_2]\cdot 2H_2O$ [61] and $[Cu(z\text{-}\alpha\text{-}alaO)_2(meim)_2]\cdot C_2H_5OH$ [62]. For these compounds, the global view of the structural and spectroscopic results [67] excludes the involvement of a second carboxylic oxygen atom in the metal ion coordination for the same reasons as those proposed above for the binary blue compounds. The Cu–N bond lengths, in the 1.959(5)–1.976(6) Å range, intermediate between the Cu–N(imidazole) bond distances of 1.95 Å in oligoglycines–$Cu^{2+}$–imidazole complexes and of 2.00 Å found in most $Cu^{2+}$–imidazole compounds, confirm the presence of a strong $\pi$-back-bonding from the copper(II) ion and the heteroatomic N-bases, which enhance the affinity of the copper(II) ion for oxygen donor sites of anionic ligands [60–62,67,68]. For many imidazole and *N*-methyl-imidazole adducts of other copper(II) N-protected amino acidates [60–62], the electronic spectra identical to those of the structurally known compounds suggest very similar features. In all cases, N-protected amino acidate ions act as simple carboxylate ligands, involving one oxygen atom of the carboxylate group in the coordination.

Finally, an apparent disagreement between structural and ESR results for the $[Cu(bzglyO)_2(im)_2]$ complex finds justification in the presence of magnetically non-equivalent sites within the unit cell in an antiferromagnetic arrangement [60].

In hydrated (or alcoholated) adducts, the water molecules are differently involved in the structure, depending on the amine types or their $pK_A$. In fact, in the imidazole and *N*-methyl-imidazole adducts, all the water molecules present are invariably involved in hydrogen bonding as part of the presumably crystal packing [61,62], while in the pyridine adducts, the water molecules participate in the metal ion coordination, completing the geometry to tetragonal octahedral. The remarkably lower $pK_A$ values (5.0–6.3) than imidazoles confers to pyridines small $\pi$-back donation power, enabling the involvement of the water molecules in the metal(II) ion coordination. This fact can lead to unusual structures, such as that observed for the $[Cu(actrpO)_2(py)_2(H_2O)_2]$ compound [47] (Fig. 5), in which a considerable lengthening of the Cu–N distance (2.02(1) Å) with respect to those found for the imidazole complexes is also observed.

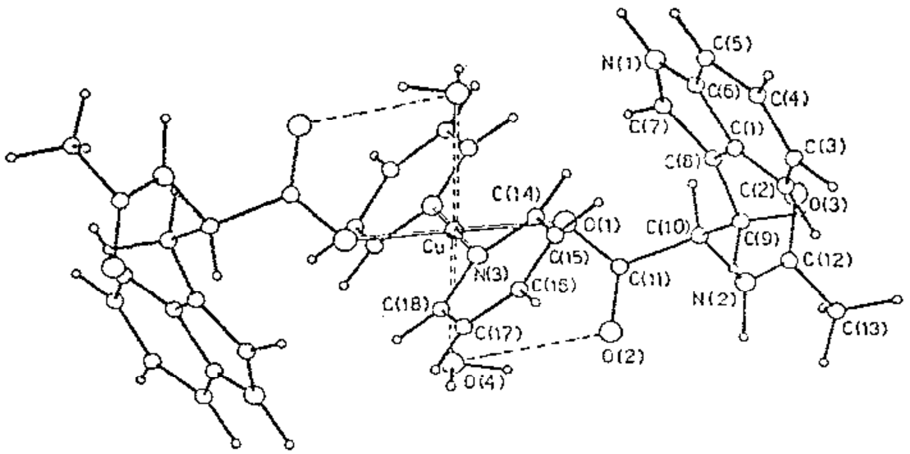


Fig. 5. Perspective view of [Cu(actrpO)$_2$(py)$_2$(H$_2$O)$_2$] [47].

In the 2,2′-bipyridine adducts of some *N*-benzoyl- and *N*-acetyl amino acids [63] as well as in the 1,10-phenanthroline adduct of *N*-acetyl-glycine [69], a slight tetrahedral distortion in the square-planar arrangement of the copper(II) ion (*cis*-CuO$_2$N$_2$ chromophore) has always been found. In these complexes, as observed in the [Cu(acleuO)$_2$(bipy)] structure [63], the *cis*-N$_2$O$_2$ coordination occurs through two nitrogen atoms of the bipy amine and two carboxylate oxygens deriving from two N-protected amino acidate anions, which act as unidentate ligands. The presence of a small tetrahedral distortion is quantitatively measured in the [Cu(acleuO)$_2$(bipy)] compound by the value of 20.8° for the dihedral angle between the CuN$_2$ and CuO$_2$ planes. A nearly identical situation is also found in bis(*N*-acetyl-glycinato)(1,10-phenanthroline)copper(II), which presents a closer square-planar arrangement with a dihedral angle between O(1)–Cu–O(1′) and N(1)–Cu–N(1′) planes of 12.2° [69].

Distinct structural features are found in the bis(*N*-benzyloxycarbonyl-glycinato)(2,2′-bipyridine)(propan-2ol)copper(II) [64], in which the metal(II) ion presents square pyramidal geometry (CuN$_2$O$_2$O′ chromophore) and two [Cu(z-glyO)$_2$(bipy)(Pr$^i$OH)] molecules are linked in dimeric units by intermolecular hydrogen bonding interactions among the amino acids (Fig. 6). Furthermore, the crystal packing of the dimeric units is mainly determined by intramolecular ring-stacking interactions between bipy ligands and by intermolecular hydrophobic interactions between phenyl groups of the amino acid moieties. Weak interactions (stacking, hydrophobic, electrostatic, etc.) are vital in the phenomena of biological recognition of molecules [70]. In particular, those between enzyme and substrate molecules coordinated to the same central metal ion are essential for the efficiency and specificity of the reactions [71] and seem to represent one of the determining factors in the constitution of the tertiary structure of proteins. Such interactions enhancing the stability of the mixed-ligand ternary complexes were first observed in solution [72].

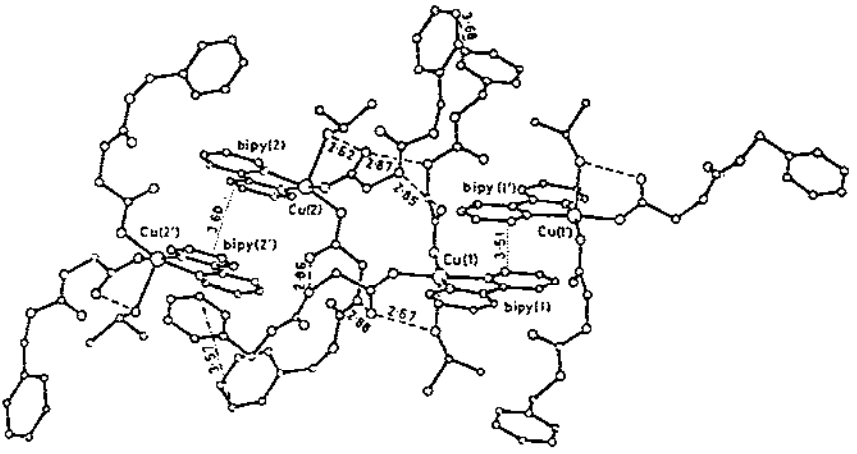


Fig. 6. ORTEP view of the complex [Cu(zglyO)$_2$(bipy)(Pr$^i$OH)] [64].

Hydrophobic ligand–ligand interactions in ternary complexes have been reported to occur between aliphatic side chains and between aliphatic chains and aromatic rings, and also between aromatic moieties [73].

*(iv) General remarks*

(a) *N*-acetyl-, *N*-benzoyl- and *N*-benzyloxycarbonyl amino acids invariably coordinate the copper(II) ion through the carboxylate group.

(b) The carboxylic group, as primary ligating site in these N-protected amino acids, is ineffective in promoting amide nitrogen deprotonation in the presence of copper(II) ions. There is no hint of amide nitrogen deprotonation before metal hydroxide precipitation (pH = 8).

(c) The perturbing effect of additional ligands, such as amines, does not affect the N-protected amino acid coordinative behaviour (invariably unidentate through one carboxylic oxygen atom). The mutual influence of the potentially active ligands indicates discriminatory properties of the examined amines for a second ligand, which is preferably O-donor rather than N-donor. The simultaneous presence of heteroaromatic N-base moieties and carboxylate O-donors enhances the complex stability.

(d) The peptide group is always involved in intermolecular hydrogen bonding in crystal packing, except in the blue anhydrous *N*-acetyl-DL-valinate and -leucinate compounds in which, surprisingly, an equatorial non-chelating coordination mode of the peptidic oxygen atom is observed.

(e) Square-planar geometries for the copper(II) ion are strongly preferred and a useful correlation among Cu···O axial distances, bipyramidal distortion angles and d–d band maximum for truly square-planar complexes of N-protected amino acids discussed in this section is reported in Table 4.

TABLE 4

Correlation between (Cu···O) axial distance (Å), bipyramidal distortion angle[a] (degrees) and d–d band maximum ($10^3$ cm$^{-1}$) for truly square-planar complexes

| Compound | Cu···$O_{ax}$ | Distortion angle | Chromophore | d–d band | Ref. |
|---|---|---|---|---|---|
| $[\mathrm{Cu(acglyO)_2(H_2O)_2}]\cdot 2\mathrm{H_2O}$ | 2.614(3) | 36.4 | $O_4$ | 15.9 | 32,33 |
| $[\mathrm{Cu(ac\text{-}\beta\text{-}alaO)_2(H_2O)_2}]$ | 2.580(2) | 33.8 | $O_4$ | 16.1 | 34 |
| $[\mathrm{Cu(acvalO)_2}]_n$ | 2.904(4) | 40.3 | $O_4$ | 16.9 | 35,40 |
| $[\mathrm{Cu(bzglyO)_2(im)_2}]$ | 2.736(4) | 37.2 | $N_2O_2$ | 17.5 | 60 |
| $[\mathrm{Cu(ts\text{-}\beta\text{-}alaO)_2(im)_2}]$ | 2.761(5) | 36.8 | $N_2O_2$ | 18.2 | 67 |
| $[\mathrm{Cu(ac\text{-}\alpha\text{-}alaO)_2(meim)_2}]\cdot 2\mathrm{H_2O}$ | 2.907(4) | 41.1 | $N_2O_2$ | 18.2 | 61 |
| $[\mathrm{Cu(z\text{-}\alpha\text{-}alaO)_2(meim)_2}]\cdot \mathrm{C_2H_5OH}$ | 2.731(5) | 36.4 | $N_2O_2$ | 17.6 | 62 |
| $[\mathrm{Cu(tsglyO)_2(meim)_2}]$ | 2.758(4) | 37.8 | $N_2O_2$ | 17.9 | 91 |
| $[\mathrm{Cu(ts\text{-}\beta\text{-}alaO)_2(pipd)_2}]$ | 2.652(1) | 36.2 | $N_2O_2$ | 18.4 | 93 |
| $[\mathrm{Cu(acleuO)_2(bipy)}]$ | 2.764(2) | 52.9 | *cis*-$N_2O_2$ | 16.7 | 63 |
| $[\mathrm{Cu(ts\text{-}\beta\text{-}alaO)_2(bipy)}]$ | 2.704(2) | 53.6 | *cis*-$N_2O_2$ | 17.6 | 63 |
|  | 2.751(3) | 52.6 |  |  |  |
| $[\mathrm{Cu(acglyO)_2(ophen)}]$ | 2.819(6) | 43.4 | *cis*-$N_2O_2$ | 14.7 | 69 |

[a] The angle between the Cu···O axial vector and the normal to O(1)O(4)O(1′)O(4′) plane.

(f) A summary of the more relevant structural parameters of the structurally known complexes discussed in this section is given in Table 5.

### D. COORDINATIVE BEHAVIOUR OF N-PROTECTED AMINO ACIDS CONTAINING A SULPHONAMIDE GROUP TOWARD COPPER(II) IONS

In this section the coordinative capabilities of *N*-tosyl amino acids and *N*-dansyl- and *N*-phenylsulphonyl-glycine will be considered. These N-protected amino acids still possess a carboxylic group as primary ligating site. However, since the $ArSO_2$ substituent has a strong inductive electrophilic effect, it confers to the sulphonamide hydrogen a more acidic character than that of the peptidic hydrogen. For this reason, peculiar chemical behaviours are observed.

In agreement with the above statements, *N*-tosyl amino acids in aqueous solution at increasing pH values show two dissociation equilibria ($pK_{A1} = 3.4–3.5$ and $pK_{A2} = 11.4–12.1$) polarographically and potentiometrically determined [74–78] with lower $pK_{A2}$ values than those observed for the acids discussed in Sect. C.

For *N*-dansyl-glycine, three dissociation equilibria have been observed [79]

$$\begin{tikzcd}
(CH_3)_2\overset{+}{N}HC_{21}H_6SO_2NHCH_2COOH \arrow[r, "pK_{A1}", shift left] \arrow[r, leftarrow, shift right] & (CH_3)_2NC_{21}H_6SO_2NHCH_2COOH \arrow[d, "pK_{A2}", shift left] \arrow[d, leftarrow, shift right] \\
(CH_3)_2NC_{21}H_6SO_2NCH_2COO^- \arrow[r, "pK_{A3}", shift left] \arrow[r, leftarrow, shift right] & (CH_3)_2NC_{21}H_6SO_2NHCH_2COO^-
\end{tikzcd}$$

The calculated $pK_A$ values are 3.1(3.4), 4.8(8.1) and 11.7(13.7), respectively, in aqueous (methanolic) solution [79]. Very similar $pK_{A1}$ and $pK_{A2}$ values are reported in ref. 80, while conflicting data are contained in ref. 81. A confirmation of the results of ref. 79 is reported in ref. 82, in which the dependence of the dissociation equilibria and the reduction processes of *N*-dansylglycine on the physicochemical properties of some organic solvents of different proticity have been investigated.

#### *(i) Copper(II)–N-$ArSO_2$–amino acidate systems in aqueous solution*

Systematic and careful investigations performed on binary copper(II) ion *N*-tosyl-glycinate, *N*-tosyl-*β*-alaninate, *N*-dansyl- and *N*-phenylsulphonyl-glycinate systems by means of polarographic and potentiometric measurements in aqueous and/or alcoholic solutions at different ligand concentrations and pH values have identified the main complex species, their pH range of existence and stability constants (Table 6) [74–76, 79].

Depending on the pH of the solutions, the results of binary copper(II) systems indicate that the $ArSO_2$ group confers a distinct coordinative ability to the amino acids, favouring the existence of a great number of complex species, which in some cases present very unique characteristics. In fact, unlike acetyl, benzoyl and benzyloxycarbonyl groups, the $ArSO_2$ group promotes the formation of stable complexes

TABLE 5

Summary of the main structural parameters for Cu(II) complexes of *N*-aryl amino acids

| Compound | Coord. geom.[a] | Chromophore | $Cu-O_{eq}$ (Å) | $Cu-N_{eq}$ (Å) | $Cu-O_{ax}$[b] (Å) | $Cu \cdots Cu$ (Å) | a.b.m.[c] | Ref. |
|---|---|---|---|---|---|---|---|---|
| $[Cu(acglyO)_2(H_2O)]_2$ | cu.a.l. | $O_5$ | 1.971(3) | | 2.108(3)w | 2.666(1) | b.b.-$(O,O)_c$ | 54 |
| $[Cu(acglyO)_2(H_2O)_2]\cdot 2H_2O$ | s.pl. | $O_4$ | 1.952(3) | | | | uni-$O_c$ | 32,33 |
| $[Cu(bzglyO)_2(H_2O)_2]_2\cdot 4H_2O$ | s.py. | $O_5$ | 1.96(1) | | 2.37(1)b.c. | | uni-$O_c$,<br>b.m.-$O_c$ | 27,28 |
| $[Cu(ac\text{-}\beta\text{-}alaO)_2(H_2O)_2]$ | s.pl. | $O_4$ | 1.959(2) | | | | uni-$O_c$ | 34 |
| $[Cu(ac\text{-}\beta\text{-}alaO)_2(H_2O)]_2\cdot 2H_2O$ | cu.a.l. | $O_5$ | 1.968(4) | | 2.156(4)w | 2.613(1) | b.b.-$(O,O)_c$ | 34 |
| $[Cu(bz\text{-}\alpha\text{-}alaO)_2(H_2O)]_2$ | cu.a.l. | $O_5$ | 1.967(3) | | 2.134(3)w | 2.660(1) | b.b.-$(O,O)_c$ | 55 |
| $[Cu(bzglyO)_2(im)_2]$ | tr.s.pl. | $N_2O_2$ | 1.976(3) | 1.964(3) | | | uni-$O_c$ | 60 |
| $[Cu(ac\text{-}\alpha\text{-}alaO)_2(meim)_2]\cdot 2H_2O$ | tr.s.pl. | $N_2O_2$ | 1.942(3) | 1.959(5) | | | uni-$O_c$ | 61 |
| $[Cu(z\text{-}\alpha\text{-}alaO)_2(meim)_2]\cdot C_2H_5OH$ | tr.s.pl. | $N_2O_2$ | 1.970(4) | 1.977(6) | | | uni-$O_c$ | 62 |
| $[Cu(actrpO)_2(py)_2(H_2O)_2]$ | te.bip. | $N_2O_4$ | 1.95(1) | 2.02(1) | 2.61(1)w | | uni-$O_c$ | 47 |
| $[Cu(acleuO)_2(bipy)]$ | d.ci.s.pl. | $N_2O_2$ | 1.936(4) | 1.996(4) | | | uni-$O_c$ | 63 |
| $[Cu(zglyO)_2(bipy)(Pr^iOH)]$ | s.py. | $N_2O_3$ | 1.96(1) | 2.00(1) | 2.30(1)alcoh. | | uni-$O_c$ | 64 |
| $[Cu(acglyO)_2(ophen)]$ | d.ci.s.pl. | $N_2O_2$ | 1.928(3) | 2.007(3) | | | uni-$O_c$ | 69 |

[a] cu.a.l. = copper acetate-like; s.pl. = square planar; s.py. = square pyramidal; tr.s.pl. = trans square planar; te.bip = tetragonal bipyramidal; d.ci.s.pl. = distorted cis square planar.

[b] w = water; b.c. = bridging carboxylate; alcoh = alcohol.

[c] a.b.m. = aminoacid bonding modes; b.b. = bridging bidentate; b.m. = bridging monodentate; uni = unidentate; c = carboxylic.

TABLE 6

Log $\beta$ of binary and ternary M(II) complexes[a] of $N$-ArSO$_2$ amino acids prevailing in aqueous or alcoholic solution and pK values of sulphonamide nitrogen deprotonation for the free ligand and for binary and ternary systems

Cu(II) species

| Solvent | tsgly<br>$H_2O$ | bsgly<br>$H_2O$ | dsgly<br>$H_2O$ | ts-$\beta$-ala<br>$H_2O$ |
|---|---|---|---|---|
| $[Cu(LO)_2]$ | 5.2 | 5.3 | | 5.5 |
| $[Cu(LNO)]$ | 7.6 | 7.7 | 8.6 | |
| $[Cu(LNO)_2]^{2-}$ | 11.3 | 11.5 | 11.4 | |
| $[Cu(LO)_2(bipy)]$ | 13.3 | 13.4 | 13.6 | 13.7 |
| $[Cu(LNO)(bipy)]$ | 16.1 | 16.2 | 17.1 | 14.7 |
| $[Cu(LNO)_2(bipy)]^{2-}$ | 18.8 | 19.1 | | |
| $pK_{NH}$ | 11.4 | 11.4 | 11.7 | 11.2 |
| $pK^{NH}_{[Cu(LNO)]}$ | 8.0 | 7.9 | 7.8 | |
| $pK^{NH}_{[Cu(LNO)(bipy)]}$ | 5.5 | 5.2 | 5.0 | 6.6 |

Zn(II), Cd(II), and Pd(II) species

| Solvent | tsgly | | bsgly | dsgly | | ts-$\alpha$-ala | ts-$\beta$-ala |
|---|---|---|---|---|---|---|---|
| | $H_2O$ | $CH_3OH$ | $H_2O$ | $H_2O$ | $CH_3OH$ | $H_2O$ | $H_2O$ |
| $[Cd(LO)]^+$ | | 3.60 | | | 3.70 | | |
| $[Cd(LO)_2]$ | | 7.30 | | | 6.78 | 4.61 | 5.21 |
| $[Cd(LO)OH)]$ | | 9.00 | | | 8.83 | | |
| $[Cd(LNO)]$ | 4.90 | 12.54 | 5.06 | 4.90 | 11.00 | 5.45 | 5.34 |
| $[Cd(LNO)_2]^{2-}$ | 6.00 | 13.30 | 7.66 | 6.14 | 12.17 | 9.45 | 9.90 |
| $[Cd(LNO)OH]^-$ | 8.84 | 14.00 | 8.95 | 9.17 | 13.25 | | |
| $[Cd(LNO)_2OH]^{3-}$ | 11.84 | 16.45 | 12.02 | 12.52 | 15.98 | | |
| $[Cd(LO)(bipy)]^+$ | 7.02 | | 7.18 | | | | |
| $[Cd(LNO)(bipy)]$ | 9.79 | | 9.90 | | | | |
| $pK^{NH}_{[Cd(LNO)]}$ | 8.0 | | 8.0 | | | | |
| $pK^{NH}_{[Cd(LNO)(bipy)]}$ | 7.6 | | 7.6 | | | | |
| $[Zn(LO)(bipy]^+$ | 8.82 | | 8.96 | | | | |
| $[Zn(LNO)(bipy)]$ | 11.86 | | 11.98 | | | | |
| $pK^{NH}_{[Zn(LNO)(bipy)]}$ | 7.8 | | 7.8 | | | | |
| $[Pd(LNO)]$ | 17.8 | | 18.9 | | 17.8 | | |
| $[Pd(LNO)_2]^{2-}$ | 23.4 | | 24.4 | | 21.8 | | |
| $[Pd(LNO)(OH)]^-$ | | | | | 21.6 | | |

[a] Overall stability constant ($\beta$) is relative to the equilibrium $M^{2+} + m\text{bipy} + n\text{LO}^-$ (or $n\text{LNO}^{2-}$) $\rightleftharpoons [M(LO)_n(\text{bipy})_m]$ (or $[M(LNO)_n(\text{bipy})_m]^{2-2n}$); $m=0$, 1 and $n=1$, 2.

in aqueous solution at pH $< 5$, in which the ligand coordinates through the carboxylic oxygen atom. At pH $> 5$, it causes copper(II) substitution of the amide proton followed by nitrogen coordination, strongly anticipating the p$K_{\mathrm{NH}}$ ligand values (Table 6). This agrees with the peptide group behaviour [2]. In particular, the sulphonamide hydrogen deprotonation seems to demand the presence of an intermediate hydroxo-complex.

The remarkable positive values (2–6) of the ratio log $K^{[\mathrm{Cu}]}_{[\mathrm{CuLNO}]}/K^{[\mathrm{CuLNO}]}_{[\mathrm{Cu(LNO)_2}]}$ displayed by the N-protected amino acidate complexes (Table 6) are interesting if compared with the corresponding values for chelate simple amino acidate copper(II) complexes (1.2–1.7) [3(b)]. The high values are reasonably attributed to the negative charge of the $[\mathrm{Cu(LNO)_2}]^{2-}$ species with respect to the neutrality of the [Cu(amino-acidato)$_2$] species [74(b)].

A strong steric hindrance of the dansyl group compared with the *N*-tosyl and *N*-phenylsulphonyl groups, which behave in a very strictly similar manner [74] (Table 6), reduces the ability of the complex formation in the adsorbed layer on the mercury electrode surface [83–85] and the dominant species present only one *N*-dansyl-glycinate NO bonded to the copper(II) ion [79].

For the aqueous solution studies of the binary Cu$^{2+}$–*N*-tosyl-$\alpha$-alaninate system [77], the ligand behaviour, in the correct interpretation of Sigel and Martin [23], agrees perfectly with the results obtained for the other *N*-tosyl amino acids [74–76]. In line with ref. 23, the anticipated Cu$^{2+}$-promoted amide deprotonation occurs only with a ligand which contains a primary ligating group, the carboxylic group in these cases. However, as demonstrated in refs. 67 and 77, this is true only if the primary ligating site is in the $\alpha$ position with respect to the N substituent. In fact, when the carboxylato group is in the $\beta$ position, as in *N*-tosyl-$\beta$-alaninate, the copper(II) ion is ineffective in promoting amide deprotonation. This is in accordance with the lower stability of six-membered compared with five-membered chelate rings.

### *(ii) Copper(II)–N-ArSO$_2$–amino acidate–bipy systems in aqueous solution*

Ternary complexes of copper(II)–*N*-tosyl-glycine, –*N*-tosyl-$\beta$-alanine, *N*-dansyl-glycine and –*N*-phenylsulphonyl-glycine with 2,2′-bipyridine in aqueous solution present overall stability constants indicating that species with a metal : ligand : bipy ratio of 1 : 2 : 1 invariably prevail when the amino acid acts as a simple carboxylate, while upon metal-promoted amide deprotonation, 1 : 1 : 1 becomes the prevailing ratio [74(b)]. The stability of ternary compounds greater than that of the corresponding binary compounds (Table 6) confirms the tendency of several carboxylate ligands to bind more strongly to the $[\mathrm{Cu(bipy)}]^{2+}$ species than to the solvated metal ion [23]. The enhanced affinity of the carboxylato group for the $[\mathrm{Cu(bipy)}]^{2+}$ species may lead to an increase in its primary ligating group capability strongly promoting the amide nitrogen deprotonation. This effect for the $[\mathrm{Cu(bipy)}]^{2+}$ intermediate complex is so pronounced as to promote amide nitrogen deprotonation in *N*-tosyl-

$\beta$-alanine, overcoming the unfavoured formation of a six-membered chelate ring [74(b)].

A correlation between the decrease of the $pK_{NH}$ values of the ligands upon metal binding in binary [Cu(LNO)] and ternary [Cu(LNO)(bipy)] systems ($\Delta pK_{NH}$) and the stability of the complexes (Fig. 7) demonstrates that, in binary and ternary systems, the species formed by different ligands present very strict relative stabilities [74(b)].

The results of the studies on these systems are particularly significant, since they confirm the important role of the presence of a very stable intermediate species, in this case a copper(II) 2,2′-bipyridine complex [74(b)], while in binary complexes, it was a copper(II) hydroxo complex, in order to promote sulphonamide hydrogen deprotonation in *N*-ArSO$_2$ amino acids.

### *(iii) Coordinative behaviour in the solid state*

For the *N*-ArSO$_2$ amino acids, the complexes prevailing in solution are the same as those isolated in the solid state under about the same pH conditions.

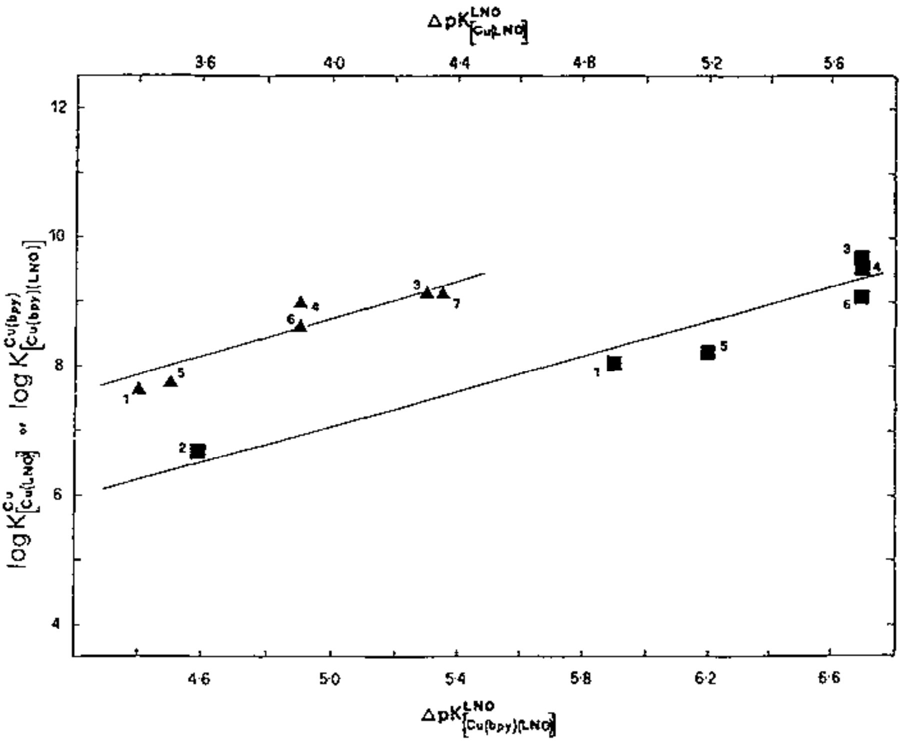


Fig. 7. Plot of stability constants for binary and ternary copper(II) species vs. metal-induced decrease of the pK value of sulphonamide nitrogen deprotonation. Upper line and upper abscissa: binary species; lower line and lower abscissa: ternary species [74(b)].

Generally, two types of coordinative behaviour of the *N*-ArSO$_2$ amino acids toward copper(II) ions, dependent on the pH value of the solution are recognized.

### *(a) Compounds obtained from aqueous (pH < 5) or alcoholic (neutral) solution*

Under these conditions, the *N*-tosyl- and *N*-dansyl amino acids, in agreement with observations in aqueous solution, parallel the coordinative behaviour of the acids of Sect. C, separating blue (pale) [21,67,76,86] and green [21,75] compounds, respectively (Table 7).

The pale blue complexes [67,76,86(a)] are discrete monomeric species in which copper(II) ions present slightly distorted tetragonally elongated bipyramidal geometries (CuO$_6$ chromophores). As structurally determined for the diaquadimethanolbis(*N*-tosyl-DL-valinato)copper(II) complex [87] (Fig. 8), the amino acids act as unidentate-O ligands and the coordination sphere of the metal ion is completed by water and/or solvent molecules. Furthermore, their ESR spectra and d-d band maximum (Table 7) are typical of compounds containing CuO$_6$ chromophores. The thermal behaviour of these compounds shows a gradual loss of water molecules during which they firstly transform into green hydrated forms and, finally, into green anhydrous forms. Both of these green materials shows strong antiferromagnetic exchange, indicating the presence of the typical carboxylate cage structure [21,86(a)].

The green solid complexes, which are generally separated from neutral alcoholic solutions (Table 7), also show magnetic properties of dimeric copper(II) acetate-like compounds. The majority of the compounds are anhydrous and present some distinct structural characteristics compared with the hydrated compounds and to the green complexes reported in Table 2. In fact, the structure of [Cu(tsglyO)$_2$]$_n$ [75] is composed of one-dimensional polymeric chains, extended along the *b* axis, of binuclear centrosymmetric [Cu$_2$(tsglyO)$_4$] units (Fig. 9). Two relevant features are present: one is the very short Cu···Cu separation (2.577(3) Å), generally found for dimeric units in polymeric structures, contrasted to the discrete dimers [57], and the second is the bond interactions between the sulphonamidic O atom and the metal ion which link the dimeric units into linear chains. No previous examples of this behaviour has hitherto been observed. In agreement with the structural results, showing 50% of the SO$_2$ groups bonded to a copper(II) atom, all the IR bands assignable to the sulphonamide group (NH, SO$_2$, SN) are split (Table 7). Similar behaviour of the sulphonamide IR bands is also observed for the green anhydrous *N*-tosyl-$\beta$-alaninato complex [67].

### *(b) Compounds obtained from aqueous solution at pH > 5 or basic solution*

All the compounds described in this section are characterized by the presence of the deprotonated amide nitrogen atom and one carboxylic oxygen atom of the amino acids chelated to the copper(II) ion, with which they form a five-membered ring.

Pale blue compounds of formula Cu(*N*-ArSO$_2$-amino acidatoNO)·3H$_2$O are separated from aqueous solutions of *N*-tosyl- and *N*-phenylsulphonyl amino acids

TABLE 7

Spectroscopic and magnetic results for binary copper(II) *N*-ArSO$_2$ amino acid compounds containing an undeprotonated sulphonamide group recovered from aqueous (pH < 5) or neutral alcoholic solution

| Compound | Colour[a] | $\mu_{eff}$ | $g_{\parallel}$ | $g_{\perp}$ | $g_3$ | $g_2$ | $g_1$ | d–d$_{max}$ ($10^3$ cm$^{-1}$) | \|2*J*\| (cm$^{-1}$) | *ν*(NH) (cm$^{-1}$) | *ν*(SO$_2$) asym (cm$^{-1}$) | *ν*(SO$_2$) sym (cm$^{-1}$) | *ν*(SN) (cm$^{-1}$) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Aqueous solution* | | | | | | | | | | | | | | |
| Cu(tsglyO)$_2$·4H$_2$O | p.b. | 1.83 | 2.388 | 2.065 | | | | 14.4 | | 3270ms | 1318vs<br>1313vs | 1158vs | 902ms | 86(a) |
| Cu(tsleuO)$_2$·4H$_2$O | p.b. | | 2.36 | 2.09 | | | | 13.2 | | 3280m | 1320vs<br>1305vs | 1150vs | 930m | 76 |
| [Cu(tsvalO)$_2$(H$_2$O)$_2$(CH$_3$OH)$_2$] | p.b. | 1.85 | | | 2.401 | 2.110 | 2.069 | 13.2 | | 3250s | 1315vs | 1150vs | | 87 |
| Cu(dsglyO)$_2$·4H$_2$O | p.b. | 1.87 | | | 2.31 | 2.11 | 2.06 | 13.5 | | 3280s | 1320vs | 1142vs | 875vs | 21 |
| *Alcoholic solution* | | | | | | | | | | | | | | |
| [Cu$_2$(tsglyO)$_4$]$_n$ | g | 1.33 | 2.363 | 2.083 | | | | 15.2 | 353 | 3285s<br>3210s | 1340ms<br>1325s<br>1290s | 1170s<br>1145s | 892m<br>865m | 75 |
| [Cu(ts-α-alaO)$_2$]$_n$ | g | 1.33 | 2.367 | 2.095 | | | | 15.0 | 358 | 3320s<br>3240s | 1330vs<br>1290vs | 1165vs<br>1155vs | 975m | 67 |
| [Cu(ts-β-alaO)$_2$]$_n$ | g | 1.44 | 2.337 | 2.063 | | | | 15.0 | 277 | 3270ms | 1320vs | 1160vs | 945ms | 67 |
| [Cu(tsvalO)$_2$(H$_2$O)]$_2$·4H$_2$O | g | 1.43 | 2.41 | 2.10 | | | | 13.5 | 322 | 3320ms<br>3280ms | 1325vs | 1160vs | | 87 |
| [Cu(dsglyO)$_2$(CH$_3$OH)]$_2$·CH$_3$OH | g | 1.70[b] | 2.40 | 2.11 | | | | 13.7 | 206 | 3280s | 1315vs | 1145vs | 865vs | 21 |

[a] p.b. = pale blue; g = green.

[b] Corrected for the presence of monomeric species with an estimated molar fraction of 0.27 [71].

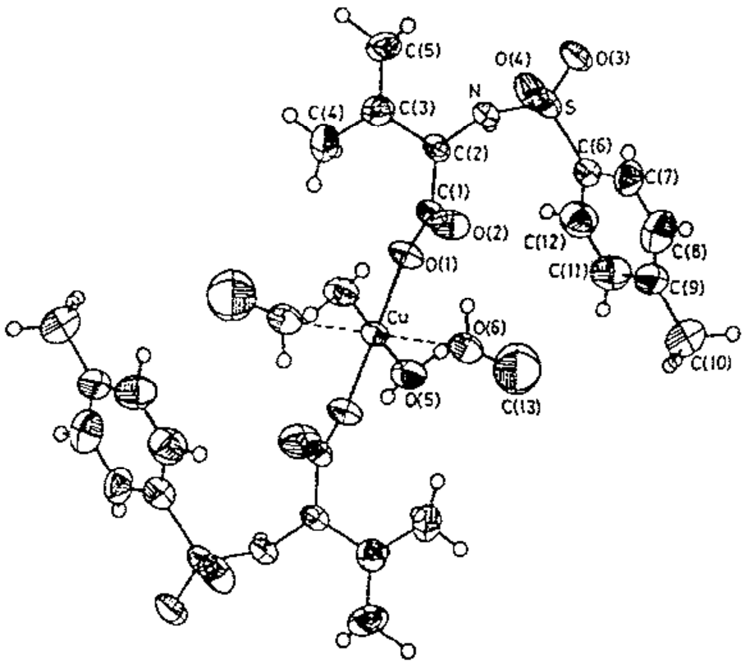


Fig. 8. ORTEP view of [Cu(tsvalO)$_2$(H$_2$O)$_2$(CH$_3$OH)$_2$] [87].

already at pH 5–7. In all complexes, the copper(II) ion displays a 4+1 tetragonal pyramidal coordination (CuNO$_4$ chromophore). However, very different structural types are observed: (a) monomeric structure in [Cu(tsglyNO)(H$_2$O)$_3$] (Fig. 10) [86(a)], identical to the *N*-phenylsulphonyl-glycine copper(II) compound [86(b)]; (b) monodimensional polymeric structure in the [Cu(ts-α-alaNO)(H$_2$O)$_2$]$_n$·$n$H$_2$O [67], in which the carboxylate group of the amino acid joins two adjacent copper(II) ions (Fig. 11); (c) monodimensional polymeric structure in the [Cu(bs-DL-alaNO)(H$_2$O)$_2$]$_n$·$n$H$_2$O (bs-DL-alaNO = *N*-phenylsulphonyl-DL-alaninate dianion) (Fig. 12) [22], in which one sulphonyl oxygen of a glide-related complex occupies the axial position. In this last compound, the proposed 4+1+1 (the latter position involving the oxygen from the chelate ring of a symmetry related complex) geometry around the copper(II) ion seems to be overemphasized, in our opinion, since the angle of the sixth axial bond is sharply deviant from the normal to the basal plane. In [Cu(ts-α-alaNO)-(H$_2$O)$_2$]$_n$·$n$H$_2$O and in [Cu(bs-DL-alaNO)(H$_2$O)$_2$]$_n$·$n$H$_2$O, the adjacent monomers are linked through bridging carboxylato groups in a *syn–anti* type configuration, —Cu···O—Cu···O—Cu—. Such bridges, which are capable of providing pathways for electron transfers to and from copper(II) ions and for magnetic superexchange between them, are characteristic of aspartato and glutamato ions [88,89].

All the pale blue complexes show very similar thermal behaviour, gradually losing water molecules on heating followed by decomposition [67,86(a)].

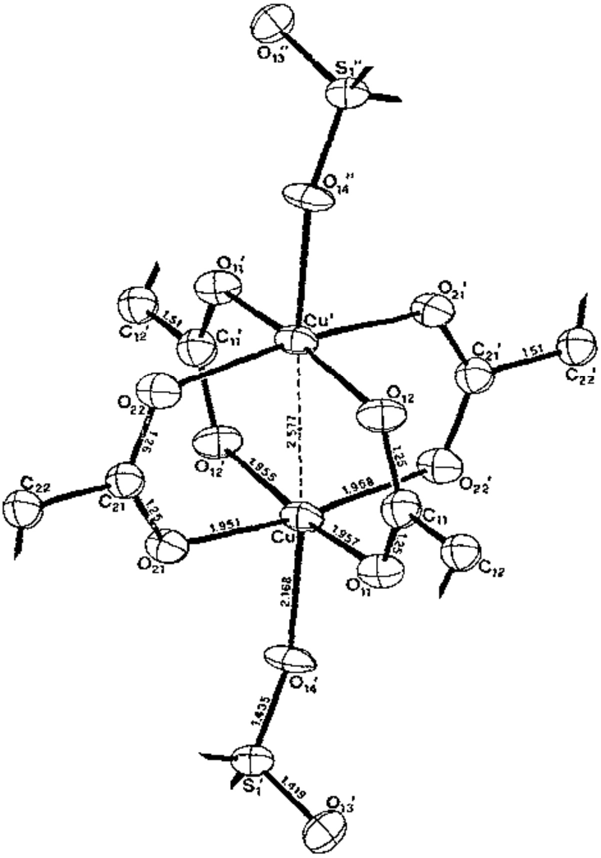


Fig. 9. A portion of the linear-chain structure of $[Cu_2(tsglyO)_4]_n$ with interatomic distances [75].

At pH > 8, the *N*-tosyl amino acids separate compounds of formula $A_2[Cu(ts\text{-}aminoacidatoNO)_2]\cdot xH_2O$ ($A = Na^+$, $K^+$, morpholinium and piperidinium cations) (Table 8), presenting a great variety of structures as shown in Fig. 13 for the dimer $\{K_2[Cu(tsglyNO)_2]\}_2$ (blue form) [86(a)], in Fig. 14 for discrete monomeric $(pipdH)_2[Cu(ts\text{-}\alpha\text{-}alaNO)_2]\cdot H_2O$ [67] (an identical structural arrangement is observed in $K_2[Cu(bsglyNO)_2]$ [86(b)] and in Fig. 15 for discrete monomeric $Na_2[Cu(tsleuNO)_2(H_2O)]\cdot 2H_2O\cdot CH_3OH$ [76] compounds. The *N*-tosyl-glycinato compound also exists in a violet form [86(a)]. The presence of several forms of amino acid–copper(II) complexes, as observed in this instance, is very common [3]. A strictly square-planar structure with $CuN_2O_2$ chromophore is suggested for all the violet species (Table 8), based on the similarity of their physical properties to those of the structurally known $(pipdH)_2[Cu(ts\text{-}\alpha\text{-}alaNO)_2]\cdot H_2O$ [67], $K_2[Cu(bsglyNO)_2]$ [86(b)] and other compounds [90].

The inability to isolate solid state compounds with two copper(II)-bound

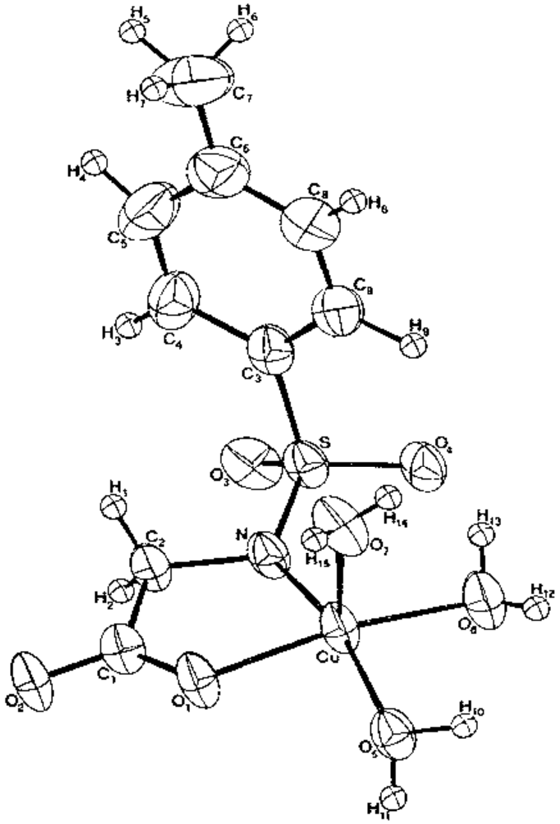


Fig. 10. ORTEP view of [Cu(tsglyNO)(H$_2$O)$_3$] [86(a)].

dsglyNO$^{2-}$ anions, presumably due to the steric hindrance of the dansyl group, is predicted on the basis of the solution investigations [79].

In all the compounds reported in this section, sulphonamide deprotonation and the successive replacement of the hydrogen atom with a Cu(II) atom influence some of the internal bond distances of the N-protected amino acidate dianion, especially the S–N and S–O bonds. This makes infrared spectroscopy an unambiguous method for revealing the presence or absence of the deprotonated N-protected amino acidate dianion, since the infrared spectra are very different in the two cases (compare the data of Tables 7 and 8).

### *(c) Solid ternary complexes with amines*

Blue and green complexes of *N*-tosyl- and *N*-dansyl amino acids react with amines similarly to the analogous compounds of *N*-acetyl, *N*-benzoyl and *N*-benzyloxycarbonyl amino acids.

In fact, with imidazoles, essentially square-planar adducts with *trans*-CuN$_2$O$_2$

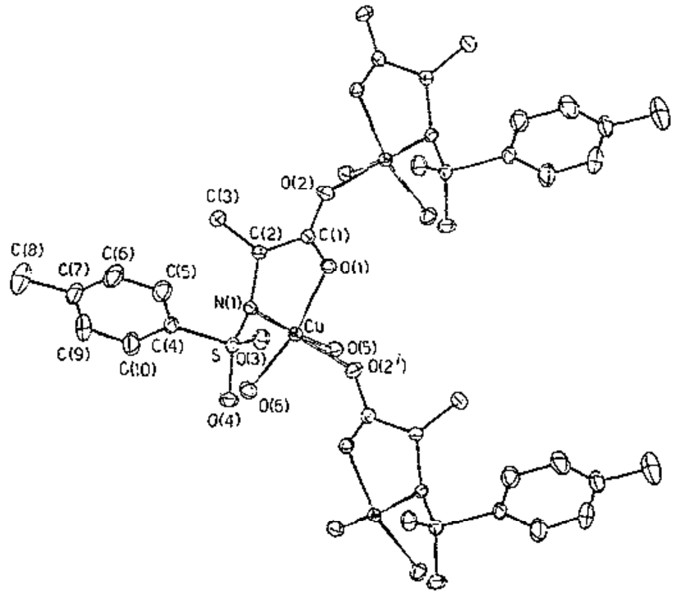


Fig. 11. ORTEP view of $[Cu(ts\text{-}\alpha\text{-}alaNO)(H_2O)_2]_n \cdot nH_2O$ [67].

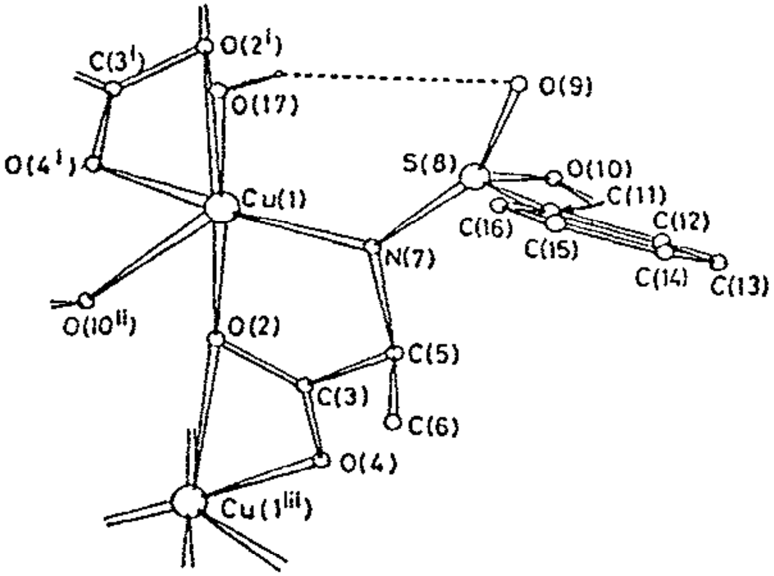


Fig. 12. Perspective view of $[Cu(bs\text{-}DL\text{-}alaNO)(H_2O)]_n \cdot 2H_2O$ down the *a* axis. The oxygen atom of the water of crystallization is not shown [22].

TABLE 8

Physical data for binary copper(II) *N*-tosyl- and *N*-phenylsulphonyl amino acidate compounds containing a deprotonated sulphonamide group

| Compound | Colour[b] | d d ($10^3$ cm$^{-1}$) | $g_\parallel$ | $g_\perp$ | $\nu(SO_2)$ asym. (cm$^{-1}$) | $\nu(SO_2)$ sym. (cm$^{-1}$) | $\nu(SN)$ (cm$^{-1}$) | Chromophore | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| $[Cu(tsglyNO)(H_2O)_3]$ | p.b. | 14.0 | 2.308 | 2.078 | 1245vs | 1132,<br>1113vs | 978s | $NO_4$ | 86(a) |
| $[Cu(bsglyNO)(H_2O)_3]$ | p.b. | 13.8 | | | 1241vs | 1135,<br>1113vs | 979s | $NO_4$ | 86(b) |
| $[Cu(ts\text{-}\alpha\text{-}alaNO)(H_2O)_2]_n \cdot nH_2O$ | p.b. | 13.7 | 2.258 | 3.153 2.08 | 1230vs | 1120vs | 1000vs | $NO_4$ | 67 |
| $\{K_2[Cu(tsglyNO)_2]\}_2$ | b. | 15.2 | 2.231 | 2.063 | 1268vs | 1140,<br>1150vs | 982vs | $N_2O_3$ | 86(a) |
| | v. | 14.7sh,16.4,<br>19.2 | 2.201 | 2.052 | 1265vs | 1145,<br>1108vs | 958s | $N_2O_2$(?) | 86(a) |
| $K_2[Cu(bsglyNO)_2]$ | b.v. | 14.7,<br>17.4sh | | | 1287,<br>1260vs | 1140,<br>1114,<br>1103vs | 982,<br>931s | $N_2O_2$ | 86(b) |
| $(pipdH)_2[Cu(ts\text{-}\alpha\text{-}alaNO)_2] \cdot H_2O$[a] | v. | 14.5,17.9,<br>19.1sh | 2.234 | 2.047 | 1260vs | 1133,<br>1120vs | 990s | $N_2O_2$ | 67 |
| $(morpH)_2[Cu(ts\text{-}\alpha\text{-}alaNO)_2]$[a] | v. | 15.3,19.1 | 2.212 | 2.060 | 1250vs | 1130vs | 988s | $N_2O_2$(?) | 67 |
| $K_2[Cu(ts\text{-}\alpha\text{-}alaNO)_2]$ | v. | 14.3,16.6,<br>19.2sh | 2.221 | 2.053 | 1250vs | 1130vs | 1000vs | $N_2O_2$(?) | 67 |
| $Na_2[Cu(tsleuNO)_2H_2O)] \cdot 2H_2O \cdot CH_3OH$ | b. | 14.3 | 2.280 | 2.084 | 1250vs | 1140,<br>1110vs | 1030ms | $N_2O_3$ | 76 |

[a] pipdH = piperidinium cation; morpH = morpholinium cation.

[b] p.b. = pale blue; b. = blue; v. = violet; b.v. = blue violet.

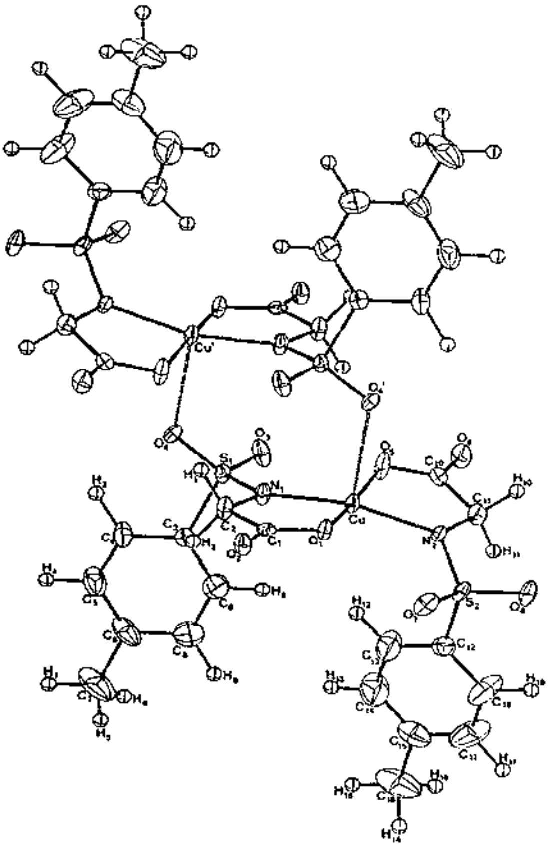


Fig. 13. ORTEP view of the $K_2[Cu(tsglyNO)_2]_2$ dimer (blue form) [86(a)].

chromophore are invariably separated. See, for example, bis(imidazole)bis(*N*-tosyl-*β*-alaninato)copper(II) [67] and bis(*N*-methyl-imidazole)bis(*N*-tosyl-glycinato) copper(II) [91], which present identical copper(II) ion configurations to that observed in the structurally known $[Cu(bzglyO)_2(im)_2]$ [60]. This confirms the discriminatory behaviour of the imidazoles for the second type of ligand to be included in the coordination sphere, with preference being given to O-donor rather than N-donor ligands.

With amines of low basicity, such as pyridines, the copper(II) ion can achieve octahedral geometry since the lowering of the in-plane ligand field donor with respect to imidazole adducts favours the axial coordination of water molecules. Although this agrees with the conclusions of Sect. C, some structural differences are observed among the compounds. In fact, in catena(*μ*-aqua)bis(*N*-tosyl-glycinato)bis(4-methyl-pyridine)copper(II) [92], the tetragonal bipyramidal geometry of the copper(II) ion is reached through formation of a linear chain water-bridged copper(II) polymer (Fig. 16), while in aquabis(*N*-dansyl-glycinato)bis(pyridine)copper(II) [21] (Fig. 17), the six coordination position of the copper(II) ion is deactivated by steric hindrance

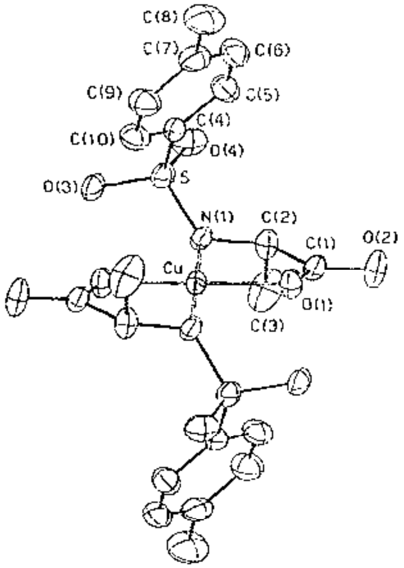


Fig. 14. ORTEP view of the $[Cu(ts\text{-}\alpha\text{-}alaNO)_2]^{2-}$ anion [67].

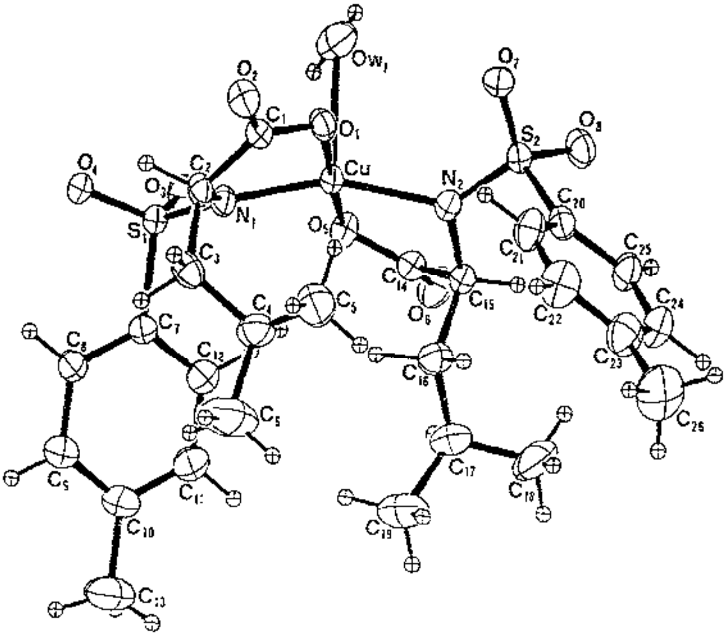


Fig. 15. ORTEP view of the $[Cu(tsleuNO)_2(H_2O)]^{2-}$ anion [76].

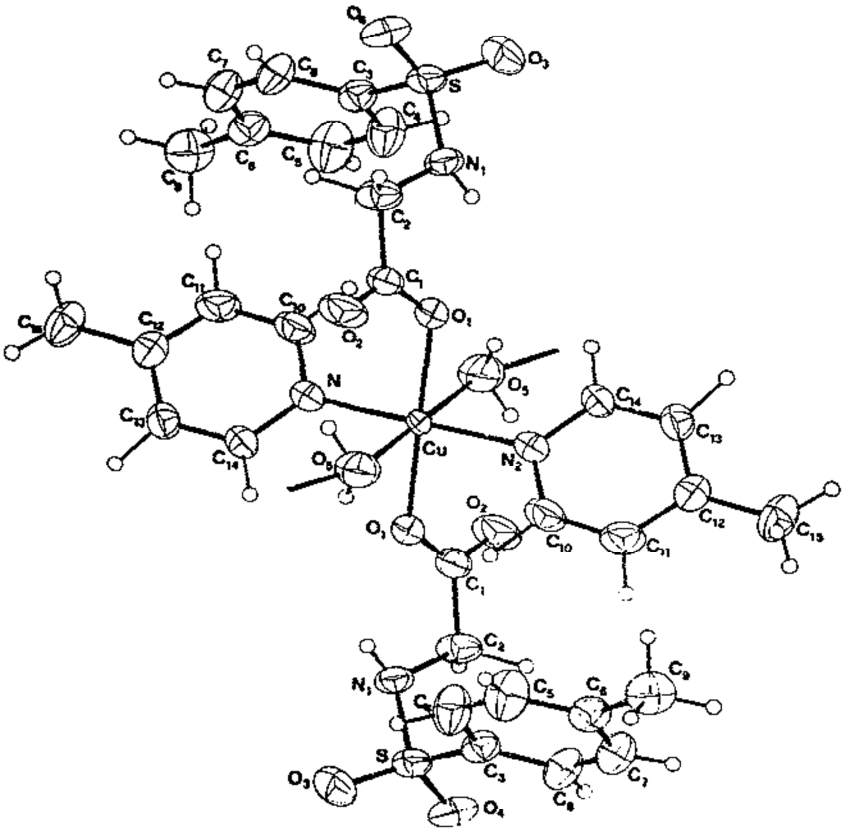


Fig. 16. ORTEP view of [Cu(tsglyO)$_2$(4-mepy)$_2$(H$_2$O)]$_n$ [92].

due to the intramolecular contact between the two uncoordinated carboxylic oxygen atoms placed under the basal coordination plane.

With monodentate cyclic aliphatic σ-bonding amines such as morpholine and piperidine [93], to which the highly basic character (p$K_A > 9.0$) assigns a weak coordinating ability, a strictly square-planar arrangement of the copper(II) ion (*trans*-$CuN_2O_2$ chromophore) is observed, similar to the ternary copper(II)–N-protected amino acidate–imidazole adducts. The only difference between saturated and aromatic amine adducts is the lengthening of the Cu–N bond, as observed in the bis(*N*-tosyl-β-alaninato)-bis(piperidine)copper(II) compound (2.028(2) Å) [93], depending on the inability toward π-back-donation of the saturated amines. In the last complex, the uncoordinated carboxylate oxygen and the amide nitrogen atoms of the amino acid molecules are involved in strong intermolecular hydrogen bonding, which are considered to be responsible for the observed coordination geometry of the copper(II) ion. In fact, the stabilization of square-planar geometries for the copper(II) ion in

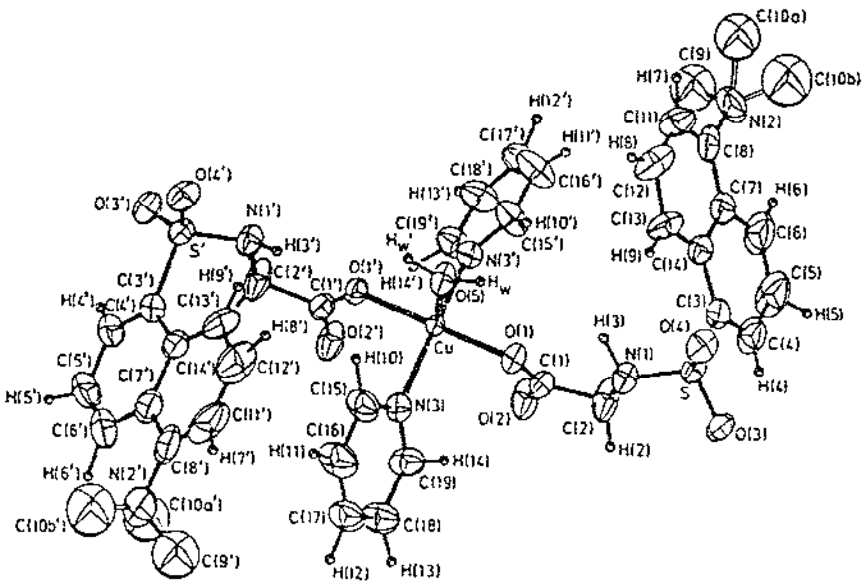


Fig. 17. ORTEP view of $[Cu(dsglyO)_2(py)_2(H_2O)]$ [21].

the presence of saturated amine adducts necessitates a further contribution since these amines generally favour other types of geometries [94].

The N-$ArSO_2$ amino acids in the presence of bipy show a different coordinative behaviour. In fact, N-tosyl amino acids are generally found to coordinate the copper(II) ions through an oxygen carboxylate, similarly to that observed for all the N-protected amino acids examined in Sect. C [63], while *N*-phenylsulphonyl- and *N*-dansyl-glycine form adducts in which the nitrogen deprotonated amino acids act as N,O ligands.

In the dimeric bis($\mu$-*N*-tosyl-glycinato)bis(*N*-tosyl-glycinato)bis-(2,2'-bipyridine)dicopper(II)dihydrate [95] (Fig. 18), the distorted square-pyramidal metal ions are bridged through monodentate carboxylate groups. The ESR spectrum at 139 K shows the $\Delta M_s = 2$ transition characteristic of magnetically coupled binuclear copper(II) complexes [95]. However, for the same reasons as reported for the structurally analogous $[Cu(bzglyO)_2(H_2O)_2]_2 \cdot 4H_2O$ compound [27,28], the exchange interaction pathway leads only to a very small $[2J]$ value [29].

The structure of $[Cu(tsvalO)_2(bipy)]_2$ is also very interesting, consisting of two crystallographically independent dimeric units [87]. Dimer **I** is very similar to the $[Cu(tsglyO)_2(bipy)]_2$ unit described above. The apex of the pyramid is occupied by a bridging carboxylate oxygen which is in a basal coordination site of the centrosymmetric copper atom in the dimer. In dimer **II** (Fig. 19), the two copper atoms are connected by two *N*-tosyl-valinate ions, each bridging through unidentate carboxylate and sulphonic oxygens. Intermolecular ring-stacking interactions between bipy

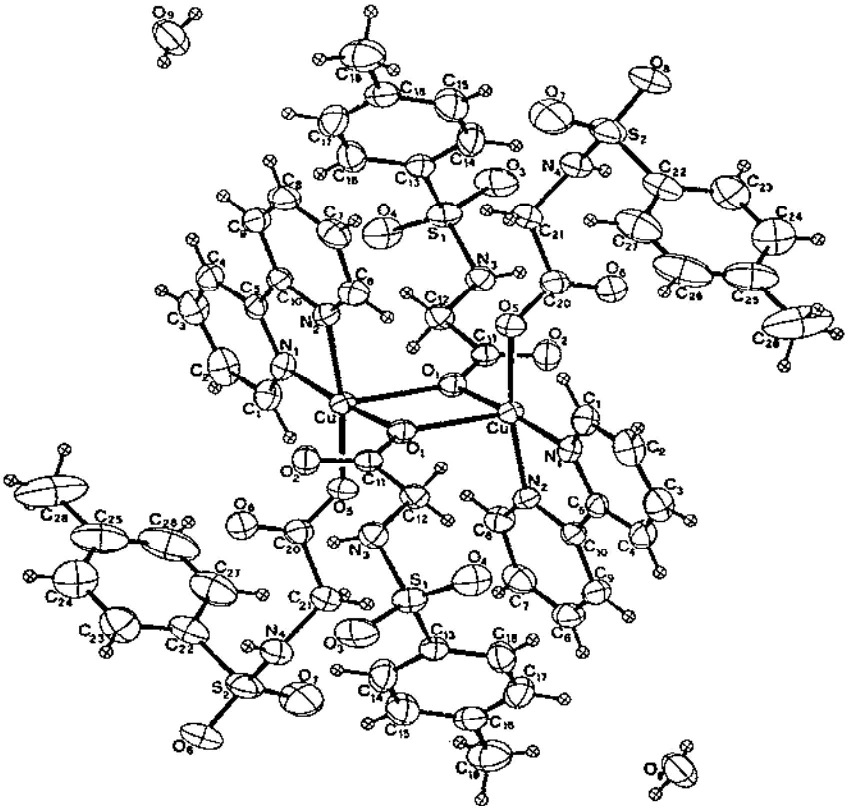


Fig. 18. ORTEP view of $[Cu(tsglyO)_2(bipy)]_2 \cdot 2H_2O$ [95].

molecules, belonging to two different dimers, are considered responsible for the complicated structure. The Cu···Cu distances of 3.501(5) Å in dimer **I** compared with 7.226(5) Å in dimer **II** account for exchange interactions being present only for dimer **I**. Again, a very small $[2J]$ value is observed, for the same reasons advanced for the compounds $[Cu(bzglyO)_2(H_2O)_2]_2 \cdot 4H_2O$ [27–29] and $[Cu(tsglyO)_2(bipy)]_2 \cdot 2H_2O$ [95].

The coordinative capability of the sulphonamidic oxygen atom was also seen in the $[Cu(tsvalO)_2(im)_4]$ complex [96], where the sulphonamidic group coordinates in place of the carboxylate group. The electronic and ESR results (d–d bands at 16200 sh and 19300 $cm^{-1}$; $g_{\parallel}=2.23$, $g_{\perp}=2.04$, $A_{\parallel} \times 10^4 = 198$ $cm^{-1}$), intermediate between the values reported for truly $CuN_4$ square-planar and $CuN_4O_2$ elongated octahedral chromophores, confirm that the axially positioned sulphonic groups, although very far from the Cu(II) ion (Cu–O(3) = 2.947(2) Å) are involved in a small but significant axial bonding (axial bonding interactions to the copper(II) ion are considered up to 3.3 Å [97]).

*N*-Dansyl-glycine and *N*-phenylsulphonyl-glycine in aqueous/methanolic solu-

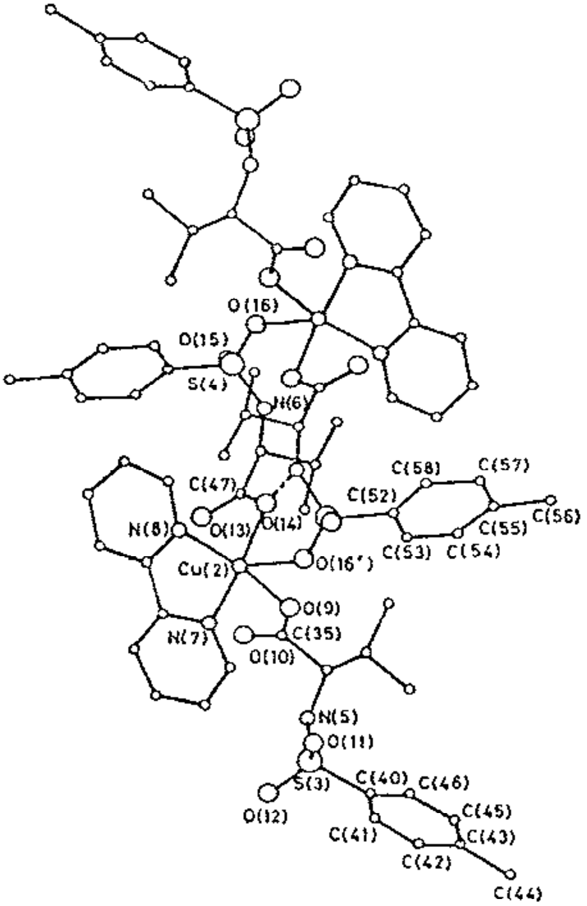


Fig. 19. Clinographic projection of $[Cu(tsvalO)_2(bipy)]_2$ dimer (II) [87].

tion in the presence of 2,2′-bipyridine anticipate amide nitrogen deprotonation separating the $[Cu(dsglyNO)(bipy)(CH_3OH)]$ [21] (Fig. 20) and $[Cu(bsglyNO)(bipy)(H_2O)]$ [74(b)] compounds, in which the copper(II) atom exhibits a tetrahedrally distorted square-pyramidal $N_3O_2$ coordination. Therefore 2,2′-bipyridine, which promotes the metal-amide deprotonation of the *N*-tosyl-, *N*-phenylsulphonyl and *N*-dansyl amino acids in solution [74(b)], exerts the same effect in the solid state complexes only for *N*-phenylsulphonyl and *N*-dansyl amino acids.

A structurally similar bipy adduct for *N*-tosyl-glycine has been obtained by starting with a binary complex already containing amide-deprotonated *N*-tosyl-glycinate ions [98]. In the bipy adducts of *N*-tosyl- and *N*-dansyl-glycinate dianions, the strong in-plane ligand field, lengthening the Cu–O apical bond, makes the molecule in the fifth axial position very easy to exchange with other molecules of

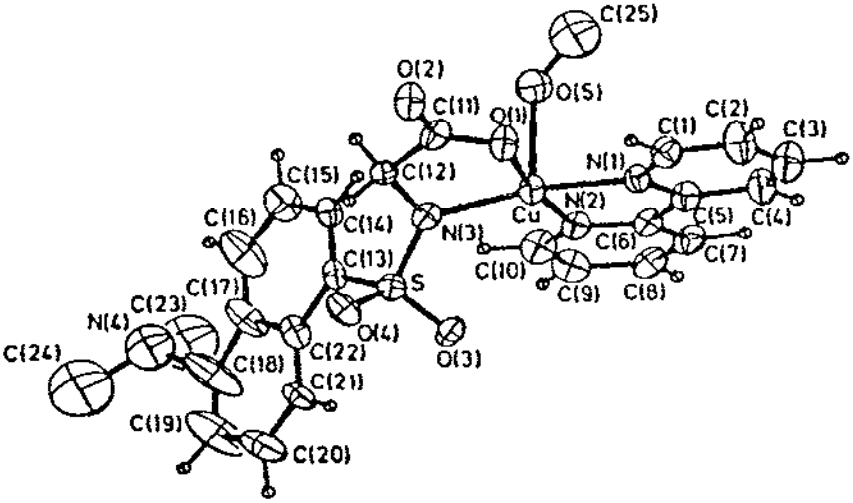


Fig. 20. ORTEP view of [Cu(dsglyNO)(bipy)($CH_3OH$)] [21].

similar coordinative type and power (methanol can be exchanged with water, ethanol, propanol, etc. and vice versa) [98].

### *(iv) General remarks*

The main conclusions on the behaviour of the copper(II) ion–N-tosyl, –*N*-phenylsulphonyl and *N*-dansyl amino acid systems in aqueous solution at $pH < 5$ or in neutral alcoholic solution and in the solid state strongly parallel those reported for the N-protected amino acids discussed in Sect. C. Further remarks are:

(a) a non-chelating coordinative ability of the $ArSO_2$ group, observed in some cases, generally involves the formation of dimeric species;

(b) the undeprotonated sulphonamide nitrogen atom is invariably involved in hydrogen bonding which determine crystal packing.

The main conclusions for the copper(II) systems in aqueous solutions at $pH > 5$ or basic alcoholic solution and for the solid compounds separated under these conditions are:

(a) in binary complexes and in ternary complexes of 2,2′-bipyridine, the pK values of the amide hydrogen deprotonation appear in the range 5–8, strongly anticipating the $pK_{NH}$ values of the free amino acids (11–12);

(b) amide hydrogen deprotonation in these amino acids gives rise to the formation of stable five-membered chelate ring copper(II) complexes, with the carboxylate oxygen and the deprotonated sulphonamide nitrogen donor atoms being involved in the metal atom coordination;

(c) the sulphonamide nitrogen deprotonation is activated by the presence of a

TABLE 9

Main structural parameters for copper(II) complexes of *N*-ArSO$_2$ amino acids containing undeprotonated (A) and deprotonated (B) sulphonamidic nitrogen atom

| Compound | Coord. geom.[a] | Chromophore | Cu–O$_{eq}$ (Å) | Cu–N$_{eq}$ (Å) | Cu–O$_{ax}$[b] (Å) | Amino acid bond. modes[c] | Ref. |
|---|---|---|---|---|---|---|---|
| *Type A* | | | | | | | |
| [Cu$_2$(tsglyO)$_4$]$_n$ | cu.a.l. | O$_5$ | 1.955(7) | | 2.168(7)sulph. | b.b.-(O,O)$_c$,<br>uni-O$_s$ | 75 |
| [Cu(tsvalO)$_2$(H$_2$O)$_2$(CH$_3$OH)$_2$] | t.b. | O$_6$ | 1.954(4) | | 2.492(4)meth. | uni-O$_c$ | 87 |
| [Cu(ts-$\beta$-alaO)$_2$(im)$_2$] | tr.s.pl. | N$_2$O$_2$ | 1.950(5) | 1.976(6) | | uni-O$_c$ | 67 |
| [Cu(tsglyO)$_2$(meim)$_2$] | tr.s.pl. | N$_2$O$_2$ | 1.967(3) | 1.970(4) | | uni-O$_c$ | 91 |
| [Cu(tsvalO)$_2$(im)$_4$] | t.b. | N$_4$O$_2$ | | 1.985(3) | 2.947(2)sulph. | uni-O$_s$ | 96 |
| [Cu(dsglyO)$_2$(py)$_2$(H$_2$O)] | s.py. | N$_2$O$_3$ | | | | uni-O$_c$ | 21 |
| [Cu(tsglyO)$_2$(4-mepy)$_2$(H$_2$O)]$_n$ | te.bip. | N$_2$O$_4$ | 1.929(4) | 1.977(5) | 2.755(1)br.w. | uni-O$_c$ | 92 |
| [Cu(ts-$\beta$-alaO)$_2$(bipy)] | ci.s.pl. | N$_2$O$_2$ | 1.939(3) | 2.000(3) | | uni-O$_c$ | 63 |
| [Cu(tsglyO)$_2$(bipy)]$_2$·2H$_2$O | ci.s.py. | N$_2$O$_3$ | 1.955(2) | 1.997(3) | 2.350(3)br.carb. | uni-O$_c$,<br>b.m.-O$_c$ | 95 |
| [Cu(tsvalO)$_2$(bipy)]$_2$[d] | ci.s.py. | N$_2$O$_3$ | 1.941(7) | 2.014(8) | 2.452(8)sulph. | uni-O$_c$,<br>b.m.-O$_s$ | 87 |
| | | | 1.954(8) | | 2.416(7)carb. | uni-O$_c$<br>b.m.-O$_c$ | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Type B* | | | | | | | |
| $[Cu(tsglyNO)(H_2O)_3]$ | s.py. | $NO_4$ | 1.957(4) | 1.964(6) | 2.259(4)w | b.-(N,O) | 86(a) |
| $[Cu(bsglyNO)(H_2O)_3]$ | s.py. | $NO_4$ | 1.928(3) | 1.966(4) | 2.270(3)w | b.-(N,O) | 86(b) |
| $[Cu(ts\text{-}\alpha\text{-}alaNO)(H_2O)_2]_n \cdot nH_2O$ | s.py. | $NO_4$ | 1.933(3) | 1.956(4) | 2.271(3)carb. | b.-(N,O) | 67 |
| $[Cu(bs\text{-}\textsc{dl}\text{-}alaNO)(H_2O)]_n \cdot 2nH_2O$ | s.py. | $NO_4$ | 1.945(2) | 1.968(2) | 2.648(2)sulph. | b.-(N,O),<br>uni.-$O_s$ | 22 |
| $\{K_2[Cu(tsglyNO)_2]\}_2$ | s.py. | $N_2O_3$ | 1.938(1) | 1.985(7) | 2.717(5)sulph. | b.-(N,O),<br>uni.-$O_s$ | 86(a) |
| $K_2[Cu(bsglyNO)_2]$ | s.pl. | $N_2O_2$ | 1.923(3) | 1.978(3) | | b.-(N,O) | 86(b) |
| $(pipdH)_2[Cu(ts\text{-}\alpha\text{-}alaNO)_2] \cdot H_2O$ | s.pl. | $N_2O_2$ | 1.928(4) | 1.930(4) | | b.-(N,O) | 67 |
| $Na_2[Cu(tsleuNO)_2(H_2O)] \cdot 2H_2O \cdot CH_3OH$ | s.py. | $N_2O_3$ | 1.972(4) | 1.989(4) | 2.353(4)w | b.-(N,O) | 76 |
| $[Cu(tsglyNO)(bipy)(C_2H_5OH)]$ | s.py. | $N_3O_2$ | 1.940(4) | 1.981(5)[e] | 2.382(4)ethan. | b.-(N,O) | 98 |
| $[Cu(bsglyNO)(bipy)(H_2O)]$ | s.py. | $N_3O_2$ | 1.938(3) | 1.990(3)[e] | 2.355(3)w | b.-(N,O) | 74(b) |
| $[Cu(dsglyNO)(bipy)(H_2O)]$ | s.py. | $N_3O_2$ | 1.97(1) | 1.97(1)[f] | 2.37(1)meth. | b.-(N,O) | 21 |

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[a] cu.a.l. = copper acetate-like; s.pl. = square planar; s.py. = square pyramidal; tr.s.pl. = trans square planar; te.bip. = tetragonal bipyramidal; ci.s.pl. = cis square planar.

[b] br. = bridging; carb. = carboxylic, sulph. = sulphonamidic; w. = water; meth. = methanol; ethan. = ethanol.

[c] b. = bridging; b.b. = bridging bidentate; b.m. = bridging monodentate; uni = unidentate; c = carboxylic; s = sulphonic.

[d] In this compound two different dimeric units are present [87].

[e] Mean values of two Cu–Nbipy and one Cu–*N*-$ArSO_2$ amino acid.

stable intermediate complex, a copper(II) hydroxo species in binary systems and a $[Cu(bipy)]^{2+}$ species in ternary systems;

(d) the $ArSO_2$ group can be involved in metal ion coordination;

(e) square-pyramidal geometries for the $Cu^{2+}$ ions are preferred because of the increased in-plane ligand field due to nitrogen coordination;

(f) in N-tosyl-β-alanine, the decreasing acidity of the NH group for the shift of the carboxylic group in the β position makes the tosyl group ineffective in promoting amide deprotonation in the binary system; in the ternary 2,2′-bipyridine system, the formation of the $[Cu(bipy)]^{2+}$ intermediate complex also promotes amide nitrogen deprotonation in this amino acid, overcoming the unfavoured formation of a six-membered chelate ring.

The more relevant structural parameters for the structurally known copper(II) complexes of *N*-tosyl-, *N*-dansyl- and *N*-phenyl-sulphonyl amino acids are summarized in Table 9.

## E. COORDINATIVE BEHAVIOUR OF N-PROTECTED AMINO ACIDS TOWARDS Co(II), Ni(II), Zn(II), Cd(II) AND Pd(II) IONS

### *(i) Cobalt(II), nickel(II) and zinc(II) ions*

The interactions among N-protected amino acids and cobalt(II), nickel(II) and zinc(II) ions have been the subject of many papers, but these studies have been less systematic than those for copper(II) ions.

#### *(a) Binary systems in solution*

For the cobalt(II), nickel(II) and zinc(II) ions–N-tosyl amino acidate [99] and zinc(II) ion–N-acetyl- and –N-benzoyl-glycinate [100] systems in aqueous solution, the polarographic analyses under varying pH conditions demonstrate the weakness of the metal–ligand interactions before metal hydroxide precipitations. Results are also confirmed by means of $^1H$ NMR [24,25] for Zn(II) systems, which evidence the presence of a solution $ZnL^+$ species, characterized by a very low value of the formation constant ($\log K = 0.71$ [24] and 0.86 [25]).

In alcoholic solution, more stable complex species are identified. In fact, for the $Z^{2+}$–N-acetyl- and –N-benzoyl-glycine systems, four complex species ($ZnL^+$, $ZnL_2$, $ZnL_3^-$ and $ZnL_4^{2-}$) have been polarographically determined and their stability constants, ranging from $10^7$ to $10^{26}$, calculated [100]. A close correlation between the polarographically determined stability constants of these complexes and the acceptor number of the solvent has been demonstrated by investigating the same systems in different solvents, such as *N*,*N*-dimethylsulphoxide, *N*,*N*-dimethylformamide and methyl cyanide [101].

In all the solution complexes, the N-protected amino acids coordinate only through the carboxylate group [100]. Similar amino acid coordination behaviour is found for the cobalt(II) and nickel(II) ions–*N*-benzyloxycarbonyl–L-tryptophanate systems in methanolic solution, in which one $CoL_2$ ($\log \beta = 7.8$) [102] and two $NiL_2$ ($\log \beta = 19$ to $20.6$) and $NiL_4^{2-}$ ($\log \beta = 32$ to $32.6$) [103] complex species, respectively, prevail.

*(b) Ternary zinc(II) systems in solution*

The aqueous zinc(II)–*N*-tosyl- and –*N*-phenylsulphonyl-glycine systems in the presence of bipy [99(b)], investigated by means of polarographic, potentiometric and $^1$H NMR measurements, show at pH < 8 the formation of a complex species, [Zn(amino acidatoO)(bipy)]$^+$, in which the amino acid coordinates through a carboxylate oxygen atom, while at pH > 8 this species is completely transformed to the [Zn(amino acidatoNO)(bipy)] species. Up to now, only one example is known of a deprotonated amide nitrogen coordinated to a zinc(II) ion at physiological pH: in the [Zn(GlyHis)] complex, the metal is bound to the terminal amino group of the dipeptide, the deprotonated peptide nitrogen, and one imidazole nitrogen of histidine [104]. It is interesting to observe that, in [Zn(amino acidatoNO)(bipy)] [99(b)], discussed above, besides the amino acid moiety, the zinc(II) ion is also coordinated to an N-donor aromatic ligand. The presence of such an additional ligand can be considered a necessary requirement for enabling the $Zn^{2+}$ ion (similarly to that observed for copper(II) ion) to substitute successfully for a proton bound to a peptide or sulphonamide nitrogen.

These results determine the condition for the separation of the corresponding solid complexes and also indicate the direction of further works on cobalt(II) and nickel(II) ions, which could be expected to behave similarly to the zinc(II) ions.

*(c) Solid state behaviour*

Cobalt(II), nickel(II) and zinc(II) ions with *N*-benzoyl-glycine in concentrated aqueous solution form binary complexes of formula $M(bzglyO)_2 \cdot 5H_2O$ [105–108]. The isostructural cobalt(II) and nickel(II) compounds (Fig. 21) provide new solid-state materials for modelling low-dimensional magnetic systems: the cobalt(II) complex is a metamagnet and the nickel(II) one is an antiferromagnet [108]. The corresponding zinc(II) ion–*N*-benzoyl glycinate complex contains discrete monomeric units in which the zinc(II) ion assumes an unusual five-coordinated, slightly distorted trigonal bipyramidal geometry [107] (Fig. 22).

The peculiar and potential characteristics of these compounds stimulate an extension of investigations to the metal(II) ion complexes of other *N*-benzoyl amino acids. Other investigations on cobalt(II) [109–111], nickel(II) [110,111] and zinc(II) [112] ion complexes with *N*-benzoyl-α- and -β-alanines and their amine adducts are reported, but since they lack structural and magnetic studies, they must be considered inconclusive.

Although *N*-acetyl-glycine and some *N*-tosyl amino acids are similar to *N*-benzoyl-glycine, the metal(II) compounds of formula [M(II)(*N*-amino acidato)$_2$($H_2O$)$_4$] (M = Co(II), Ni(II), Zn(II); *N*-amino acidato = *N*-acetyl-glycine [113], *N*-tosyl-glycine [99(a)] and *N*-tosyl-β-alanine [99(a)]) have very simple structures,

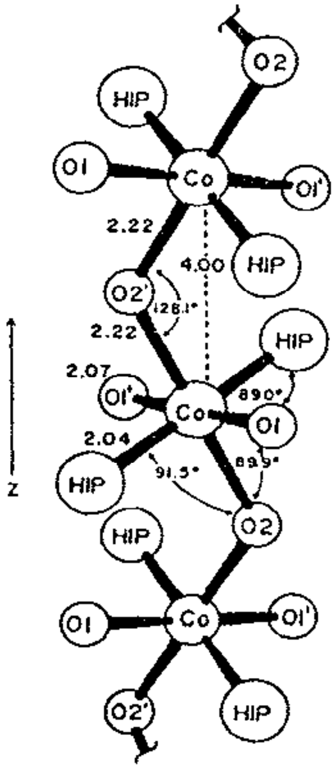


Fig. 21. Projection view of the site symmetry about the Co(II) ions for $[Co(bzglyO)_2(H_2O)_3]_n \cdot 2nH_2O$ [105,106].

all consisting of discrete monomeric units, in which the metal ion exhibits a slightly elongated octahedral geometry, being coordinated by two amino acids, through a carboxylate oxygen atom, and four water molecules (Fig. 23).

Other studies on cobalt(II) [114-117], nickel(II) [114-117] and zinc(II) [115-118] complexes of some *N*-acetyl amino acids and their amine adducts, based on magnetic, electronic and infrared measurements, confirm that the amino acid coordinates only through the carboxylate group. Although the ability of zinc(II) ions in deprotonating the sulphonamide nitrogen atom in *N*-$ArSO_2$ amino acids in the presence of 2,2'-bipyridine in aqueous solution has been demonstrated [99(b)], there is no separation of ternary complexes in which N-protected amino acidateNO dianions are coordinated to the zinc(II) ion.

### (ii) Cadmium(II) ion

#### (a) Binary and ternary systems in aqueous or ethanolic solutions

The cadmium(II) ion behaviour with *N*-acetyl- and *N*-benzoyl-glycines in aqueous solution [26,119] is strictly similar to that of Co(II), Ni(II) and Zn(II) ions

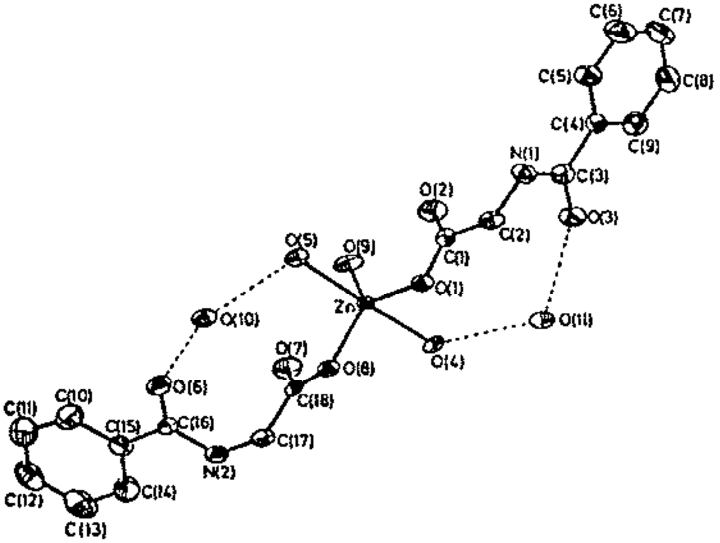


Fig. 22. ORTEP view of $[Zn(bzglyO)_2(H_2O)_3]\cdot 2H_2O$ [107].

discussed above. In alcoholic solution, it parallels the zinc(II) ion behaviour and four species of the type $CdL^+$, $CdL_2$, $CdL_3^-$ and $CdL_4^{2-}$ are found to coexist and their stability constant values have been determined [119]. In all the solution species, the amino acids are found to coordinate only through the carboxylate group.

The ability of the cadmium(II) ion in substituting for the nitrogen-bound hydrogen of *N*-tosyl- and *N*-dansyl-glycines in aqueous and methanolic solutions [120] and of *N*-tosyl-$\alpha$- and *N*-tosyl-$\beta$-alanines [121] and *N*-phenylsulphonyl-glycine [99(b)] in aqueous solution is revealed by means of $^1H$ NMR, polarographic and potentiometric investigations. The binding modes of these amino acids with cadmium(II) ions is pH-dependent, acting as simple carboxylate ligands at $pH < 7$ and as N,O-bidentate ligands at $pH > 7$. The species present in solution (Table 6) are well comparable with those obtained for the copper(II) ions, although less stable by factors varying from 10 to $10^4$.

The ability of the cadmium(II) ion in the binary complexes to promote amide nitrogen deprotonation is also relevant in *N*-tosyl-$\beta$-alaninate systems. This is also observed for copper(II) ions, but these require the presence of a $[Cu(bipy)]^{2+}$ intermediate species in order to overcome the unfavourable formation of a six-membered chelate ring [74(b)].

The importance of these results derives from the fact that the cadmium(II) ion has been considered unable to promote peptide nitrogen deprotonation [122], even though definitive evidence has not been found; thus, its ability in substituting for the amide hydrogen in *N*-$ArSO_2$ amino acids finds a reasonable explanation in the more acidic character of this hydrogen compared with that of the peptide hydrogen.

Worth reporting are the $^{113}Cd$ NMR results [120], which show a chemical

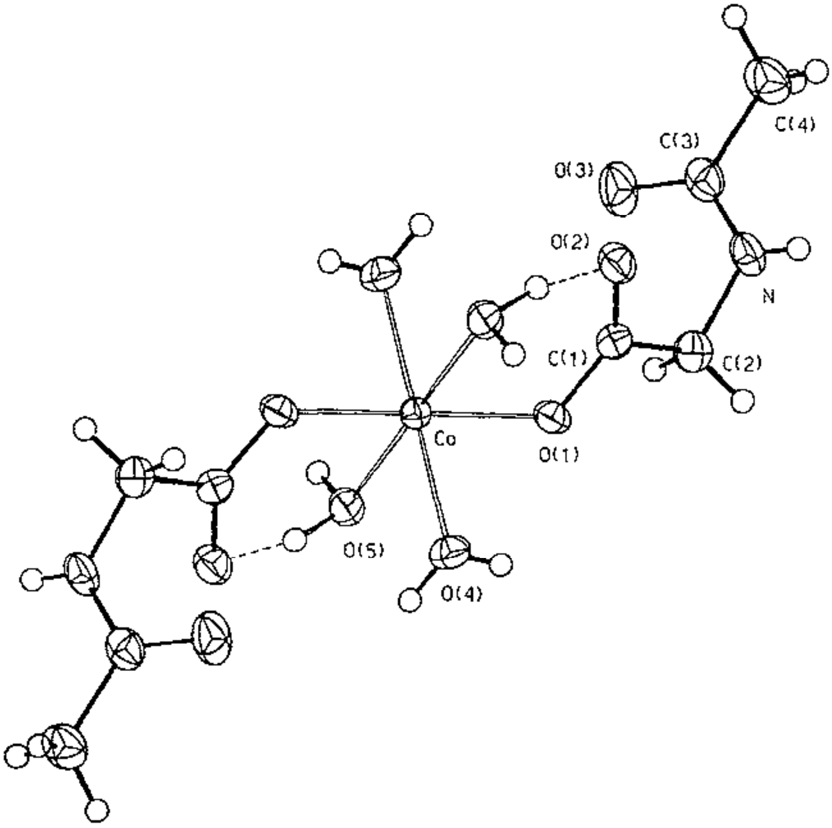


Fig. 23. ORTEP view of [Co(acglyO)$_2$(H$_2$O)$_4$] [113].

shift remarkably sensitive to the nature of the donor atoms as well as to the coordination number, geometry and solvent, as is also observed in a wide variety of Cd-containing systems such as simple inorganic salts, metal complexes and biological macromolecules [123], thus demonstrating the suitability of this technique for this type of research. In fact, for the control of the changes in N-protected amino acid coordination at increasing pH, the $^{113}$Cd NMR technique appears particularly suitable, since oxygen and nitrogen donor ligands exert opposite effects on the $^{113}$Cd resonance: the former shield the cadmium nucleus and the latter cause a deshielding effect [124]. The behaviour of *N*-ArSO$_2$ amino acids in aqueous and alcoholic solutions [120,121] compared with that of *N*-benzoyl-glycine, coordinating the cadmium(II) ions only through the carboxylate group [26,119], is illustrated in Fig. 24. Only upfield shifts are observed for all ligands up to pH 5.4 and 6.5 (aqueous and alcoholic solution, respectively); at increasing pH, *N*-benzoyl-glycine further shifts the cadmium resonance to lower frequencies with no change in the line widths, while the *N*-ArSO$_2$-glycines give rise to an "inversion" of the shielding effect, causing shifts

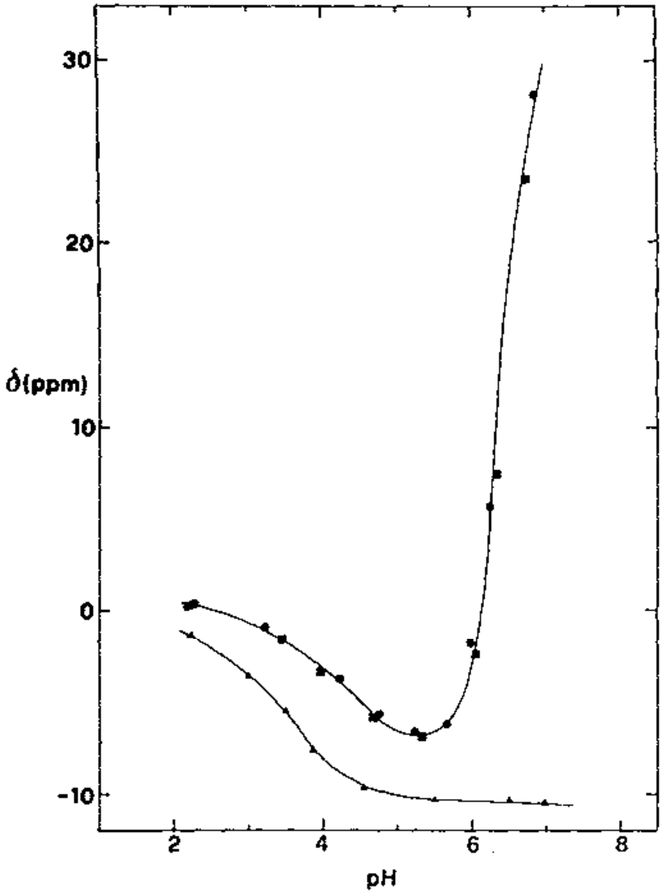


Fig. 24. Chemical shift of $7 \times 10^{-3}$ M $^{113}$Cd-enriched Cd(ClO$_4$)$_2$ with $1.4 \times 10^{-2}$ M ligands vs. pH in aqueous solution: ■, *N*-tosyl-glycine; ●, *N*-dansyl-glycine; ▲, *N*-benzoyl-glycine. T = 60°C. The chemical shift of the solvated $^{113}$Cd$^{2+}$ ion at pH 2.5 is found to be 1.80 ppm [120].

to more deshielded values and increasing broadening of the signals (detectable up to pH 7 in water and 8.2 in methanol) [120]. The upfield shift is considered to be a result of cadmium complexation through the carboxylate group of the ligands, while the subsequent downfield shift detected only for *N*-ArSO$_2$-glycines may only be due to an involvement of a nitrogen in metal complexation.

Ternary cadmium(II) ion–*N*-phenylsulphonyl- and –N-tosyl-glycine systems with 2,2′-bipyridine in aqueous solution have been investigated by means of $^1$H NMR, polarographic and potentiometric techniques. In both the systems, it was observed that the Cd(II) ion promoted deprotonation of the sulphonamide nitrogen with a lowering of the pK$_A$ from 8 to 7.6 with respect to the binary systems, and the formation of very stable solution species (Table 6) [99(b)].

### (b) *Solid state behaviour*

No compounds have been separated with the N-protected amino acids discussed in Sect. C. From aqueous methanolic solutions at pH values lower than 7.5. *N*-ArSO$_2$ amino acids (tsgly and dsgly) separate crystalline compounds of formula [CdL$_2$(H$_2$O)$_4$] [119,120], which are structurally similar to the analogous monomeric cobalt(II). nickel(II) and zinc(II) compounds [99(a),113], in which the carboxylate groups act as unidentate ligands. Similar metal arrangements are found in tetrahydrated cadmium(II) *N*-tosyl-α- and *N*-tosyl-β-alanines [120]. The structural details for the [Cd(ts-β-alaO)$_2$(H$_2$O)$_4$] are reported in ref. 120.

The structures of these compounds show some unusual features with respect of the known cadmium(II) carboxylates in which the ligands are found to act as bidentate toward the Cd(II) ion forming chelates and/or bridges, which enable the formation of dimeric units and, more often. polymeric species [125]. Moreover, the Cd(II) ion generally exhibits distorted pentagonal-bipyramidal (seven) coordination and, less frequently, octahedral coordinations. In the cadmium(II) N-protected amino acidates, the carboxylate groups act as unidentate ligands and the structures consist of monomeric units. These uncommon features [126], up to now observed in the same complex, find explanation in the high hydration of the complex.

At pH > 7.5, and in the presence of bipy, no solid complexes are separated owing to the competitive precipitation of the cadmium(II) hydroxide, which presents at these pH values a stability [127] comparable with that of the cadmium(II) complexes [119]. This behaviour is similar to that observed for the Zn(II) ion.

### (iii) *Palladium(II) ion*

The palladium(II) ion, among the metal(II) ions, such as cobalt(II), nickel(II), copper(II) and zinc(II), is known to present the greatest efficiency in substituting for a peptide hydrogen in oligopeptides and related ligands [23] and therefore there are some expectations in their chemistry toward N-protected amino acids. The interactions of this metal ion with *N*-ArSO$_2$ amino acids were recently investigated and so far only four papers have been published on the subject [128–131], but they are sufficient to delineate a satisfying picture of the chemistry and of the versatility of these systems.

### (a) *Binary systems in aqueous solution*

The palladium(II)-*N*-tosyl-, -*N*-phenylsulphonyl- and -*N*-dansyl-glycine systems in aqueous solution, investigated by electrochemical methods, show a very similar behaviour, giving rise in the pH range 4-11.5 to [Pd(LNO)] and [Pd(LNO)$_2$]$^{2-}$ species, the latter prevailing at high pH values [128]. It is interesting to note that the pK$_A$ for amide-hydrogen deprotonation in these complexes is less than 4, at least four units lower than that observed for analogous copper(II) and cadmium(II) systems [79,120,121]. Furthermore, their stability constants, reported in Table 6, are greater than those observed for the analogous copper(II) and cadmium(II) systems [79,120,121]. With *N*-dansyl-glycine, in agreement with the previous results on copper(II) and cadmium(II) systems [79,120,121], the coordination of only one ligand molecule is favoured. This behaviour and the concomitant lower stability of the $[Pd(dsglyNO)_2]^{2-}$ species among the other investigated ligands, still ascribed to the steric hindrance of the bulky naphthalene side chain, justifies the presence of a very stable mixed hydroxo species ($[Pd(dsglyNO)(OH)]^-$ at high pH, which is not observed for the other ligands [128].

All these results strongly confirm that the palladium(II) ion is the most effective metal ion not only in promoting peptide-nitrogen deprotonation, but also in displacing the nitrogen-bound hydrogen in *N*-$ArSO_2$ amino acids. While the difference between $pK_{NH}$ values induced by palladium(II) and copper(II) ions in peptides and related ligands is about two units ($pK_{NH}$ 2 and 4, respectively), such a difference is greatly increased for the *N*-$ArSO_2$ amino acids ($pK_{NH} < 4$ and 8, respectively). This effect is attributed to the peculiar ability of palladium(II) ion to interact with the aromatic ring [132,133] and the S and O atom of the ligands.

### *(b) Solid state behaviour*

In the solid state, two compounds of formula $Na_2[Pd(tsglyNO)_2]$ and $Na_2[Pd(bsglyNO)_2] \cdot H_2O$ have been separated at pH > 6 and their crystal and molecular structures determined [129]. Both the structures consist of monomeric $[Pd(aminoacidateNO)_2]^{2-}$ anions in which the palladium(II) atom shows a square-planar trans-coordination given by two amino acidateNO dianions chelating through one carboxylate oxygen and the deprotonated sulphonamide nitrogen. In the former complex, the palladium atom is involved in intramolecular contacts with the S, O ($SO_2$ group), and C (phenyl) atoms and shows an intermolecular contact with the $CH_3$ group, while in the latter, the presence of additional palladium–ligand skeletal contacts, such as intramolecular stacking interactions between phenyl rings, accounts for the conclusive considerations on the binary systems in solution discussed above [129].

At pH about 3.5, palladium(II) ions interact with the same *N*-$ArSO_2$ amino acids, giving rise to "cyclometallation" reactions which lead to the formation of unusual compounds, of formula $Na_2[Pd_4Cl_2(bsglyO,N,C)_2(bsgly\text{-}O,O')_2] \cdot 6H_2O$ (Fig. 25) and $Na_2[Pd_4Cl_2(tsglyO,N,C)_2(tsgly\text{-}O,O')_2] \cdot 4.5H_2O \cdot 2tsglyH$. Both structures consist of two tetrameric units, symmetry generated from two independent $[Pd_2Cl(tsglyO,N,C)(tsgly\text{-}O,O')]^-$ monoanions, in which the palladium(II) atoms show a slightly distorted square-planar coordination geometry. In the tetramer, two symmetrically related ligand molecules are monoanions with only the carboxylate group in the ionized form, which acts as *syn–syn* bridge, while the other amino acids present three active binding sites, the deprotonated sulphonamide nitrogen, the carbon atom of the aromatic ring in the *ortho* position to the sulphonyl group and the deprotonated carboxyl group, and two bridge Pd(II) atoms through the deproto-

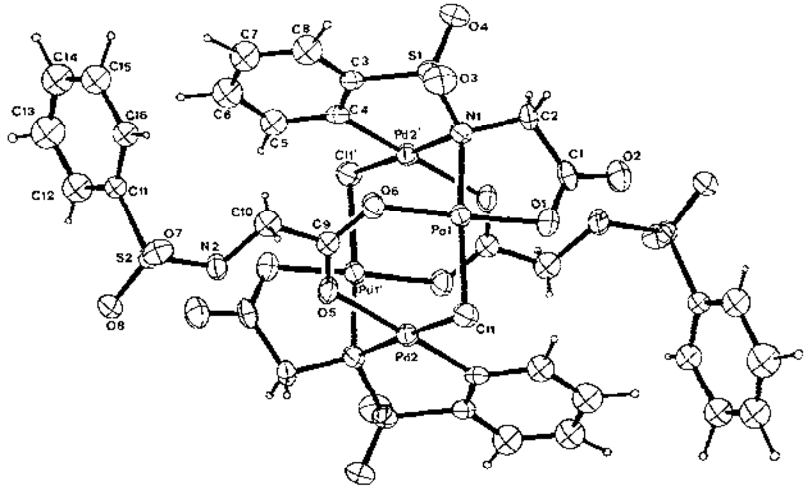


Fig. 25. ORTEP view of the two crystallographically independent tetramers of $[Pd_4Cl_2(bsgly\text{-}O,N,C)_2(bsgly\text{-}O,O')_2]^{2-}$ with numbering scheme and thermal motion ellipsoids (35%) for non-hydrogen atoms. The hydrogen atoms are represented as spheres of arbitrary radius [131].

nated sulphonamide nitrogen, which gives rise to two five-membered chelate rings. In the tsgly derivative, two neutral crystallographically independent tsglyH molecules are also present [131].

Some features of these structures are worth emphasizing as they demonstrate the coordinative versatility of *N*-ArSO$_2$-glycine: (i) two differently ionized forms of the coordinated ligands are present; (ii) the deprotonated sulphonamide nitrogen atom surprisingly acts as a bridging group (only one previous report exists on similar behaviour for a peptide nitrogen [134]; (iii) the formation of the N,O-glycine-like ring, as observed for *N*-ArSO$_2$ amino acids–metal(II) complexes (metal(II)=copper(II) [76], palladium(II) [128,129]) at high pH, in these cases do not prevent the cyclometallation reaction, unlike what is reported for simple amino acid complexes [135].

These results classify the *N*-ArSO$_2$-glycines into the cyclometallating ligands for palladium(II) ions since they satisfy the major requirements for cyclometallization: (a) the cyclometallated ring will contain five atoms, (b) the nitrogen atom is sterically hindered, (c) the carbon atom must be substituted by electrophilic attack, as indicated for phenyl-substituted nitrogen-containing ligands such as benzylamines, azobenzenes, benzoylamines, phenyldiimides, etc. [136].

### *(iv) General remarks*

(a) Co(II), Ni(II) and Zn(II) ions are ineffective in promoting amide nitrogen deprotonation in N-protected amino acids containing either a peptide or a sulphonamide group;

(b) in ternary bipy–zinc(II) ion–*N*-tosyl- and –*N*-phenylsulphonyl-glycine systems, the presence of a stable metal(II)–bipy species in solution activates sulphonamide nitrogen deprotonation, which initiates zinc(II) hydroxide precipitation.

(c) Cd(II) and Pd(II) ions give rise to amide nitrogen deprotonation in *N*-$ArSO_2$ amino acids in binary and ternary (bipy) systems in solution;

(d) in all the binary complexes of Co(II), Ni(II), Zn(II) and Cd(II) ions isolated in the solid state, the N-protected amino acids invariably act as unidentate ligands through one carboxylic oxygen atom, the peptide or sulphonamide groups being always involved in intra and/or intermolecular hydrogen bonding in crystal packing;

(e) the *N*-benzoyl-glycinate complexes are the most original, presenting very unusual and interesting structures;

(f) the Pd(II) ion separates binary solid compounds in which the *N*-$ArSO_2$ amino acids act as chelating N,O-bidentate ligands through one carboxylic oxygen and the deprotonated sulphonamide nitrogen atoms;

(g) the Pd(II) ion is the most effective among the metal(II) ions described in this review in displacing the nitrogen-bound hydrogen in *N*-$ArSO_2$ amino acids;

(h) under particular pH conditions (about 3.5), Pd(II) ions interact with the *N*-$ArSO_2$ amino acids, giving rise to "cyclometallation" reactions which lead to the formation of unusual compounds,

(i) in Table 10, a summary is given of the main structural parameters for the structurally known M(II) (M = Co(II), Ni(II), Zn(II), Cd(II) and Pd(II)) complexes discussed in Sect. E.

## F. CONCLUDING REMARKS

The reaction pathway proposed for explaining anticipated amide nitrogen deprotonation in metal–oligoglycine systems involves the initial chelation of the metal ion through the terminal amino nitrogen and the neutral amide oxygen, with closure of a five-membered ring, thus preventing metal hydrolysis [23,66,137].

On the other hand, for *N*-benzoyl-, *N*-acetyl- and *N*-benzyloxycarbonyl amino acids, which also possess a peptide group, the numrous experimental results invariably rule out nitrogen deprotonation in the presence of metal ions, even in strong alkaline media. This behaviour may be due to unfavourable structural conditions (e.g. the closure of seven-membered chelate rings) as well as to a weaker donor ability of the active sites (e.g. amidic and carboxylic oxygens) in these N-protected amino acids with respect to oligo-glycine ones, which make the formation of the starting complex very unlikely. Thus the only active site which could act as anchor remains the carboxylate group, and although solution carboxylate species are formed ($ML^+$), they present too low a stability ($\log K = 0.7$ to 1.8) to enhance the acidic character of the peptide nitrogen ($pK_{NH} = 14$) sufficiently to compete with metal hydrolysis in alkaline media.

The other class of N-protected amino acids discussed in this review is repre-

TABLE 10

Summary of the principal structural results for the M(II) (M = Co, Ni, Zn, Cd, Pd) complexes of N-protected amino acids

| Compound | Coord. geom.[a] | Chromophore | M–O (Å) | M–N (Å) | M–Oeq (Å) | M–$O_w$eq (Å) | M–$O_w$ax[b] (Å) | Aminoacid bond modes[c] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| $[Co(bzglyO)_2(H_2O)_3]_n \cdot 2nH_2O$ | t.d.o. | $O_6$ | | | 2.04 | 2.06 | $2.22_b$ | uni-$O_c$ | 104,105 |
| $[Ni(bzglyO)_2(H_2O)_3]_n \cdot 2nH_2O$ | s.t.d.o. | $O_6$ | | | 2.00 | 2.07 | $2.12_b$ | uni-$O_c$ | 105 |
| $[Zn(bzglyO)_2(H_2O)_3] \cdot 2H_2O$ | t.bi. | $O_6$ | | | 1.978(4) | 2.007(4) | 2.165(5) | uni-$O_c$ | 106 |
| $[Co(acglyO)_2(H_2O)_4]$ | s.t.d.o. | $O_6$ | | | 2.089(2) | 2.089(2) | 2.137(2) | uni-$O_c$ | 112 |
| $[Co(tsglyO)_2(H_2O)_4]$ | r.o. | $O_6$ | | | 2.100(4) | 2.077(5) | 2.082(4) | uni-$O_c$ | 99 |
| $[Zn(ts\text{-}\beta\text{-}alaO)_2(H_2O)_4]$ | s.t.d.o. | $O_6$ | | | 2.083(4) | 2.085(5) | 2.157(3) | uni-$O_c$ | 99 |
| $[Cd(ts\text{-}\beta\text{-}alaO)_2(H_2O)_4]$ | r.o. | $O_6$ | | | 2.285(5) | 2.287(6) | 2.283(6) | uni-$O_c$ | 120 |
| $Na_2[Pd(tsglyNO)_2]$ | t.s.pl. | $N_2O_2$ | 1.979(2) | 2.042(3) | | | | c.-(NO) | 129 |
| $Na_2[Pd(bsglyNO)_2] \cdot H_2O$ | t.s.pl. | $N_2O_2$ | 2.001(4) | 2.032(4) | | | | c.-(NO) | 130 |

[a] t.d.o. = tetragonal distorted octahedral; t.bi. = trigonal bipyramidal; s.t.d.o. = slightly tetragonally distorted octahedral; r.o. = regular octahedral; t.s.pl. = trans square planar.

[b] b. = bridging.

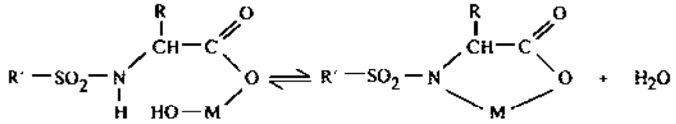
[c] uni-$O_c$ = unidentate oxygen carboxylic; c.-(NO) = chelate.

sented by *N*-tosyl-, *N*-phenylsulphonyl- and *N*-dansyl-α-amino acids, which undergo sulphonamide nitrogen deprotonation at pH values greater than 11. With Cu(II), Cd(II) and Pd(II) ions they should give rise to the "biuret reaction" [137]. Conversely, they form stable carboxylate and N,O-chelate complexes in the presence of these metal(II) ions from acidic to basic pH values, without metal hydrolysis, and sulphonamide nitrogen deprotonation occurs in the physiological pH range, as found for oligoglycines.

Taking a panoramic view of this survey for the *N*-ArSO$_2$ amino acids, the effectiveness of the carboxylic group as primary ligating group, although less than that of the amino group in oligoglycines, is fully demonstrated. This capability, together with the cooperative electrophilic effect of the ArSO$_2$ group on the amide nitrogen, causes much greater reduction of the deprotonation pH than occurs in peptides.

These experimental results clearly confute the opinions that the COO$^-$ cannot act as the effective primary ligating group and that the additional contribution of an SO$_2$–metal(II) ion interaction is required in the solution carboxylate complexes to activate sulphonamide nitrogen deprotonation [23], and strongly suggest that the carboxylate group plays an effective key role in the process acting as a primary binding group ("anchoring group") and decreasing the competition from the metal hydroxide precipitation.

As regards this problem, the involvement of an intermediate very stable mixed metal(II)-hydroxy species in the deprotonation equilibria of the *N*-ArSO$_2$ amino acids, interacting with the Cu(II), Cd(II) and Pd(II) ions, is particularly interesting. The experimental evidence that Cu(II), Cd(II) and Pd(II) ions give rise to mixed hydroxy carboxylate species at low pH values suggests that the OH ion bound to the metal may act as a Lewis base towards the nitrogen-bound hydrogen in the metal-induced sulphonamide deprotonation, as depicted in the scheme [128]



where R = H or alkyl and R′ = aryl. Therefore the metal ions that are predictable to be effective in sulphonamide deprotonation are those that form hydroxo species, [M(OH)]$^+$, at low pH (such as Cu(II) and Pd(II) ions [138–140]), or undergo metal hydroxide precipitation at high pH (such as the Cd(II) ion) so that the metal substitution for the sulphonamide hydrogen via the metal-bound hydroxy group may occur without competition from the metal hydroxide precipitation.

The deprotonation of the peptide nitrogen is promoted by the metal to a different extent following the order Pd(II) > Cu(II) > Ni(II) > Co(II) [132]. The metal-promoted deprotonation of the sulphonamide nitrogen in *N*-ArSO$_2$ amino acids follows the order Pd ≫ Cu > Cd > Zn, as also observed for oligopeptides [23], being

Co(II) and Ni(II) ineffective under the investigated experimental conditions. In all cases the Pd(II) ion is the most effective metal ion in substituting for the amide hydrogen.

In the ternary bipy systems of Cu(II), Cd(II) and Zn(II) ions, the metal(II)-promoted amide nitrogen deprotonation is determined by the presence of a very stable intermediate $[M(bipy)]^{2+}$ species, which enhances the "anchoring effect" of the carboxylate group of $ArSO_2$ amino acids [141].

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