Thermodynamics of Formation of Binuclear Complexes of some Sulphur-containing Dipeptides with Silver(I) and Copper(II). Crystal Structure of a Methionyl-*S*-methylcysteine Complex of Copper(II) †

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Formation constants are reported at 25 °C and I = 0.10 mol dm^{-3} (KNO_3) for binuclear complexes of nine sulphur-containing dipeptides with Ag^I and Cu^{II}, together with the formation constants of the parent Cu^{II} complexes. Dipeptides (HL) studied were Gly-L-Met, L-Met-Gly, L-Met-L-Met, L-Met-D-Met, Cys(Me)-L-Met, Cys(Me)-D-Met, L-Met-Cys(Me), D-Met-Cys(Me), and Cys(Me)-Cys(Me) [Met = methionine, Cys(Me) = *S*-methyl-L-cysteine]. The major ternary complex with dipeptides of two sulphur-containing amino acids of the same chirality was $[AgCuH_{-1}L]^+$. When the amino-acid residues were of opposite chirality, ternary complexes were less stable by a factor of over 20, giving very dramatic stereoselectivity. The crystal structure of $[CuH_{-1}\{$L-Met-Cys(Me)O$\}]$ [L-Met-Cys(MeO) = L-methionyl-*S*-methylcysteinate(1−)] is reported. The copper atom is five-co-ordinate (square pyramidal) with no Cu–S interaction.

A polynuclear complex containing two or more metal ions can be formed if the ligand co-ordinated to a metal ion still has the ability to donate further electrons. This is the case when the co-ordinated donor atom still possesses unshared pairs of electrons, when the number of donor groups exceeds the maximum co-ordination number of the first metal ion, or when the steric arrangement of the donor atoms makes it impossible for all donors to co-ordinate with the same metal ion. A further factor encouraging polynuclear complex formation is the presence in the ligand molecule of donor centres which differ considerably in donor character, *e.g.* class (a) and class (b) or 'hard' and 'soft' character. Polynuclear complexes can contain identical metal ions, different spin states or valencies of the same metal ion, or different metal ions.

Many binuclear complexes containing Cu^I/Cu^{II} have been characterized using, for example, cryptate ligands[1–4] or D-penicillamine.[5] Compartmental ligands contain two adjacent but dissimilar co-ordination compartments. Using these ligands a wide range of binuclear complexes have been prepared containing both identical (*e.g.* Cu_2, Ni_2) and dissimilar (*e.g.* Ni/Cu, Cu/UO_2) metal ions.[6,7] As a general rule, heterobinuclear complexes require the presence of two complexing sites of different donor properties (*e.g.* S and N), although there may be exceptions to this rule.[8] Sulphur-containing amino acids contain two such different donor sites. In solutions of amino acids containing thioether donor centres, Cu^{II} co-ordinates almost exclusively to N and O sites while Ag^I shows a marked preference for S. This has been demonstrated in spectroscopic and potentiometric studies of mixed Cu^{II}/Ag^I complexes of L-methionine (Met),[9,10] although these studies reported very different solubilities for the binuclear species.

If it is assumed that the bis-complex, $[Cu(MetO)_2]$ [MetO- = methioninate(1−)], involves glycine-like (NO) co-ordination only, then the S-containing side-chains will be both on the same side of the co-ordination plane in $[Cu(L\text{-}MetO)_2]$ if co-ordination is *trans* or on opposite sides if co-ordination is *cis*. The opposite will be true for [Cu(L-MetO)(D-MetO)].

† *Supplementary data available* (No. SUP 56392, 6 pp.): H-atom co-ordinates, thermal parameters, full bond lengths and angles. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1986, Issue 1, pp. xvii—xx. Structure factors are available from the editorial office.

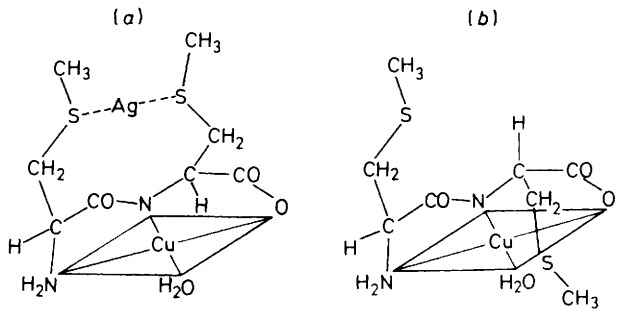

Figure 1. Structures of (*a*) $[CuH_{-1}\{$Cys(Me)-Cys(Me)O$\}]$ (showing how Ag^+ can be co-ordinated) and (*b*) $[CuH_{-1}\{$Cys(Me)-D-Cys(Me)O$\}]$

Binuclear complex formation with Ag^I bonded to the two sulphur atoms can only take place when both sulphur donors are on the same side of the plane but *cis–trans* isomerism would permit binuclear complex formation with both chirally pure and racemic isomers of $[Cu(MetO)_2]$. With dipeptides such as Met-Met (HL) the normal complex with Cu^{II} at intermediate pH, $[CuH_{-1}L]$, does not allow such isomers. The complex with L-Met-L-Met (Met-Met, chirality is assumed to be L unless stated otherwise) will have both S atoms on the same side of the plane while L-Met-D-Met (Met-D-Met) will have the S atoms on opposite sides as shown in Figure 1. Hence only Met-Met would be able to form a stable, discrete complex, $[AgCuH_{-1}L]^+$. The nearest comparable complex with Met-D-Met would either contain a single Ag–S bond or would be a polymer.

We report the results of a study of the binuclear Cu/Ag complexes of the range of dipeptides: Gly-Met and Met-Gly, Met-Met and Met-D-Met, Cys(Me)-Met and Cys(Me)-D-Met, Met-Cys(Me) and D-Met-Cys(Me), and Cys(Me)-Cys(Me) [Gly = glycine, Met = methionine, and Cys(Me) = *S*-methyl-L-cysteine]. This necessitated the measurement of formation constants of the parent Cu^{II} complexes; those of the Ag^I complexes have already been published.[11] Formation constants for the parent Cu^{II} dipeptide complexes showed the presence of only weak Cu–S co-ordination, and to provide further evidence for the absence of such interaction in the solid state we report

the crystal structure of the complex $[CuH_{-1}L]$ where L = L-Met-Cys(Me)O.

Experimental

The synthesis of the ligands, together with the determination of formation constants of hydrogen ion and Ag^{I} complexes has been described previously.[11]

Potentiometric Studies.—Complex formation constants were calculated from titrations in the presence of Ag^{I} and Cu^{II} following changes in both hydrogen ion and silver ion concentrations with glass and Ag–AgCl indicator electrodes respectively,[12] both calibrated in terms of concentrations.[13] Perchloric acid (0.001 mol dm^{-3} in 0.10 mol dm^{-3} KNO_3) was used as a standard for hydrogen ion concentrations. The potentials of the electrodes were measured relative to a saturated $HgSO_4$ reference electrode, linked through a K_2SO_4 salt bridge. Concentrations used were 0.001 to 0.003 mol dm^{-3} and the ionic strength of all solutions was adjusted to 0.10 mol dm^{-3} with KNO_3.

Formation constants were calculated using the computer program MINIQUAD,[14] which can handle 'two-electrode, two metal ion' titrations. Refinement was carried out both with constants for parent complexes fixed and with all metal complexes 'floating'. Differences in calculated constants between the two methods were generally less than 0.1 log units, confirming the stoicheiometry of the binuclear species. Constants calculated with constants for the parent complexes fixed have been accepted as the more reliable.

Crystal Structure Determination.—Data were collected on a Syntex $P2_1$ diffractometer using Mo-K_α radiation. Cell dimensions and their standard deviations were obtained by least-squares treatment of the setting angles for 15 reflections having $35 < 2\theta < 40°$. The structure analysis used 1 718 independent reflections in the range $5 < 2\theta < 40°$ and a further 130 reflections were 'unobserved'. Lorentz polarization and absorption corrections were applied. The structure was solved with Patterson and difference syntheses followed by full-matrix least-squares refinement. Refinement for atoms other than hydrogen converged at $R = 0.0384$ and a difference map allowed 31 of the 32 H atoms to be located. On calculating the position of the last H atom the co-ordinates of all the atoms were again refined to $R = 0.0242$.

Crystal data. $C_9H_{16}CuN_2O_3S_2$, $M = 327.9$, monoclinic, $a = 10.535(2)$, $b = 8.836(2)$, $c = 14.188(2)$ Å, $\beta = 99.08(2)°$, $U = 1\,304.3(5)$ Å^3, space group $P2_1$, $Z = 4$, $D_c = 1.68$ g cm^{-3}, Mo-K_α radiation, $\lambda = 0.710\,69$ Å, μ(Mo-K_α) = 19.83 cm^{-1}.

Results and Discussion

Values for the formation constants of the hydrogen ion, and Cu^{II} and Ag^{I} complexes of the ligands studied are given in Table 1. Data on the Cu^{II} complexes have not been reported although the structures of the Ag^{I} complexes have been discussed previously.[11] Also included in Table 1 are values for the binuclear complexes which are the main topic of study here.

The first point to establish is the extent of Cu^{II}–S co-ordination with dipeptides containing thioether side-chains. At low pH simple dipeptides co-ordinate to Cu^{II} through the N atom of the terminal $-NH_2$ group and the carbonyl oxygen of the neighbouring peptide bond to give the [CuL] complex (charges are omitted from now onwards for clarity). Around pH 5 the Cu^{II} promotes ionization of the proton on the peptide nitrogen to allow formation of a Cu–N^- bond in place of the bond to the carbonyl O atom. This, together with the bond to the carboxylate O^-, forms the planar tridentate complex $[CuH_{-1}L]$.[15] Donor centres in short peptide side-chains can only co-ordinate to the Cu^{II} axially unless they can displace one of the co-ordination centres in the plane. Copper(II) complexes of a number of S-containing amino acids and dipeptides have been studied by potentiometry,[16] n.m.r.,[17] and e.s.r.[18] and results show only very limited interaction between Cu^{II} and the S atom of methionine with somewhat more (but still weak) interaction with Cys(Me). With dipeptides, the Cu^{II}–S interaction was found to be greater for Cys(Me)-Gly than for Gly-Cys(Me).[16] The Cu^{II} can be 'forced' to bond to the S of Met using micro-emulsions[19] or very low pH values[20] but these complexes rapidly revert to normal modes of co-ordination in aqueous solutions of intermediate pH. In the solid state the crystal structures of *trans*-$[Cu(MetO)_2]$[21] and of $[CuH_{-1}$-(Gly-MetO)][22] show no S atom co-ordination.

We have confirmed the absence of significant Cu^{II}–S interaction in S-containing dipeptides. E.s.r. spectroscopy of aqueous solutions at room temperature showed the spectra to be very similar to those for simple Cu–dipeptide complexes but it was impossible to obtain results at liquid nitrogen temperatures (and hence values for $g_{\|}$) with the equipment available. Comparison of the Cu^{II} complex formation constants with the protonation constants given in Table 1 demonstrates the absence of significant stabilization of S-containing dipeptides relative to Gly-Gly or Gly-Met, with the possible exception of dipeptides containing Cys(Me). Cu^{II}–S interaction in S-

Table 1. Formation constants of parent binary complexes and of binuclear Cu^{II}/Ag^{I} complexes of some dipeptides at 25 °C and $I = 0.10$ mol dm^{-3} (KNO_3). Standard deviations are given in parentheses

	log β values							
Dipeptide	HL[a]	[CuL]	$[CuH_{-1}L]$	$[AgH_2L]$[a]	[AgHL][a]	[AgCuL]	$[AgCuH_{-1}L]$	$[(AgCuL)_2H_{-1}]$
Gly-Met[b]	8.22	5.98(3)	1.743(2)	17.4	11.91		5.473(7)	18.64(2)
Met-Gly[b]	7.56	5.73(5)	1.454(4)	15.47	10.72		4.72(1)	17.54(2)
Met-Met	7.43	5.40(4)	1.695(3)	16.31	11.86	10.94(4)	6.754(7)	
Met-D-Met	7.63	5.66(4)	1.396(3)	17.3	12.40		5.54(2)	
Cys(Me)-Met	7.03	5.51(3)	1.825(1)	14.55	11.02	10.71(1)	6.876(5)	
Cys(Me)-D-Met	7.23	5.34(3)	1.524(3)	15.51	11.76		5.29(1)	
Met-Cys(Me)	7.40	5.49(3)	1.755(3)	16.61	12.05	10.9(1)?	6.807(6)	
D-Met-Cys(Me)	7.62	5.42(3)	1.392(3)	17.1	12.40		5.31(1)	
Cys(Me)-Cys(Me)	7.03	5.32(3)	1.814(2)	14.75	11.53	11.1(1)?	7.815(4)	

[a] Values from ref. 11. [b] Values reported in ref. 16: Gly-Met, log $\beta_{HL} = 8.19$, log $\beta_{CuL} = 5.8$, log $\beta_{CuH_{-1}L} = 1.81$; Met-Gly, log $\beta_{HL} = 7.56$, log $\beta_{CuL} = 4.7$, log $\beta_{CuH_{-1}L} = 1.48$.

Table 2. Fractional atomic co-ordinates for [CuH_{-1}{Met-Cys(Me)O}] with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
Cu(1)	0.041 17(5)	0*	0.098 75(4)	C(2)	0.295 2(4)	−0.026 4(6)	0.189 7(3)
Cu(2)	0.540 15(5)	−0.031 98(7)	0.091 61(4)	C(3)	0.224 2(5)	−0.236 5(6)	0.087 5(4)
S(1)	0.405 7(2)	0.391 5(2)	0.383 4(1)	C(4)	0.104 6(5)	−0.268 5(6)	0.014 7(4)
S(2)	0.125 1(2)	−0.440 9(2)	0.208 1(1)	C(5)	0.279 6(5)	0.116 8(7)	0.340 7(4)
S(11)	0.958 6(2)	0.177 7(2)	0.412 7(1)	C(6)	0.271 1(6)	0.268 3(7)	0.390 9(4)
S(12)	0.642 3(2)	−0.469 9(2)	0.288 4(1)	C(7)	0.521 6(6)	0.319 7(9)	0.483 5(5)
O(1)	0.411 0(3)	−0.064 9(4)	0.206 9(2)	C(8)	0.256 9(5)	0.373 3(6)	0.151 6(4)
O(2)	0.012 4(4)	−0.175 1(4)	0.006 2(3)	C(9)	0.135 6(7)	−0.322 4(9)	0.311 6(5)
O(3)	0.106 3(3)	−0.388 8(4)	−0.033 0(2)	C(11)	0.744 7(5)	0.110 2(6)	0.220 3(4)
O(11)	0.909 0(3)	−0.075 4(4)	0.208 2(2)	C(12)	0.792 1(4)	−0.042 7(6)	0.187 8(3)
O(12)	0.514 9(3)	−0.222 6(4)	0.015 2(3)	C(13)	0.728 4(5)	−0.269 2(6)	0.097 9(4)
O(13)	0.609 3(3)	−0.439 8(4)	−0.012 4(3)	C(14)	0.607 6(5)	−0.313 8(6)	0.027 4(4)
N(1)	0.117 2(4)	0.157 7(5)	0.195 1(3)	C(15)	0.710 8(5)	0.098 9(6)	0.320 8(4)
N(2)	0.200 6(4)	−0.099 2(5)	0.138 8(3)	C(16)	0.819 3(6)	0.056 2(7)	0.399 0(4)
N(11)	0.658 8(4)	0.154 9(5)	0.154 6(3)	C(17)	0.892 0(7)	0.353 7(9)	0.439 9(6)
N(12)	0.700 1(4)	−0.126 5(5)	0.140 8(3)	C(18)	0.767 8(5)	−0.397 1(6)	0.168 2(4)
C(1)	0.255 5(5)	0.123 8(6)	0.231 8(4)	C(19)	0.638 5(7)	−0.333 6(8)	0.320 4(6)

* Co-ordinate fixed.

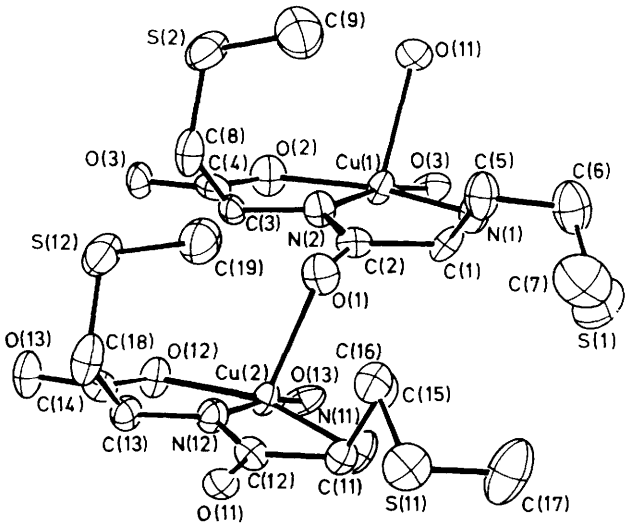

Figure 2. ORTEP drawing of the complex [CuH_{-1}{Met-Cys(Me)O}]

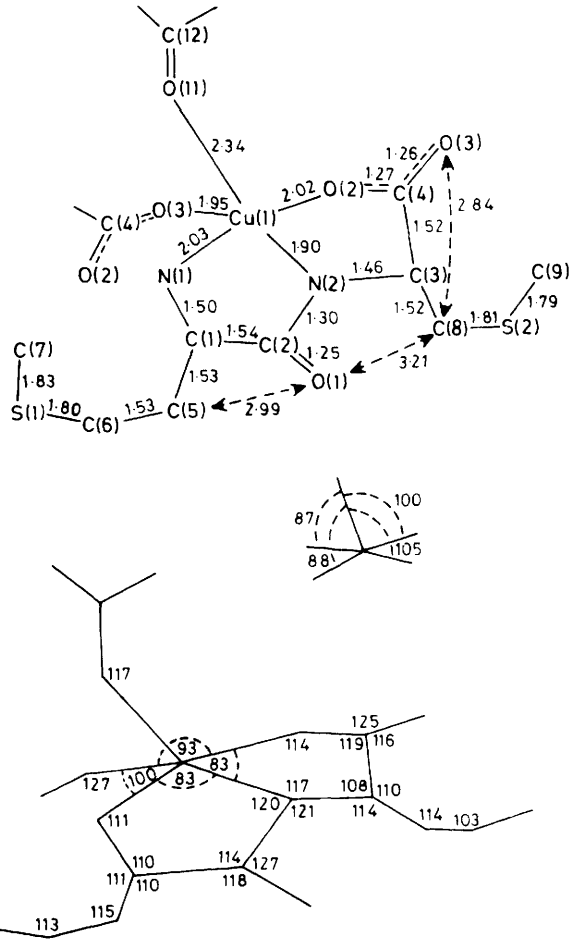

Figure 3. Bond lengths (Å) and bond angles (°) about the Cu(1) unit of [CuH_{-1}{Met-Cys(Me)O}]

containing dipeptides has been discussed previously,[16,23] and our results support the conclusion that while interaction is insignificant in [CuL] complexes with Met-Gly, Gly-Met, and Gly-Cys(Me) it is indeed significant with Cys(Me)-Gly. Results reported in Table 1 are in good agreement with those reported for Gly-Met and Met-Gly,[16] with the exception of the stability constant for the [CuL] complex of Met-Gly. However this is only a very minor species in the equilibrium, hence reported formation constants may contain significant systematic errors. Comparison is complicated by stereoselective effects in the [CuH_{-1}L] complexes which generally favour the formation of complexes with dipeptides having amino acid residues of the same optical hand (here referred to as 'chiral') rather than *meso* dipeptides.[24] The results reported in Table 1 agree well with this generalization. This stereoselectivity amounts to 0.3 log units in the diastereoisomeric pairs studied.

The crystal structure of [CuH_{-1}{Met-Cys(Me)O}] was determined using *X*-ray diffraction in order to check on the possible existence of Cu^{II}–S interaction in the solid state since no determinations have been reported on Cu^{II}–dipeptide complexes containing two potential S donors. Since other evidence suggests that Cu^{II} interaction with the Cys(Me) sulphur is more likely than with that of Met, a dipeptide containing a sulphur of each type was selected. It proved impossible to prepare suitable crystals of the *meso* analogue, [CuH_{-1}{D-Met-Cys(Me)O}], or

of the binuclear cationic species $[AgCuH_{-1}L]^+$. The crystal structure is shown in Figure 2, using the system numbering recommended by Freeman *et al.*,[25] and the atomic co-ordinates are given in Table 2. Figure 3 shows the inter-atomic distances and angles.

The unit cell contains two complex molecules. Both Cu^{II} ions are five-co-ordinate, with square-pyramidal geometry. Equatorial co-ordination is *via* N(amino), N(peptide), and O(carboxylate) from one dipeptide molecule and the un-co-ordinated carboxylate oxygen of a dipeptide molecule in an equivalent neighbouring unit cell. The axial site is occupied by an O(peptide) atom of the other molecule of the unit cell. Hence each dipeptide molecule participates in the co-ordination of three Cu^{II} ions while each copper is bonded to three different dipeptide molecules. The axial Cu–O bond is comparatively short (2.34 Å compared to the planar Cu–O bond of 2.02 Å) and the Cu^{II} ion is raised a little above the peptide co-ordination plane making the chelate rings puckered with the dihedral angles close to those found by Freeman for comparable complexes.[25] The two complex molecules are very similar in geometry, the most important difference being in the puckering of the NH_2-terminal chelate rings about Cu(1) and Cu(2). The effect (or cause) of this puckering can be seen in the torsion angles about C(α) and C(β) in the side chains (Figure 2). Calculated torsion angles in the CO_2^--terminal chelate rings [the angles Cu(1)–C(3)–C(8) and Cu(2)–C(13)–C(18)] are similar, being 129.6° and 132.6° while those in the NH_2-terminal chelate rings [angles Cu(1)–C(1)–C(5) and Cu(2)–C(11)–C(15)] are significantly different at 128.8° and 107.5°. However, the most important point to emerge from the structure is the total absence in the crystalline state of Cu–S interaction with both the Met and the Cys(Me) side-chains.

Ternary complexes formed between the dipeptides studied, Cu^{II}, and Ag^I are reported in Table 1. The major species was always $[AgCuH_{-1}L]$. In some cases inclusion of the species [AgCuL] and $[(AgCuL)_2H_{-1}]$ improved the statistics of the fit significantly although they were never more than minor components (always <30%) of the equilibrium mixtures. The $[(AgCuL)_2H_{-1}]$ species were found only with the dipeptides containing one S donor (Gly-Met and Met-Gly) while the [AgCuL] complexes were found only with 'chiral' dipeptides.

The major ternary species, $[AgCuH_{-1}L]$, is significantly more stable when the dipeptide has S-amino acid residues of the same chirality. In this complex the side-chains containing the sulphurs both lie on the same side of the the co-ordination plane so allowing them to co-ordinate linearly to an Ag^I ion as shown in Figure 1. When the component amino acid residues are of opposite chirality (*meso*) the sulphurs cannot both co-ordinate to the same Ag^I ion, hence the complex would be expected to be less stable. In practice, with *meso* dipeptides, precipitation took place around pH 7. The results given in Table 1 show that their stabilities (log β = 5.3—5.5) are comparable to those for the analogous complex with Gly-Met (log β = 5.47) suggesting that only one S donor is co-ordinated, probably the sulphur from the O-terminal residue. The ternary complex with Met-Gly is significantly less stable than with Gly-Met (Δ log β =

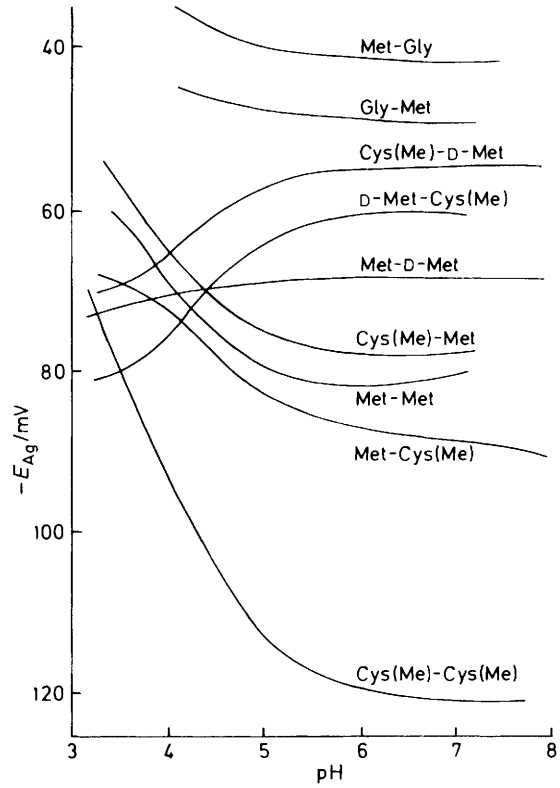

Figure 4. The relationship between $-E_{Ag}$ and pH for Cu/Ag titrations with dipeptides

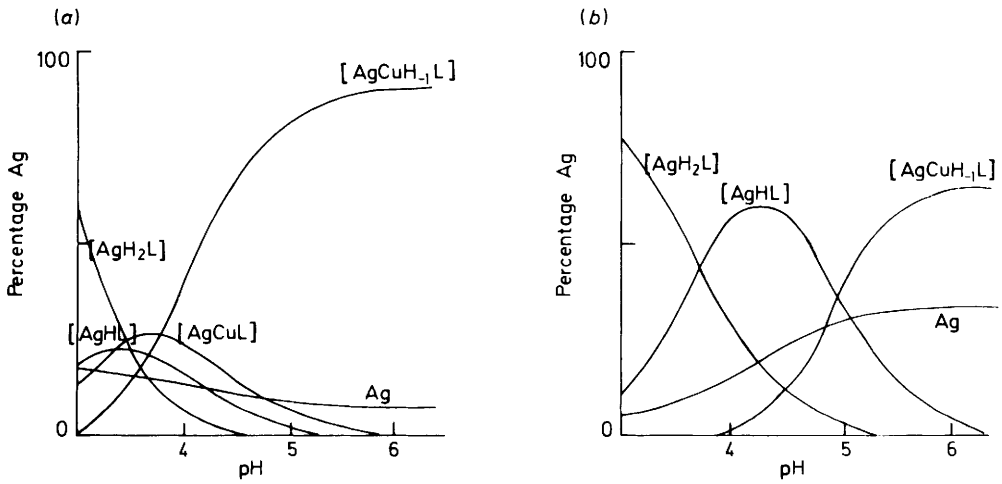

Figure 5. Species distributions curves for 1:1:1 mixtures (10^{-3} mol dm^{-3}) of Cu^{2+}, Ag^+, and dipeptide: (*a*) L = Cys(Me)-MetO, (*b*) L = Cys(Me)-D-MetO

0.75) demonstrating that the side-chain S is a better donor to silver when at the O-terminal end of the dipeptide. This effect is also observed in the parent binary complexes with Ag^{I}.[11] Ternary complex formation is also favoured by the shorter side-chain of Cys(Me) rather than that of Met, which contains an additional methylene group. This again parallels the parent binary Ag^{I} complexes. In ternary complexes involving Cys(Me) the Cu^{II} and Ag^{I} ions will be closer together than in the Met analogues but, in the $[CuH_{-1}L]$ species, the shorter chain length of Cys(Me) will mean that the S donors are presented in more suitable positions for co-ordination to Ag^{I} without the greater randomness possible with the longer Met chain.

The different behaviour of the chiral and *meso* dipeptides on ternary complex formation is best demonstrated in Figure 4 where $-E_{Ag}$ is plotted against pH for the systems studied. Two classes of curve are formed, those with the chiral dipeptides show a negative gradient while those with *meso* ligands show a positive gradient. The curves for Met-Gly and Gly-Met tend to resemble those for the chiral dipeptides but the gradient is smaller. These curves show that, as the pH is raised, complexation of Ag^{I} increases with chiral ligands but actually tends to decrease with *meso* ligands. With these ligands at low pH, Ag^{I} is co-ordinated in the form of $[AgH_2L]$ and [AgHL] species. As the pH is raised Cu^{II} displaces the Ag^{I} to form the stable $[CuH_{-1}L]$ complex with only limited ternary complex formation. This is demonstrated in the species distribution curves for Cys(Me)-Met and Cys(Me)-D-Met with Ag^{I} shown in Figure 5 where it is seen that more Ag^{I} is co-ordinated in total at low pH than at high pH. In contrast, with the chiral dipeptides, the ternary complex $[AgCuH_{-1}L]$ is much more stable. This has the effect of reducing the concentrations of both $[CuH_{-1}L]$ and free silver ion significantly; hence the negative gradient for the plot of E_{Ag} against pH. With Cys(Me)-Met at pH 6, about 10% of the ligand is held as $[CuH_{-1}L]$ leaving 10% of the total silver as the free ions in a 1:1:1 mixture (Figure 5). With Cys(Me)-Cys(Me) the higher stability of the $[AgCuH_{-1}L]$ complex means that virtually all the silver and the dipeptide is in this form with a negligible concentration of $[CuH_{-1}L]$. The [AgCuL] species included with the chiral dipeptides has only a short range of existence (pH 3—5).

Figure 4 shows different variation of free silver ion concentration with pH for *meso* dipeptides (positive gradient) and Gly-Met and Met-Gly (negative gradient), while it is probable that both classes are bonded similarly with one Ag–S bond. This arises from the formation of stable protonated complexes ($[AgH_2L]$ and [AgHL]), particularly with dipeptides containing two sulphur donors, and also stereoselectivity in the [AgHL] species which favours the *meso* complexes.[11] As a result more silver is co-ordinated to 'two-sulphur' dipeptides at low pH than to the 'one-sulphur' ligands.

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