5. *Complexes of Biochemical Interest*

PS5.1 — MO

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METAL COMPLEXES OF SULFUR-CONTAINING LIGANDS OF BIOLOGICAL INTEREST: *S*-METHYL-L-CYSTEINE, α-LIPOIC ACID AND GLUTATHIONE

S-methyl-L-cysteine (SMC) offers three possible binding sites for metal atoms: The carboxylate group, the amino nitrogen atom and the thioether linkage. Since sulfur atoms are soft bases, they are expected to interact most favorably with soft acids as Hg(II), Pt(II), Ag(I) or Cu(I), but to a less extent with borderline acids as *e.g.* Cu(II).
We have grown single crystals of a copper(II) complex *Cu(SMC)$_2$* from solution on the surface of solid copper(II) hydroxy salts. The crystal structure determination ($R = 0.045$, $R_w = 0.052$) confirms spectroscopic evidence that the thioether sulfur is not coordinated to copper(II), even though there is a potentially favorable five-membered chelate ring with sulfur and nitrogen as coordinating atoms. Bridgeing of the copper centers by carboxylate groups leads to a two-dimensional polymeric structure approximately isostructural with its cadmium analogue [1]. The copper(II) atom exhibits a (4+2) tetragonally elongated CuN_2O_4 coordination octahedron.
α-Lipoic acid (LIP, DL-6,8-thiooctic acid) is a biomolecule widely distributed in animals and plants. Obviously there are two binding sites for metal atoms: The carboxylate group and the disulfide moiety.
Single crystals of a zinc complex, *Zn(LIP)$_2$·2H$_2$O*, were grown on the surface of solid zinc hydroxy salts. The crystal structure determination ($R = 0.068$, $R_w = 0.084$) proofs the occurence of isolated molecules $[Zn(LIP)_2(H_2O)_2]$ with the carboxylate groups acting as bidentate ligands. As suggested [2] there is no interaction of the disulfide moiety of α-lipoic acid with the metal atom. The coordination geometry of the zinc(II) atom is a ZnO_6 octahedron with pronounced distortion.
This is the first crystal structure reported of a metal complex of lipoic acid.
Glutathione (GSH): A copper(II) complex with the formula *Cu(II)$_2$GSSG·6H$_2$O* could be isolated. From the interpretation of UV- and EPR-spectra it seems plausible that this complex exhibits a dimeric structure with the disulfide moiety linking two copper(II) atoms as it is found in $Cu(II)_2GSSGNa_4 \cdot 6H_2O$ [3].

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PS5.2 — TH

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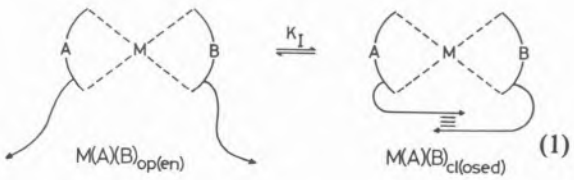
INTRAMOLECULAR HYDROPHOBIC AND STACKING INTERACTIONS IN BINARY AND TERNARY AMINO ACID COMPLEXES

Selectivity is one of the outstanding features of biological systems; it is often caused by non-covalent interactions, like aromatic-ring stacking or hydrophobic interactions [1]. After our recent observations [2-4] that both these types of intramolecular ligand-ligand interactions in mixed ligand complexes may be promoted by the addition of ethanol or dioxane to an aqueous solution of these complexes, we screened the stability data available in the literature for evidence of such intramolecular interactions in binary and ternary amino acid complexes.

The considered intramolecular equilibrium is schematically represented in (1).



(1)

The position of this equilibrium is independent of the concentration; it is quantified by the dimensionless equilibrium constant K_I (eq. (2)),

$$K_I = [M(A)(B)_{cl}]/[M(A)(B)_{op}] \qquad (2)$$

and this constant may be calculated from the stability data obtained from potentiometric pH titrations; the percentage of the «closed» isomer follows from K_I [1,5,6].

There are two careful studies available, which deal with the effect of dioxane on the stability of amino acid complexes: in one [7] the Cu^{2+}/alaninate (Ala^-) system is described and in the other [8] the Cu^{2+}/leucinate (Leu^-) system. For both systems complex stability increases with increasing amounts of dioxane, but the $Cu(Leu)_2$ complex is in the dioxane-water mixtures by 0.2 to 0.7 log units more stable than expected [3]. This additional stability increase may be attributed to intramolecular hydrophobic interactions between the isopropyl residues in $Cu(Leu)_2$; the extent of this interaction (eq. (1): A = B = Leu) changes in dependence on the amount of dioxane added to water: $Cu(Leu)_{2/cl}$ reaches 21% in water, 81% in 50% (v/v) dioxane-water, and 64% in 70% (v/v) dioxane-water (I = 0.1; 25°C) [3]. This shows that addition of some dioxane *favors* the intramolecular hydrophobic interaction in $Cu(Leu)_2$, while high concentrations of the organic solvent (>60%) destabilize it. This observation of an initial promotion of the interaction contrasts with the common experience made at simple unbridged adducts: they are always destabilized by the addition of dioxane or other organic solvents [4,9]. In several mixed ligand complexes [3,4], however, intramolecular stacking is also promoted by the addition of ethanol or dioxane.

The stability data of other binary and ternary metal ion/amino acid systems are summarized in the Table; they provide further evidence that hydrophobic and aromatic-ring stacking interactions in complexes of amino acids with suitable side chains are quite common.

It must be mentioned in this connection that the increased stability in aqueous solution of the Cu^{2+} bis-complexes of phenylalanine, tyrosine and similar amino acids has been repeatedly attributed to Cu^{2+}/aromatic-ring interactions [10,11]. However, the often used argument based on the *solid*-state structures is not conclusive, because even in the solid state the interaction is weak, if it exists at all; this follows from two different crystal structure analyses of the bis(L-phenylalaninato) copper(II) complex: in one case [12] the phenyl ring is located below Cu^{2+}, while in the other it is not [13]. In addition, in a recent study [14] of Pd^{2+} complexes it is shown that the decreasing interaction energies in the complexes follow the order phenyl-aromatic > phenyl-propyl (or