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Looking for the missing link between the chemistry and the biology of Cu-diimine compounds as cytotoxic agents

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Diimines, such as phenanthroline (phen) and their derivatives, are extensively studied in medicinal inorganic chemistry searching for new antitumor compounds. [1] Differentiating the biological effects of metal ions versus their coordinated ligands can be difficult in coordination compounds, especially for those formed by labile ions as Cu(II). Whether the cytotoxic activity of diimine coordination compounds results from the intact complex, or the ligand itself, if the metal ion transfers the ligand into the cell, or if the coordination is lost in the culture media, are still issues of debate. [2] Our research group is devoted to finding new coordination compounds with antitumor activity, especially of Cu(II). [3] As a part of it, we are directing our efforts to elucidate the role of the different species of Cu-diimine-coligands systems in the biological activity. In this work we present the obtained results for the Cu-diimine-dipeptide system (diimine: phen, neocuproine and tetramethylphen and dipeptide: ala-gly and ala-phe), which are potent cytotoxic agents on several tumor cell lines. Equilibrium constant values were determined by potentiometry, including studies of ligand protonation and Cu(II) hydrolysis, Cu-diimine, Cu-dipeptide and Cu-diimine-dipeptide formation. Results show that ternary species [Cu(dipeptide$_{\text{H-1}}$)(diimine)], are formed even at micromolar concentration, *i.e.* the conditions of the cellular studies, especially for neocuproine. We went on to study the interaction of the binary and ternary species with bovine albumin, by UV-vis and EPR spectroscopy, finding that the complex retains its identity, that is, ligands remain coordinated in presence of high concentrations of albumin. Finally, the cytotoxicity of the ligand (determining IC50) and complexes was studied under different conditions to asses the relevance of the different species, evidencing the central role of the Cu-diimine complex for the activity of the diimine itself and the other species.

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