Volume: 2
Year: 2012
Symposium Edition: XXIII

ISMEC GROUP SERIES
http://mat520.unime.it/ismecacta/
ISSN: 2239-2459

ISMEC2012

International Symposium on Metal Complexes

Lisbon 18-22 June

* Acta of the International Symposia on Metal Complexes

INSTITUTO SUPERIOR TÉCNICO
Universidade Técnica de Lisboa

Coordination abilities of mono and multi-histidinic and glutamate peptide fragments towards manganese(II) and cobalt(II)

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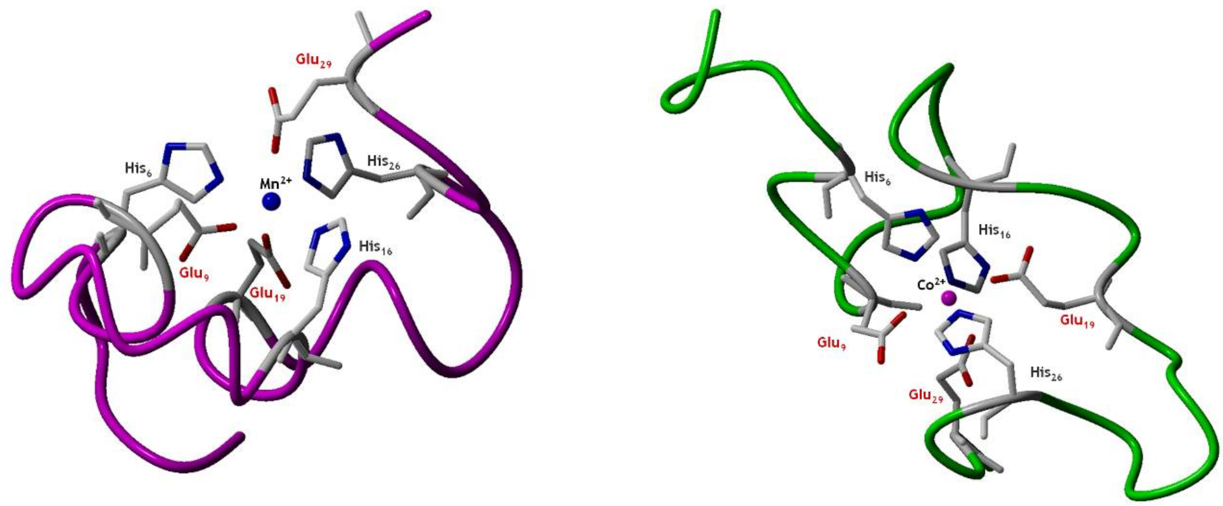
It is known that rich repeat domains in peptides can be of interest as the models for the study of molecular phenomena related to metal ion binding in proteins involved in neurodegenerative disorders. Imbalances in transition metal ions are assumed to contribute to the conversion of the multi-histidinic amyloid β-peptide (Aβ) from its soluble form to an amyloidogenic form, and to Aβ deposition. Of these ions, it has been reported that manganese binding to PrP is detrimental and causes a conformational change in the protein, suggesting that manganese binding could potentially play a role in prion disease progression *in vivo*. It appears that PrP is less stable on binding manganese and quickly converts to a misfolded form. The binding of manganese to PrP potentially results in the conversion of the protein to an abnormal isoform with properties reminiscent of PrP^{sc}. In particular, although PrP can bind the same number of manganese atoms as of copper atoms, the resulting protein becomes proteinase resistant, forms fibrils and loses function.[1,2]

Regarding cobalt, a novel low-affinity binding site for Co(II) was discovered between PrP residues 104 and 114, with residue His_{111} being the key amino acid for coordinating Co(II).[3] Thus, despite the interest in manganese and cobalt binding to PrP, a thorough analysis of the interaction of both metals with proteins related to brain pathies has not yet been reported. The $(T_1R_2S_3R_4S_5H_6T_7S_8E_9G_{10})_3$ fragment from Cap43 protein, which is induced by metal ions, is characterized by a decarepeat domain comprising three decapeptide units with one histidine and one glutamate residue in each repeat. Therefore the study of the interaction of the 30-aminoacid peptide from Cap43 protein with metal ions can contribute to the understanding of the crucial role of multi-imidazol and glutamate sites in the protein coordination processes and the possible role of divalent metal ions in the pathogenesis of prion disease and other related protein pathies.[4-8]

Here we present our recent results on the Cobalt(II) and Manganese(II) complexes of terminally protected mono- and multi-histidine-glutamate peptides studied by combination of potentiometric measurements and spectroscopic techniques (NMR, UV-Vis and EPR). Metal complexation induces important structural changes with the C-terminal portion of the ligand, constraining it to leave its disordered conformation and promoting side chain orientation. Our results give rise to a molecular model of the induced structure for the peptides complexed with cobalt and manganese.



Models of the most likely coordination spheres of Mn(II) and Co(II) with a multi-histidine-glutamate peptide fragment.

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