MOLECULAR ASPECTS OF CHROMIUM TOXICITY. CHEMISTRY OF BINARY SYSTEMS IN RELEVANCE TO FOOD AND BIOSYSTEMS

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Abstract

Chromium in its various oxidation states has been characterized by variable toxicity with as yet unclear molecular traits. In an effort to comprehend the molecular basis of chromium toxicity we embarked on research activities probing the structural speciation of Cr(III) in the presence of physiological substrates unlike those present in human and plant fluids. The results point to species of distinct structural and chemical reactivity characteristics that shed light on the molecular basis of Cr(III) reactivity in biologically relevant fluids.

Keywords: chromium toxicity, citric acid, soluble complexes, quinic acid

Introduction

Chromium occurs in the environment mainly in the elemental state Cr\textsuperscript{0}, in compounds of hexavalent Cr(VI) or Cr(III) (Sigel, 1995). In soils and sediments, chromium may be present in one of the two thermodynamically stable oxidation states: Cr(III) or Cr(VI) (James, 1983). Cr(VI) constitutes a significant health hazard and the World Health organization has, therefore, established a limit of 0.05 mg/lit for Cr(VI) in drinking water (Sheehan, 1991). Compounds of Cr(VI) are generally more soluble in water than are those of Cr(III).

Cr(III) as a metal ion, is an intermediate of the reductive processing of Cr(VI) under variable environmental or biologically relevant conditions. Low molecular mass organic acids (e.g. citrate, oxalate and tartrate) are among the best-characterized and abundant organic molecules in terrestrial and aquatic ecosystems (Liang, 1990). Such substrates have been known to bind and subsequently solubilize metal ions. One such organic acid is citric acid, which possesses structural characteristics that render it an excellent chelator in several binary and
ternary systems with metal ions (Hue, 1986), resulting in the formation of soluble metal ionic complexes.

Another metal ionic binder-substrate is the naturally occurring D-(-)-quinic acid in plants. The arising soluble metal-substrate complexes could become bioavailable and lead to (bio)chemical interactions at the cellular level. The arising interactions are key crucial in laying the foundations for understanding Cr(III) toxicity at the molecular level.

To this end, the scope of the present study aims at investigating the synthetic, structural and physicochemical properties of soluble and potentially bioavailable binary species between Cr(III) and physiological substrates such $\alpha$-hydroxycarboxylic acids. Advances in this area of chemistry will undoubtedly aid in the delineation of the interactions of Cr(III) with physiological low molecular mass binder $\alpha$-hydroxycarboxylic acids in aqueous media. In turn such knowledge will serve as the basis for understanding the molecular mechanisms involved in Cr(III) toxicity in diverse biological fluids and furthermore in environmental fluids.

**Experimental**

The entire study was based on the development of the structural speciation methodology probing binary systems of Cr(III) with low molecular mass substrates. In this case as low molecular mass substrates served the $\alpha$-hydroxycarboxylic acids citric and quinic acids. The implementation of the aforementioned methodology included a) investigation of the aqueous speciation of the binary systems Cr(III)-citric acid and Cr(III)-quinic acid, and b) investigation of the synthesis and detailed characterization of soluble Cr(III)-hydroxycarboxylate species in compliance with the aqueous speciation of the requisite binary system.

The aqueous speciation of the binary systems mentioned above was investigated through potentiometric titrations in the requisite systems employing the metal ion Cr(III) and the substrate ligand (e.g. citric acid and quinic acid). Complementary information to the system’s behavior in aqueous solution was provided by UV-Visible spectroscopic studies. In all cases, the arising distribution curves in the corresponding binary systems were suggestive of the presence of
specific mononuclear as well as dinuclear species conforming to
distinct types of metal-ligand stoichiometries and degrees of ligand
deprotonation. All of the information extracted covered species
distribution in the entire spectrum of physiological pH values and a
variable molecular ratio of Cr(III):substrate. That helped considerably
in the subsequent phase of synthesis and physicochemical;
characterization of new Cr(III)-hydroxycaboxylate binary species.

In compliance with the aqueous speciation distribution of the
examined Cr(III)-citrate system, synthetic efforts were launched
targeting mononuclear species of Cr(III) with bound citrate ligands.
The synthetic efforts consisted of pH-dependent reactivity studies
which ultimately led to the isolation of new species, including the
anionic complexes $[\text{Cr(C}_6\text{H}_4\text{O}_7)(\text{C}_6\text{H}_5\text{O}_7)]^{4-}$ and
$[\text{Cr(C}_6\text{H}_5\text{O}_7)(\text{C}_6\text{H}_5\text{O}_7)]^{3-}$. These species were isolated in the presence
of ammonium and sodium counter ions emerging from the use of the
appropriate bases for pH adjustment. An analogous synthetic endeavor
was launched in the case of the binary Cr(III)-quinic acid system with
analogous results. Following the isolation of the arising metal ionic
products, the new species were characterized by a host of analytical
and physicochemical techniques culminating with X-ray
crystallographic studies and EPR spectroscopic techniques in the solid
state and in solution (Gabriel, 2007).

### Results and Discussions

In the course of the present study, new aqueous Cr(III)-citrate
species, considered to be binary structural speciation variants of the
same mononuclear family of soluble complexes, were synthesized.
Key to the implementation of the study were detailed aqueous
speciation studies on the binary Cr(III)-citrate system. The aqueous
speciation suggests the presence of a number of species, among which
stand out the mononuclear $[\text{Cr(C}_6\text{H}_4\text{O}_7)(\text{C}_6\text{H}_5\text{O}_7)]^{4+}$ (1) complex, and
the mononuclear $[\text{Cr(C}_6\text{H}_5\text{O}_7)(\text{C}_6\text{H}_5\text{O}_7)]^{3+}$ (2) species, optimally
present at specific pH values. The $\text{NH}_4^+$ and $\text{Na}^+$ salts of the new
species were characterized by elemental analysis, spectroscopic,
structural, thermal, EPR and magnetic susceptibility studies. The
comprehensive in-depth perusal of their properties in the solid state
and in solution correlate their chemical nature with corresponding
interactions of Cr(III) with various substrates in diverse media and formulate the basis of the toxicity chemistry at the molecular level.

Conclusions

The effort to understand the molecular basis of chromium toxicity in biological fluids entails perusal of the nature and physicochemical properties of that metal’s ionic forms in the presence of physiological substrates. Our research in this area extends to binary systems of Cr(III) in the presence of α-hydroxycarboxylate systems and through structural speciation approaches reveals distinct types of species arising as a function of pH and metal:ligand stoichiometries. The physicochemical properties of the synthetically derived species confirm the suggestions of the aqueous speciation results and uncover the specific structural and chemical attributes of the binary species of Cr(III) interacting with low molecular mass substrates. These attributes formulate the basis for understanding the interactions of Cr(III) as a metallotoxin with biological targets of variable molecular mass and the molecular mechanisms through which binary and ternary Cr(III) components exert toxic effects at the cellular level.

Acknowledgments

The present study is co-funded by European Union-European Social Fund and National fund PYTHAGORAS-EPEAEK II. The authors would also like to acknowledge the financial support to this project by a “PENED” grant from the General Secretariat of Research and Technology, Greece.

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