

Chelation therapy: evaluation of the coordination ability of bis-kojic and hydroxypyridinone derivative ligands towards Cd^{II} ions via NMR spectroscopy

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The soft acid Cd^{II} is an accumulative toxic metal ion which is able to substitute for the essential borderline Zn^{II} ion in many zinc enzymes. Nuclear magnetic resonance (NMR) spectroscopy was used to assess the coordination ability of two ligands, an amine-bearing bis-kojic acid: 6'-(2-(diethylamino)ethylazanediy)bis(methylene)bis(5-hydroxy-2-hydroxymethyl-4H-pyran-4-one) [1,2] and a hydroxypyridinone derivative: 5-hydroxy-2-(hydroxymethyl)pyridin-4(1H)-one [3], for their use as potential chelating molecules towards Cd^{II} ions in detoxification treatments. A combination of 1D, 2D total correlation spectroscopy (TOCSY), heteronuclear single quantum coherence spectroscopy (HSQC) and rotating-frame Overhauser effect spectroscopy (ROESY) experiments was used to assign the signals of both free and metal-bound ligands, as previously reported for similar systems [4-6]. The metal-ligand system was studied at physiological pH and different temperature values. Competition experiments with essential Zn^{II} ions were also performed.

Human Exposure to Cadmium

Human exposure to Cd occurs chiefly through inhalation or ingestion. Absorption through skin contact is negligible. About 5% to 10% of ingested Cd is absorbed, depending on the particle size. Intestinal absorption is greater in persons with iron, calcium, or zinc deficiency. Cigarette smoking is considered to be the most significant source of human cadmium exposure. Blood and kidney Cd levels are consistently higher in smokers than nonsmokers. Inhalation due to industrial exposure can be significant in occupational settings, for example welding or soldering, and can produce severe chemical pneumonia. Cadmium exposure occurs from ingestion of contaminated food (e.g., crustaceans, organ meats, leafy vegetables, rice from certain areas of Japan and China) or water (either from old Zn/Cd sealed water pipes or industrial pollution) and can produce long-term health effects. Contamination of drugs and dietary supplements may also be a source of exposition [7]. Chelation therapy therefore plays a key role in the detoxification treatment [8].

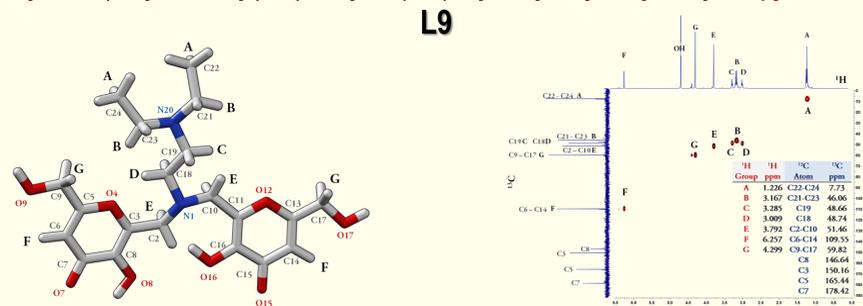
poisoning therapy treatment
Deferasirox administered medical lead binding
toxicity administration distinguished conventional Two alternative
groups ligands used arsenic Chelator done antidote metals
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EDTA thalassemia intoxication consider
TTFD various body values some number iron overload
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acute control currently databases coordinating severe affinities
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Considering dimercaptopropanesulfonic testing DMSA DMPS
most effects including medicine approved agents common
Dimercaptosuccinic chelators available
chelating metal

Cadmium vs Zinc in the Organism

Many toxic effects of cadmium action result from interactions with essential elements, including zinc. These interactions can take place at different stages of absorption, distribution in the organism and excretion of both metals, and at the stages of Zn biological functions. Exposure to Cd leads to disturbance in Zn absorption in the organism on one hand, while dietary Zn intake has an important effect on Cd absorption, accumulation and toxicity on the other. The Zn status in the body is important in relation to the development of Cd toxicity. Numerous data show that increased Zn supply may reduce Cd absorption and accumulation, and prevent or at least reduce the adverse actions of Cd, whereas Zn deficiency can intensify Cd accumulation and toxicity. Here we tested the coordination ability of bis-kojic and hydroxypyridinone derivative ligands towards Cd^{II} in order to evaluate their chelation ability in a potential cadmium detoxification treatment. Experiments were carried out including in the system the essential Zn^{II} as a competitor of toxic Cd^{II} ions.

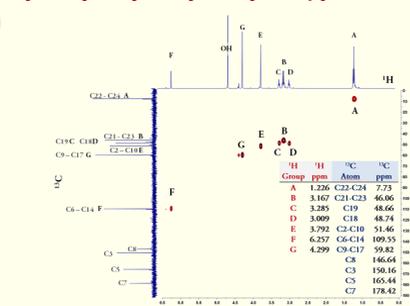
Results

(diethylamino)ethylazanediy)bis(methylene)bis(5-hydroxy-2-hydroxymethyl-4H-pyran-4-one)



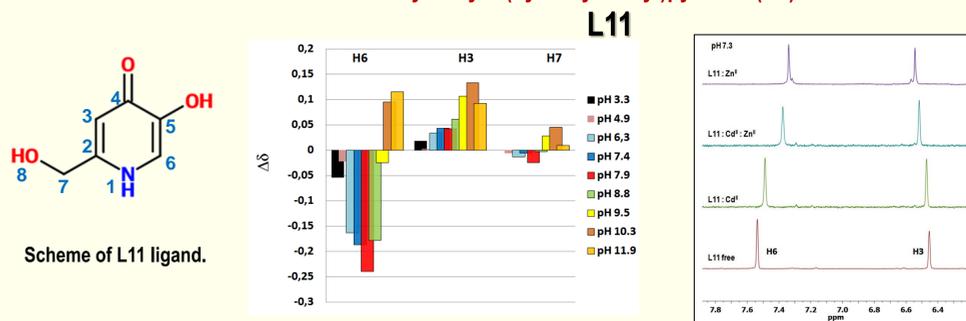
Scheme of L9 ligand with atom labels for carbon, nitrogen, oxygen and proton groups from A to G.

L9



2D ¹H-¹³C HSQC spectrum of the L9 in D₂O at 298 K and physiological pH. In the horizontal trace, the relative 1D ¹H spectrum, while in the vertical trace the 1D ¹³C one. Inset: a table collecting the proton and carbon NMR assignment.

5-hydroxy-2-(hydroxymethyl)pyridin-4(1H)-one



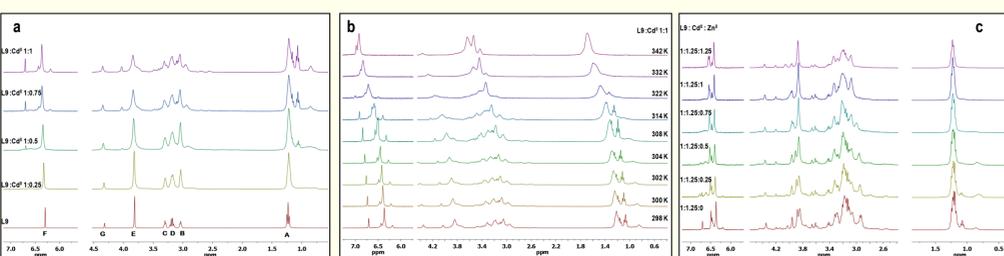
Histogram of proton (H3, H6 and H7) chemical shifts differences ($\Delta\delta = \delta_{\text{bound}} - \delta_{\text{free}}$) for the L11:Cd^{II} system at various pH values.

Competition experiments between Cd^{II} and Zn^{II} with L11 revealed the equilibrium of a mixture of Cd and Zn species in fast exchange on the NMR time scale.

Conclusions

Preliminary results show that:

- L9 is able to bind Cd^{II} ions forming several species in equilibrium at physiological pH.
- L11 is also able to bind Cd^{II} and the pH values influences its chelation ability. The L11:Zn system [3], showed two main species: ML above pH 8 and ML₂ at higher pH. Potentiometric techniques will help understand, in detail, the species formed in solution also by Cadmium. In fact, owing to its larger size, Cd^{II} can assume coordination number 6 more easily than Zn^{II}.
- The competition experiments showed that both ligands are not selective toward Cd^{II}. They bind both ions forming a mixture of species in solution.
- Therefore in a potential use of L9 and L11 as detoxification agents against Cd^{II}, zinc supplementation is indispensable.



a) 1D ¹H spectra for the free L9 ligand at physiological pH with increasing amounts of Cd^{II} to reach the final molar ratio of L9:Cd 1:1. Several species in equilibrium are observed. b) Selected VT-NMR spectra of L9- Cd^{II} system, 1:1 molar ratio, revealed a coalescence and broadening of peaks. c) 1D ¹H NMR competition experiments between Cd^{II} and Zn^{II} with L9 showed an equilibrium in solution with a mixture of species in fast exchange on the NMR time scale.

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