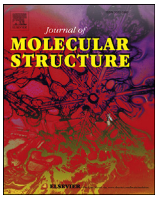
Journal of Molecular Structure 1154 (2018) 225–231

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc



Characterization of metal-bound water in bioactive Fe(III)-cyclophane complexes

A.J. Salazar-Medina [a, *], R. Gámez-Corrales [b], J.Z. Ramírez [c], G.A. González-Aguilar [a], E.F. Velázquez-Contreras [c]

[a] *Centro de Investigación en Alimentación y Desarrollo, Hermosillo, Sonora, 83304 Mexico*
[b] *Departamento de Física, Universidad de Sonora, Hermosillo, Sonora, 83000 Mexico*
[c] *Departamento de Investigación en Polímeros y Materiales, Universidad de Sonora, Hermosillo, Sonora, 83000 Mexico*

ARTICLE INFO

Article history:
Received 19 July 2017
Received in revised form
3 October 2017
Accepted 4 October 2017
Available online 6 October 2017

Keywords:
Fe(III) complexes
Cyclophanes
Bioactive
Metal-bound water
Coordination geometry
Theoretical calculation

ABSTRACT

Binuclear Fe(III) complexes, Fe_2PO and Fe_2PC, have functions of antioxidants as well as superoxide dismutase and peroxidase mimickers. The role of water molecules in the non-cytotoxic properties of these complexes have been studied by thermogravimetric and IR/Raman-spectroscopic methods. The thermogravimetric analysis of Fe_2PO shows the presence of nine water molecules ($Fe_2PO\cdot 9H_2O$), three of which are directly coordinated to the metallic ion; the remaining six molecules occupy the secondary coordination sphere. For Fe_2PC, eight water molecules were detected ($Fe_2PC\cdot 8H_2O$), and only one of them directly coordinates to the metallic ion. IR/Raman spectrum analyses corroborate the presence of water molecules in both metallic complexes and the mode of coordination to the ligand, on the basis of bands characteristic of hydration water at ~3300 cm^{-1} and bands of adsorbed water between 430 and 490 cm^{-1}. A pentacoordinate geometry is proposed for Fe_2PO and a hexacoordinated geometry for Fe_2PC. Those results are consistent with theoretical calculations performed through a semiempirical PM7 method. The presence of coordinated water molecules is closely related to the reactivity of Fe_2PO and Fe_2PC in solution.

1. Introduction

Even though water molecules are small and composed of just two different atoms, they are involved in a wide variety of biological and chemical processes. Water molecules can act as recognizers and stabilizers of the interaction in a host-guest complex [1]. These properties can be exerted not only by directly coordinated water molecules but also by non-coordinated water molecules such as, hydration water or even by water from the reaction medium [2].

This has remarkable implications on drug or additive design due to the dynamic nature of these systems [2]; the identification and characterization of water molecules, involved in any potential drug, is a mandatory procedure [3].

In medicine, some metallic complexes have been successfully employed as scavengers in therapies against free radical and reactive oxygen species [4,5]. Iron complexes stand out in this regard due to their well-known bioinorganic chemistry involved in central life processes, assembling complexes, acting as redox cofactors for metalloproteins and managing a wide number of biochemical transformations. All these properties are possible due to coordination properties and the variable oxidation state of iron ions [6].

Since interaction of water molecules with metal complex molecules is extremely important, the bioactive properties of Fe(III) complexes are elucidated, in relation to the possibility of the use as a drug or food additive.

Knowledge of the number of water molecules coordinated to a metal ion is extremely important in understanding the nature and reactivity of metal complexes in solution. For example, molecules employed as MRI contrast agents require one or more water molecules coordinated to the paramagnetic metal ion, and the number of such water molecules is of crucial importance in controlling the molar relaxivity of the agent [5]. For these reasons, it is desirable to have a reliable experimental method for determining if there are water molecules occupying the first coordination sphere of metal ion in metal complexes.

Metal complexes of macrocycles derived from ethylenediaminetetraacetate (EDTA) have been extensively studied by our

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[*] Corresponding author.
E-mail address: alex.salazar.medina@gmail.com (A.J. Salazar-Medina).

https://doi.org/10.1016/j.molstruc.2017.10.018

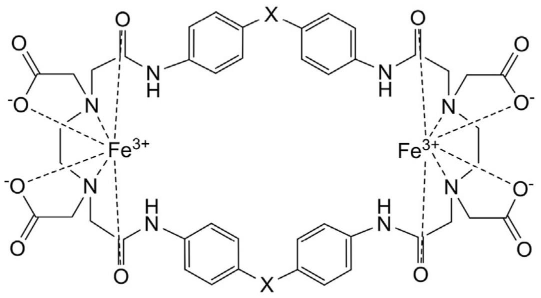

Fig. 1. A schematic structure proposed for binuclear Fe(III) complexes: Fe_2PO (X = O) and Fe_2PC (X = CH_2).

group, especially in relation to their bioactive properties [3,7]. Fe_2PO and Fe_2PC, which are binuclear Fe(III)complexes of EDTA-derived macrocycles, have shown the capacity to mimic peroxidase and SOD activities. Detailed information about the structure of these complexes in solution is indispensable for the understanding of such catalytic properties. Since the base scaffold used to construct Fe_2PO and Fe_2PC is the Fe(III)-EDTA complex, they are expected to have similarities in some features and coordination properties. EDTA molecule provides specific coordination atoms to interact with Fe(III) ion, but this property can changed by the functionalization of the EDTA molecule with aromatic diamines which are required to form Fe_2PO and Fe_2PC metal complexes.

2. Materials and methods

2.1. Syntheses of binuclear Fe(III) complexes

All employed reagents and solvents were analytical grade. To obtain the binuclear Fe(III) complexes (Fe_2PO and Fe_2PC) we synthesized the host molecules PO and PC, which are (2,9,25,32-tetraoxo-4,7,27,30-tetrakis (carboxymethyl)-1,4,7,10, 24,27,30,33-octaaza-17,40-dioxa[10.1.10.1] paracyclophane and 2,9,25,32-tetraoxo-4,7,27,30tetrakis(carboxymethyl)-1,4,7,10,24,27,30,33-octaaza [10.1.10.1] paracyclophane), respectively, according to the methodological procedure reported by Inoue et al. [8]. The formation and purity were confirmed by the melting/decomposition point and ^{1}H NMR studies.

Fe_2PO and Fe_2PC were obtained by mixing aqueous solutions of each receptor, PO and PC, with an aqueous solution of $FeCl_3{\cdot}6H_2O$, in a molar ratio 1:2, as reported by Salazar-Medina et al., [3]. The formation and purity were confirmed by high-resolution electrospray-ionization (ESI) mass spectrometry and the melting/decomposition point, and electron paramagnetic resonance (EPR).

2.2. Thermogravimetric analyses

The TGA measurements of the iron complexes were carried out with a Perkin-Elmer, Pyris 1 TGA apparatus, at a heating rate of 10 °C/min and an airflow rate of 20 mL/min in a temperature range of 25–600 °C, under an O_2 atmosphere. Spectrum evaluations were performed using the Pyris version 11.1.1.0492 software package.

2.3. Spectroscopic measurements

The infrared spectra in the spectral range between 4000 and 250 cm^{-1} were recorded in KBr pellets with a Perkin-Elmer Spectrum GX FT-IR instrument. A total of 32 scans were performed. Raman spectra in the same range were observed using a HORIBA OLYMPUS micro-RAMAN X'PLORA BX41 microscope at room temperature. The laser employed was a class 3B with different energies (532, 638 and 785 nm) from 20 mW to 100 mW and a slit of 100 μm. The X-ray photoelectron spectroscopy (XPS) were obtained on a Perkin-Elmer PHI5100 model (X-ray energy source of 0.025 eV). All the spectra were obtained at a pass energy of 22.36 eV to identify all the elements present in the analyzed samples.

2.4. Theoretical calculations

Models of the metal complexes Fe_2PO and Fe_2PC were generated based on 2D structures previously proposed by employing a molecular editor, including the water molecules in calculation of each metal complex. Its optimization was made at molecular mechanics level with a UFF force field [9]. The model construction and

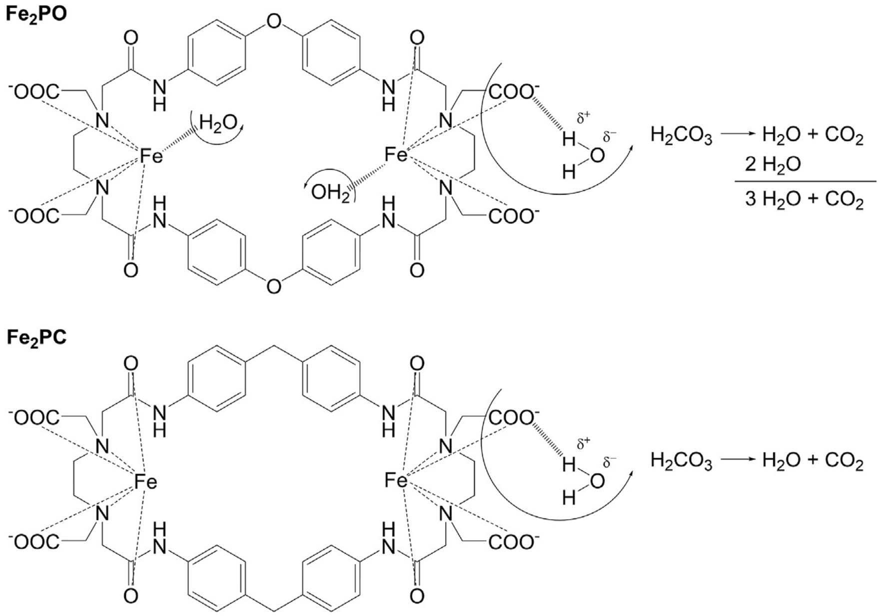

Fig. 2. Coordinated water molecule release during TAG analysis.