

Theoretical and spectroscopic studies of new lanthanum(III) complex of orotic acid

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Abstract

The complex of lanthanum(III) was synthesized by reaction of lanthanum(III) nitrate with sodium salt of orotic acid in amounts equal to metal:ligand molar ratio of 1:2. The structure of the final complex was determined by means of vibrational (IR and Raman) spectra and elemental analysis. Significant differences in the IR and Raman spectra of the complex were observed as compared to the spectra of the ligand. The geometry of orotic acid (HOA) was computed and optimized for the first time with the Gaussian 03 program using the B3PW91/6-311++G**, B3PW91/LANL2DZ, B3LYP/6-311++G**, and B3LYP/LANL2DZ methods, while the geometry of the La(III) complex of orotic acid was also first calculated and optimized with B3PW91/LANL2DZ and B3LYP/LANL2DZ methods. Detailed vibrational analysis of HOA and La(III)–OA systems based on both the calculated and experimental spectra confirmed the suggested metal–ligand binding mode. The density functional theory (DFT) calculated geometries, harmonic vibrational wavenumbers including IR and Raman scattering activities for the ligand and its La(III) complex were in good agreement with the experimental data, a complete vibrational assignment being proposed.

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1. Introduction

The coordination chemistry of orotic acid (2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid, Vitamin B₁₃, H₃L; Fig. 1) has been an area of great activity [1–14], research in this area ranging from bioinorganic to pharmaceutical and materials chemistry. Orotic acid occupies a unique position in biology by being the only effective precursor in the biosynthesis of pyrimidine bases of nucleic acids in living organisms [15,16]. It has been established that during these processes the presence of metal ions, especially Mg²⁺, is necessary, particularly during the phosphoribosylation of orotic acid [17].

Metal orotates are widely applied in medicine [18]. Platinum, palladium and nickel orotate complexes have been screened as therapeutic agents for cancer [19]. More recent interest has focused on the proposed biological carrier function

of orotic acid and the corresponding anionic species for metal ions, which is held responsible for the successful application of orotate complexes in curing syndromes associated with a deficiency of a variety of metals such as calcium, magnesium, zinc or iron [4,5,18].

Orotic acid, H₃L (see Fig. 1), acts as a diacid in aqueous solution, with the acidic function suggested to be located on the carboxylic group (pK_{a1} = 2.09) and on the N3 site (pK_{a2} = 9.45) [20]. The monobasic form, hydroorotate, H₂L[−], appears to predominantly form complexes with coordination through the carboxyl oxygen atoms [21]. Compounds with the Zn(II) [22] and Mg(II) [23] cations, where the H₂L[−] anion does not enter the inner coordination sphere of the cation have also been reported. The multifunctionality of the hydroorotate, H₂L[−], and orotate, HL^{2−} anions (see Fig. 1) offer interesting possibilities in crystal engineering as a versatile ligand for supramolecular assemblies. The coordinated orotate anions exhibit a ligand surface with double or triple hydrogen-bonding capabilities, depending on the metal coordination mode, and has thus a potential to adopt several modes of interligand hydrogen bonding to allow the formation of extended, self-assembled structures.

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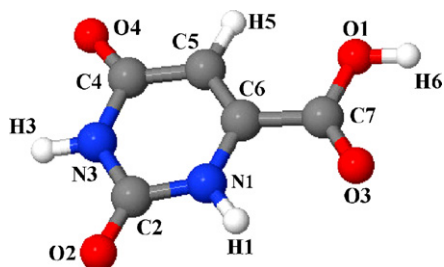


Fig. 1. B3LYP/LANL2DZ optimized geometry of orotic acid together with its labeling.

This ligand has demonstrated versatile coordination modes during the formation of coordination frameworks, that is why it was a challenge for us to obtain new lanthanide(III) coordination complexes with orotic acid, especially in view of their application as anticancer agents. To the best of our knowledge, little is known about lanthanide(III) coordination compounds with orotic acid and such kind of lanthanide(III) complexes, possessing cytotoxic activity has not been previously reported. We have recently synthesized lanthanide complexes with a number of biologically active ligands, and we reported their significant cytotoxic activity in different human cell lines [24–30]. These promising results prompted us to search for new lanthanide complexes with orotic acid (H_3L , see Fig. 1). Thus, the aim of this work was to synthesize and characterize a complex of lanthanum(III) with orotic acid in view of determination of its cytotoxic activity in the future.

In this paper, we report theoretical and spectroscopic results about a new La(III) complex of orotic acid (HOA). The complex was identified and characterized with elemental analysis, IR and Raman spectroscopies. For estimation of the most preferred reactive sites of HOA for electrophilic attack and metal binding, its geometry was calculated. The La(III)–OA binding mode was elucidated on the basis of DFT calculations of the molecular and vibrational structures of HOA and La(III)–OA model systems.

2. Experimental

2.1. Computational details

The geometry of orotic acid and its La(III) complex were optimized using the Gaussian 03 program [31]. Becke's three-parameter exchange functional (B3) [32] with Perdew and Wang's gradient-corrected correlation functional (PW91) [33,34] and Becke's three-parameter hybrid exchange functional (B3) [35,36] using the LYP correlational functional of Lee, Yang and Parr (LYP) [37] were employed in the DFT calculations. The 6-311++G** Pople split valence basis sets along with the LANL2DZ basis set implemented in the Gaussian 03 program [31] were chosen in the geometry optimization and normal mode calculations. The LANL2DZ basis set [38] was chosen with the intention to optimize the new La(III) complex of the orotic acid because of the atomic number of the lanthanum.

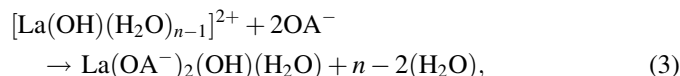
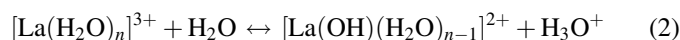
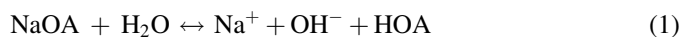
Using the fully optimized molecular geometry we performed the density functional theory (DFT) calculations on harmonic

vibrational modes. Harmonic vibrational wavenumbers including IR and Raman intensities were calculated analytically for the fully optimized molecular geometries. Only real harmonic vibrational wavenumbers were obtained for all structures, confirming the localization of global minima on the potential energy surfaces.

2.2. Synthesis of the coordination complex

The compounds used for preparing the solutions were Merck products, p.a. grade: $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$. The sodium salt of orotic acid was used for the preparation of the metal complex as a ligand.

The complex was synthesized by reaction of lanthanum(III) nitrate and the sodium salt of orotic acid in aqueous solution, in amounts equal to metal:ligand molar ratio of 1:2. The formation of the complex may be represented by the following equations:



where $\text{HOA} = \text{C}_5\text{N}_2\text{O}_4\text{H}_4$ and $\text{OA}^- = \text{C}_5\text{N}_2\text{O}_4\text{H}_3^-$.

The synthesis of the complex was made in different ratio (1:1, 1:2, 1:3) but in all the cases the product was with composition 1:2. The complex was prepared by adding an aqueous solution of lanthanum(III) salt to an aqueous solution of the sodium salt of orotic acid. The reaction mixture was stirred with an electromagnetic stirrer at 25 °C for 1 h. At the moment of mixing of the solutions, precipitate was obtained. The precipitate was filtered (pH of the filtrate was 5.0), washed several times with water and dried in a desiccator to constant weight.

The complex was insoluble in water, methanol and ethanol and well soluble in DMSO.

2.3. Device descriptions

The carbon, hydrogen and nitrogen contents of the compound were determined by elemental analysis.

The water content was determined by Metrohn Herizall E55 Karl Fisher Titrator.

The solid-state infrared spectra of the ligand and its La(III) complex were recorded in KBr in the 4000–400 cm^{-1} frequency range by FT-IR 113V Bruker spectrometer.

The Raman spectra of orotic acid and its new La(III) complex were recorded with a Dilor Labram spectrometer (Horiba-Jobin-Yvon, model LabRam) using the 784.8 nm excitation line from a near infrared Diode laser. The Labram integrated system is coupled through an Olympus LMPlanFL 50× objective to the optical microscope. The spectra were collected in the backscattering geometry with a resolution of 2 cm^{-1} . The detection of Raman signal was carried out with a

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