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Electronic structure and vibrational spectra of *cis*-diammine-(orotato)platinum(II), a potential cisplatin analogue: DFT and experimental study

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Abstract

Orotic acid (vitamin B_{13}) is a key intermediate in biosynthesis of the pyrimidine nucleotides in living organisms, moreover, it may serve as the biological carrier for some metal ions. *cis*-Diammine(orotato)platinum(II), *cis*-[$Pt(C_5H_2N_2O_4)(NH_3)_2$] can be considered as a new potential cisplatin analogue. The FT-Raman and FT-IR spectra of the title complex are reported, for the first time. The molecular structure, vibrational frequencies, and the theoretical infrared and Raman intensities have been calculated by the density functional mPW1PW91 method. The detailed vibrational assignment has been made on the basis of the calculated potential energy distribution. The theoretically predicted IR and Raman spectra show very good agreement with experiment. Natural bond orbital (NBO) analyses were performed for cisplatin, carboplatin and the title complex. The results provided new data on the nature of platinum–ligand bonding in these compounds. Strong intramolecular hydrogen bond between the orotate ligand and the coordinated ammonia group stabilizes the structure of the platinum(II) complex. Thus, it is suggested that the orotate ligand in the title complex is more inert to the substitution reactions than the chloride ligands in cisplatin.

Keywords: Cisplatin analogues; Platinum(II) complexes; Raman and infrared spectra; Vibrational assignment; Density functional theory; Natural bond orbital analysis

1. Introduction

Platinum complexes are amongst the most widely used anticancer agents. Cisplatin, *cis*-diamminedichloroplatinum(II), (**a**, in Scheme 1) is one of extremely effective drugs against various types of human malignancies, such as: small cell lung cancer, bladder and testicular tumors, ovarian carcinomas, and tumors of the head and neck [1–3]. However, chemotherapy with cisplatin is associated with many serious side effects, such as: nephrotoxicity, ototoxicity, neuropathy and nausea. The therapeutic efficacy of cisplatin is also limited by inherent or acquired resistance [3]. The second-generation platinum drug, carboplatin [*cis*-diammine(1,1-cyclobutanedicarboxylato)-platinum(II)] (**b**) has lower toxicity than cisplatin [4]. This is attributed to slower hydrolysis of the cyclobutanedicarboxylate leaving group, in comparison to the chloride ligands in cisplatin [5]. When platinum drug binds to DNA, the major product is 1,2 intrastrand GG adduct, where the *cis*-diammineplatinum(II) complex is bound to the N7 sites on two neighboring guanines [1]. However, before such binding can occur, the platinum drug undergoes the hydrolysis (aquation) process, in which the chloro or other leaving ligands are replaced by the water molecules. Unfortunately, the hydrolyzed species can bind to the sulfur atoms of glutathione and peptides leading to toxic effects. Much effort has been devoted to design complexes, which exhibit different pharmacokinetics than cisplatin or carboplatin. This can be

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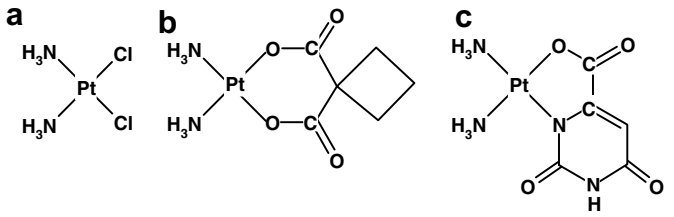

Scheme 1. Structures of cisplatin (a), carboplatin (b) and *cis*-[Pt(oro)$(NH_3)_2$] (c).

achieved by replacing the labile chloride or dicarboxylate ligands by other leaving groups. Among them, the orotate ligand seems to be an interesting potential candidate.

Orotic acid (vitamin B_{13}) is a key intermediate involved in biosynthesis of the pyrimidine nucleotides in living organisms [6,7]. Recently, metal orotates have attracted growing attention in medicine. Orotic acid has been used as the carrier for some metal ions in curing syndromes associated with a deficiency of Mg^{2+} and Ca^{2+} ions, for example magnesium-orotate treatment gives excellent results in prevention and therapy of heart and blood vessels diseases [8,9]. An interesting structural feature of the orotate ligand is the presence of the uracil ring, which is able to form complementary hydrogen bonds with the adenine residues, analogous to those formed by uracil and thymine nucleosides, in biological systems. Thus, it is possible that the orotate ligand may serve as the carrier molecule, which transports the DNA-active anticancer platinum drug through the cell membranes.

In recent years, several research groups [10–15] performed extensive theoretical calculations on the structure and bonding of platinum(II) complexes and their interactions with water molecules and DNA nuclebases. In our earlier studies [16–18], we have shown that the modified Perdew–Wang density functional model (mPW1PW91) [19,20] is superior to other DFT methods (including B3LYP) in a simultaneous prediction of both the molecular structure and vibrational spectra of platinum(II) drugs. In the case of Pt(II) complexes, Raman spectroscopy is of special interest, because some of the platinum–ligand vibrations, for example Pt–NH_3 stretches, can be hardly observed in infrared due to their low intensity, while they are very strong in the Raman spectra [17,18]. Moreover, water is a weak Raman scatterer, therefore, the Raman spectra of samples in aqueous solution can be obtained without major interference from water vibrations. Thus, Raman spectroscopy is ideal for monitoring the cleavage of the Pt–L bonds (where L is a leaving group) in the hydrolytic process. For such studies, the clear-cut assignment of the Pt–ligand vibrations in the Raman spectra becomes very important.

The main goal of the present work is to investigate the structural, electronic and vibrational properties of *cis*-diammine(orotato)platinum(II), *cis*-[Pt(oro)$(NH_3)_2$] (**c**). The crystal and molecular structure of (**c**) was determined [21], but no other studies have been reported, as yet. In this work, the FT-Raman and FT-IR spectra of the title complex are measured and compared with the theoretical Raman and IR spectra, computed by the DFT method. The calculated potential energy distribution (PED) has enabled us to make a detailed assignment of the vibrational spectra. Natural bond orbital (NBO) analysis [22] has provided a thorough insight into the nature of platinum ligand bonds in this complex. Comparison has been made with the results obtained for cisplatin and carboplatin.

2. Methods

2.1. Experimental

Orotic acid ($C_5H_4N_2O_4$) and cisplatin (*cis*-[$PtCl_2$-$(NH_3)_2$]) were purchased from Sigma Chemical Co. The *cis*-[Pt(oro)$(NH_3)_2$] complex was prepared by modifying the method reported in Ref. [21]. The yellow crystalline product was obtained from sodium orotate (instead of using orotic acid, which requires higher temperature and larger volume of water to dissolve). The pH of the solution was about 6–7. After a day the yellow complex precipitated. There were no traces of green and dark-blue microcrystals, as reported earlier [21]. Elemental analyses confirmed the purity of the complex. Found: H, 2.17%; C, 16.08%; N, 14.06%. Calcd. for [Pt$(C_5H_2N_2O_4)(NH_3)_2$]: H, 2.11%; C, 15.67%; N, 14.62%.

The Raman spectrum of the title complex was recorded on Bruker 88 FT-Raman spectrometer equipped with a Nd:YAG laser (operating at 1064 nm) with a max. power of 200 mW and resolution 4 cm^{-1}. The sample was studied in the solid state, placed in the capillary tube. The FT-IR spectrum (4000–400 cm^{-1}) was measured on a Bruker IFS 113 V spectrometer, in KBr pellets. The far-infrared spectrum (600–50 cm^{-1}) was recorded on Perkin–Elmer 2000 FT-IR spectrometer using Nujoll mull technique.

2.2. Theoretical

The optimized geometry, harmonic frequencies, IR intensities and Raman scattering activities of the title complex were calculated by the density functional theory model, mPW1PW91 [19,20] abbreviated as mPW, in this work. This is the Becke-style one-parameter hybrid protocol consisting of the modified Perdew–Wang exchange and Perdew–Wang 91 correlation. For comparison, calculations were also performed by the second-order Möller–Plesset (MP2) method and by the B3LYP functional [23]. The effective core potential (ECP) of Hay and Wadt [24] was used for the platinum atom. The calculations were carried out using two basis sets: the LanL2DZ basis set on all atoms (I basis set) and the D95V(d,p) basis set for all non-metal atoms [25] combined with the LanL2DZ for Pt (II basis set). The II basis includes d polarization functions on C, N and O atoms, and p polarization functions on hydrogen atoms. Natural bond orbital (NBO) analysis [22] has been performed at the mPW/LanL2DZ level of