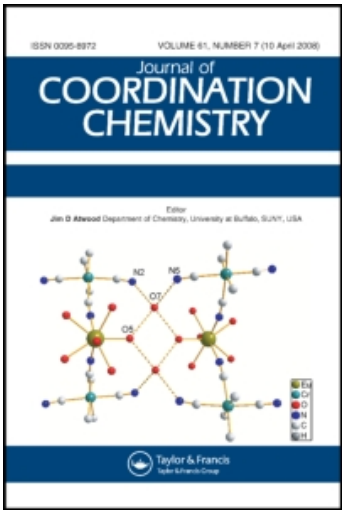

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Pedro P. Corbi[a]; Antonio C. Massabni[a]; Claudio M. Costa-Neto[b]
[a] Departamento de Química Geral e Inorgânica, Instituto de Química - UNESP, Araraquara, SP, Brazil [b] Departamento de Bioquímica e Imunologia, Faculdade de Medicina de Ribeirão Preto - USP, Ribeirão Preto, SP, Brazil

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Synthesis and characterization of a new platinum(II) complex with L-mimosine

PEDRO P. CORBI*†, ANTONIO C. MASSABNI† and CLAUDIO M. COSTA-NETO‡

†Departamento de Química Geral e Inorgânica, Instituto de Química – UNESP, CP 355, CEP 14801-970, Araraquara, SP, Brazil
‡Departamento de Bioquímica e Imunologia, Faculdade de Medicina de Ribeirão Preto – USP, 14049-900, Ribeirão Preto, SP, Brazil

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Synthesis and characterization of a new Pt(II)–mimosine complex are described. Elemental, mass spectrometry and thermal analyses for the complex are consistent with the formula $[PtCl_2(C_8H_{10}N_2O_4)] \cdot 1.5H_2O$. ^{13}C NMR, ^{15}N NMR and infrared spectroscopy indicate coordination of the ligand to Pt(II) through the N and O atoms in a square-planar geometry. The final residue after thermal treatment was identified as metallic Pt. The complex is soluble in dimethylsulfoxide.

Keywords: Platinum(II); L-Mimosine; Amino acids; Metal complex; ^{15}N NMR

1. Introduction

Platinum complexes have been widely studied as anticancer drugs since Rosenberg discovered the anticancer properties of cisplatin or *cis*-diammindichloroplatinum(II) [1]. Cisplatin has been used as an anticancer drug since 1978, particularly for treatment of testicular cancer, for which it has a cure rate over 90% [2]. Currently cisplatin and analogs have been used for cancer treatment of bladder, cervix, head and neck, small cell lung cancer as well as some pediatric malignancies [3]. Side effects, especially nephrotoxicity, neurotoxicity and ototoxicity limit its widespread use in high doses [4–6]. The necessity for the development of new drugs like cisplatin but with reduced side effects has stimulated the syntheses of many new complexes. Platinum complexes with amino acids and their palladium analogs have been prepared and studied as possible anticancer drugs. Complexes of Pt(II) and Pd(II) containing the amino acids tyrosine, alanine and methionine displayed anticancer activities against some

*Corresponding author. Fax: +55 16 3322 7932. Email: pedrocorbi@yahoo.com

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lymphocytic leukaemia cells [4]. Recently, a new Pd(II) complex with the amino acid deoxyalliin showing antiproliferative and citotoxic activities over HeLa and TM5 cell lines, as well as antitumoral activity against murine melanoma was prepared and analyzed in our laboratories [7].

L-Mimosine or leucenol [mmo, $C_8H_{10}N_2O_4$, β-*N*-(3-hydroxy-4-pyridone)-α-aminopropionic acid] is an amino acid present in plants of genus *Mimosa* and *Leucaena* [8]. This rare amino acid exhibits a wide range of effects, including inhibition of folate metabolism [9], inhibition of deoxyribonucleotide metabolism [10], induction of apoptosis [11, 12], inhibition of different cell line proliferation and *in vivo* inhibition of tumor growth [13–15]. It also inhibited different mammalian enzymes such as tyrosinase, dopamine β-hydroxylase and deoxyhypusine hydroxylase [16, 17]. Mimosine has also been shown to improve antiproliferative and antitumoral action of the anticancer drug 5-fluorouracil [18].

The structure of L-mimosine is of great interest because it contains two different residues, one of the 3-hydroxy-4-pyridone type and another of the α-amino acid type. The presence of different bonding sites confers to L-mimosine a more versatile coordination activity to metal ions. Metal complexes of L-mimosine with Cu(II), V(IV), Ni(II) and Zn(II) were recently described in the literature [19]. The present article describes the synthesis and characterization of a new Pt(II) complex with L-mimosine.

2. Experimental

2.1. *Reagents and equipment*

L-Mimosine and potassium tetrachloroplatinate(II) of analytical grade were purchased from Sigma and Acros laboratories, respectively. Elemental analyses for carbon, hydrogen and nitrogen were performed using a CHNS-O EA1110 Analyzer, CE Instruments; cystine was used as a reference substance. Platinum content was quantified by the residue of the thermal treatment of the complex at 500°C. Electrospray ionization mass spectrometry (ESI-MS) measurements were carried out using Fissons VG Platform equipment; sample was studied in aqueous solution. Infrared spectra were recorded on a FT-IR Spectrophotometer Spectrum 2000, Perkin–Elmer, with samples prepared as KBr or CsI pellets. ^{13}C NMR and ^{15}N NMR were recorded on a Varian 500 MHz Spectrometer; samples were analyzed in deuterium oxide and dimethylsulfoxide-d_6 (DMSO-d_6) solutions. Thermal analyses were performed on a Thermoanalyzer TG/DTA simultaneous SDT 2960 TA Instruments in the following conditions: air, 100 $cm^3\,min^{-1}$ and heating rate of 10°C min^{-1}, from 40 to 900°C.

2.2. *Synthesis of the complex*

The Pt(II) complex was synthesized by reaction of 4.8×10^{-4} mol of a freshly prepared aqueous solution of potassium tetrachloroplatinate (K_2PtCl_4) with a freshly prepared solution of mimosine hydrochloride containing 4.8×10^{-4} mol of the ligand (molar proportion Pt(II)/mimosine of 1 : 1). The synthesis of the complex was carried out with stirring at room temperature. A pale yellowish solid of the complex slowly precipitated. The complex was filtered, washed with cooled water and ethyl ether, and dried

Table 1. Electrospray mass spectrum (m/z) of Pt(II)–mimosine (ESI = −70 eV).

Complex	Origin	m/z
$[PtCl_2(mmo)]$	$[PtCl_2(mmo)–H]^-$	463
	$[Pt^{37}Cl_2(mmo)–H]^-$	465
	$[PtCl(mmo)–HCl]^-$	428
	$(mmo–H)^-$	197

in a desiccator over P_4O_{10}; yield 50%. No single crystals of the complex were obtained, even after several attempts.

Mimosine hydrochloride used in the synthesis was prepared by the reaction of a dilute solution of HCl with a suspension of L-mimosine in water with stirring at room temperature. Final pH of this solution was in the range 2–3.

3. Results and discussion

3.1. *Analytical results*

Anal. Calcd for $[PtCl_2(C_8H_{10}N_2O_4)] \cdot 1.5H_2O$ (%): C, 19.6; H, 2.67; N, 5.70; Pt, 39.7. Found: C, 19.2; H, 2.32; N, 5.79; Pt 39.1.

3.2. *Mass spectrometry*

The most significant m/z peaks in the electrospray mass spectrum of Pt(II)–mimosine complex are given in table 1.

The spectrum of the Pt(II)–mimosine complex shows an intense peak assigned to the $[PtCl_2(mmo)–H]^-$ molecular ion preceded by another peak corresponding to the lack of a chloride ion. ^{37}Cl isomer peaks are also observed. Other peaks observed are assigned to recombination of Cl^- ions, free ligand and the metallic complex.

3.3. *^{13}C and ^{15}N NMR spectroscopy*

^{13}C NMR and ^{15}N NMR spectra of the Pt(II)–mimosine complex are useful for assigning metal bonding sites. The NMR spectra of the complex were analyzed in comparison to the spectra of mimosine hydrochloride. The structure of the ligand with carbon numbering is shown in figure 1.

The ^{13}C NMR spectra indicate coordination of mimosine to Pt(II) through the oxygen atom of COOH and the nitrogen atom of 3-hydroxy-4-pyridone group. According to the ^{13}C NMR data, the chemical shift at 161.9 ppm in the spectrum of the mimosine hydrochloride is assigned to the carbon atom of the COOH group (C_1 in figure 1). In the spectrum of the complex the chemical shift for C_1 appears at 181.7 ppm. These results indicate coordination through the oxygen of COOH. Minor changes are also observed for the chemical shifts of C_3 and C_4 in the spectrum of the Pt(II)–mimosine complex when compared to the ligand. These changes also indicate coordination of mimosine to Pt(II) through the nitrogen atom of the 3-hydroxy-4-pyridone group. Chemical shifts for C_5, C_6 and C_7 in the spectrum of the complex do not change when compared to the spectrum of mimosine hydrochloride. The ^{13}C NMR

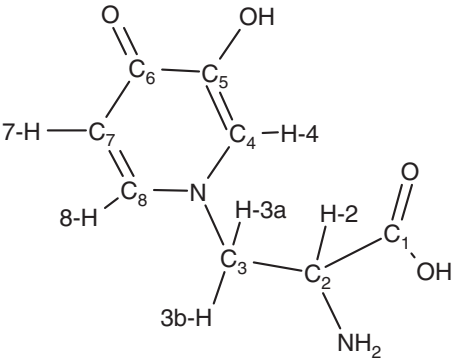

Figure 1. Structure representation of L-mimosine.

Table 2. ^{13}C chemical shifts (ppm) for mimosine hydrochloride and for the Pt(II)–mimosine complex.

Compound	C1	C2	C3	C4	C5	C6	C7	C8
Mimosine · HCl	161.9	53.25	57.69	131.1	139.8	168.8	113.9	145.6
Pt(II)–mimosine	181.7	58.00	60.10	126.0	138.6	168.3	112.7	145.6

chemical shifts for mimosine hydrochloride and the Pt(II)–mimosine complex are given in table 2.

The ^{15}N chemical shifts for mimosine hydrochloride and for the Pt(II)–mimosine complex were indirectly obtained from the two dimensional (2D) spectra via the heteronuclear multiple bond coherence (HMBC) technique [20]. Analysis of the HMBC spectrum of mimosine hydrochloride permitted identified the ^{15}N isomer shift of the α-amino group (NH_2) at 40 ppm and the ^{15}N isomer shift of the 3-hydroxy-4-pyridone group at 176 ppm. In the spectrum of the complex the ^{15}N isomer shift of the NH_2 group is also observed at 40 ppm while the ^{15}N isomer shift of the 3-hydroxy-4-pyridone group appears upfield at 154 ppm. The observed $\Delta\delta = -22$ ppm confirms coordination through nitrogen atom of the 3-hydroxy-4-pyridone group [20]. The HMBC spectra of mimosine hydrochloride and of the Pt(II)–mimosine complex are shown in figure 2.

3.4. *Infrared spectroscopy*

Pt(II)–mimosine infrared spectrum was analyzed in comparison to the infrared spectrum of mimosine hydrochloride, the latter considering the ionic form of the free ligand. The infrared spectrum of mimosine hydrochloride exhibits a strong absorption band at 1730 cm^{-1}, assigned to the uncoordinated, protonated carboxylic group. The absence of this band in the spectrum of the Pt(II)–mimosine complex confirms coordination through the oxygen of COOH (C=O–Pt). Both mimosine hydrochloride and Pt(II)–mimosine complex show very strong absorption bands at 1630–1660 cm^{-1} which can be assigned to the ν(C=O) stretching modes [21].

Bands at 1540 and 1330 cm^{-1} are observed in the mimosine hydrochloride spectrum, being attributed to the $\delta(NH_2)$ vibration modes. For the complex these bands are observed at 1550 and 1350 cm^{-1}. These slight changes observed in the $\delta(NH_2)$ frequency

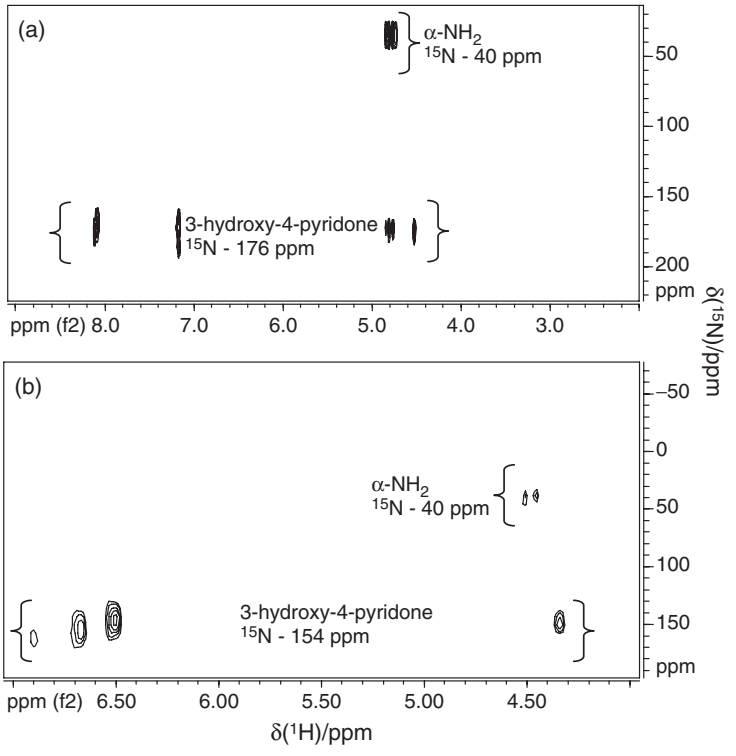

Figure 2. ^{1}H–^{15}N HMBC spectra of (a) mimosine hydrochloride and (b) Pt(II)–mimosine.

in the spectrum of the complex when compared to the ligand spectrum confirm that the α-amino group (see figure 1) is not involved in the coordination to the metal [21].

An infrared spectrum of the Pt(II)–mimosine complex was also obtained in the region 700–150 cm^{-1} in order to identify frequencies related to M–Cl, M–O and M–N bonds. The IR spectrum shows vibrational absorption frequencies at 323, 348 and 565 cm^{-1} which could be assigned to ν(Pt–Cl), ν(Pt–O) and ν(Pt–N), respectively. These values are in agreement with literature values [21–23].

3.5. *Thermal analysis*

Thermogravimetric analysis (TGA) and differential thermal analysis (DTA) curves for the Pt(II)–mimosine complex are shown in figure 3. According to the thermogravimetric data the composition of the complex formulated as $[PtCl_2(C_8H_{10}N_2O_4)] \cdot 1.5H_2O$ is confirmed. Water molecules are lost at the beginning of heating, at temperatures not exceeding 180°C. The oxidation of the ligand starts almost simultaneously with the end of water loss, at temperatures near 180°C. The residue formed after thermal treatment of the Pt(II)–mimosine complex was identified by powder X-ray diffraction as metallic Pt [24].

The DTA curve of the Pt(II)–mimosine complex shows a strong exothermic peak with a maximum at 418°C and also weak peaks in the range 200–290°C. These are assigned to ligand oxidation of the complex in two steps, leading to the formation of Pt^0 as the final residue.

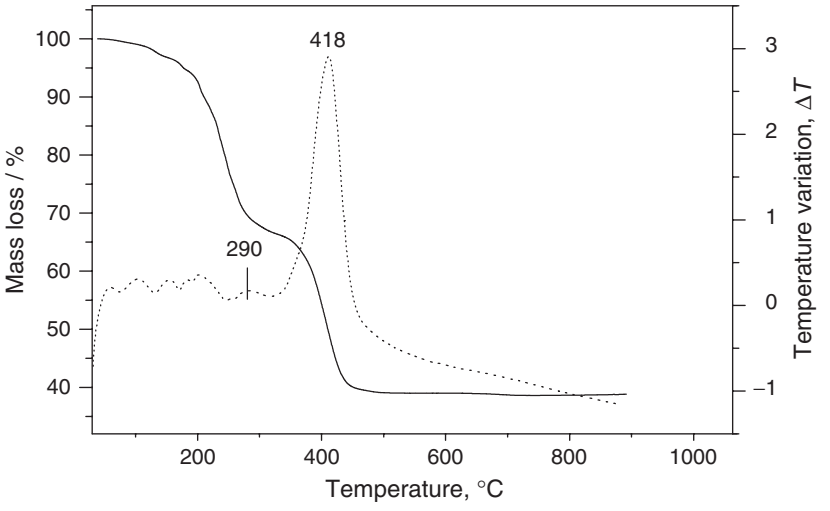

Figure 3. TGA (solid line) and DTA (dotted line) curves for $[PtCl_2(C_8H_{10}N_2O_4)] \cdot 1.5H_2O$.

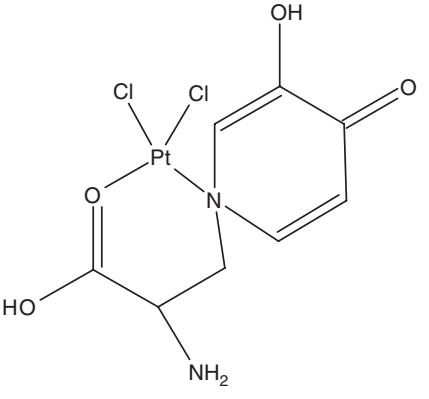

Figure 4. Structural formula proposed for the Pt(II)-mimosine complex.

4. Conclusions

Composition of the Pt(II) complex with L-mimosine is 1 : 1 (metal/ligand). IR, ^{13}C and ^{15}N NMR data indicate coordination of the ligand to Pt(II) via oxygen of COOH and nitrogen of the 3-hydroxy-4-pyridone group in a square-planar geometry.

Based on the chemical and spectroscopic results, the proposed structure for the Pt(II)–mimosine complex is shown in figure 4.

Acknowledgements

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