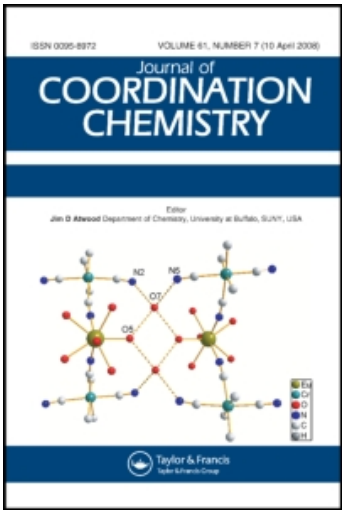

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Synthesis and characterization of a platinum(II) complex with N-acetyl-L-cysteine

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Synthesis and spectroscopic studies in the solid-state of a platinum(II) complex with N-acetyl-L-cysteine are described. Elemental analyses are consistent with composition $Pt_2(C_5H_8NO_3S)_4 \cdot 3H_2O$. Solid-state ^{13}C NMR, infrared, and U-Vis spectroscopic results are consistent with coordination of the ligand to platinum(II) through sulfur. Thermal analyses confirmed water in the complex composition. Final residue of the thermal treatment was identified by powder X-ray diffractometry as metallic platinum.

Keywords: N-Acetyl-L-cysteine; Platinum(II); Solid-state NMR; Infrared spectroscopy; Thermal analysis

1. Introduction

Platinum-based compounds have been widely described as antitumor-active metal complexes since the serendipitous discovery of the antiproliferative and cytotoxic activities of cisplatin by Rosenberg in 1965 [1–3]. Cisplatin, or *cis*-diamminedichloridoplatinum(II), is a square-planar platinum(II) complex which has been used as an anticancer drug since 1978, particularly for treatment of bladder, cervical, head, neck, and also testicular cancer, with a cure rate over 90% [4]. Nevertheless, toxic side effects of cisplatin, especially nephrotoxicity, neurotoxicity, ototoxicity, and gastrointestinal toxicity, have limited its widespread use in high doses [5–7]. Second generation compounds based on the cisplatin structure have been prepared and tested as anticancer drugs. Carboplatin and nedaplatin are two analogues, which have been used for treatment of ovarian, head, neck, testicular, bladder, and lung cancers [8].

Metal-based compounds with rhodium, rhenium, ruthenium, gallium, gold, cobalt, copper, and tin have also been studied as potential anticancer drugs. Recently, a new gold(III) complex with 2-(phenylazo)pyridine was tested *in vitro* in a number of tumor

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cell lines, such as human ovarian cell lines A2780 and A2780R (sensitive and resistant to cisplatin) and murine lymphocytic leukemia cell lines [9]; the gold(III) complex presented IC_{50} values within the micromolar range, which is considered to be promising cytotoxic activity [9].

Platinum complexes with amino acids and their palladium analogues have also been studied as possible anticancer drugs. Recently, new palladium(II) and platinum(II) complexes with deoxyalliin (S-allyl-L-cysteine) show *in vitro* antiproliferative and cytotoxic activities over HELA tumorigenic cells [10–12]. In addition, a new palladium(II) complex with methionine sulfoxide, showing N- and O-coordination, and a platinum(II) complex with L-alliin, showing N- and S-coordination, were also obtained in our laboratories [13, 14]. Preliminary *in vitro* cytotoxic studies showed low activity of these complexes against HELA cells. Structural and kinetic reactivity of platinum complexes with L-cysteine-derived ligands are of high interest in the field of metallodrugs due to the Pt–S bond lability in the presence of other nucleophiles [15].

N-Acetyl-L-cysteine ($C_5H_9NO_3S$, NAC) is a sulfur-containing amino acid present in vegetables and fruits such as asparagus, red pepper, lemons, and tomatoes [16]. Biological activities of N-acetyl-L-cysteine were recently described [17–21]. Synthesis, characterization, and reactivity of a dinuclear platinum(II) complex with N-acetyl-L-cysteine and bipyridine were described, where N-acetyl-L-cysteine is coordinated to Pt(II) through sulfur and bridges the two metal centers [22]. More recently, a new palladium(II) complex with NAC, in the anionic form, was synthesized in our laboratories [21]. The present article describes the synthesis of a new platinum(II) complex with NAC and its spectroscopic and thermal characterization in the solid-state.

2. Materials and methods

2.1. *Reagents and equipment*

N-Acetyl-L-cysteine and potassium tetrachloridoplatinate(II) of analytical grade were purchased from Sigma-Aldrich laboratories. Elemental analyses for carbon, hydrogen, and nitrogen were performed with a CHNS-O EA1108 Analyzer, CE Instruments. Infrared (IR) spectra were recorded on a FT-IR spectrophotometer Nicolet Impact 400, Perkin Elmer, with samples prepared as KBr pellets. Solid-state ^{13}C NMR spectra were recorded on a Varian INOVA 300 MHz spectrometer equipped with a MAS 7-mm probe. The CP/MAS spectra were measured at a spin rate of 4.5 KHz and rf pulse of $\pi/2$. The contact time was 2.0 ms and the recycle delay time was 7 s. The ^{13}C NMR-MAS spectra were acquired at 75 MHz. Samples were analyzed at room temperature and the chemical shifts were referenced to TMS. Solution-state ^{1}H and ^{13}C NMR spectra of NAC and the Pt(II)–NAC complex were acquired in deuterium oxide (D_2O) on a Varian INOVA 500 MHz spectrometer using a 5 mm probe at 303 K. ^{1}H NMR spectra were acquired at 499.6 MHz while ^{13}C NMR spectra were acquired decoupled at 125.6 MHz. The UV-Vis spectrum of the Pt(II)–NAC complex was acquired by diffuse reflectance of the solid compound using an Ocean Optics USB 4000 spectrophotometer. Thermal analyses were performed on a Thermoanalyzer TGA/DTA simultaneous SDT Q 600, TA Instruments, in air, at flux rate of $50\,cm^3\,min^{-1}$ and heating rate of $10^{\circ}C\,min^{-1}$, from 40 to 900°C. Powder X-ray

characterization of the thermogravimetric residue was performed on a Siemens D5000 Diffractometer, Cu-Kα_1 radiation (1.5406 Å). Sample was scanned over 2θ range from 4 to 70°.

2.2. *Synthesis of the complex*

The platinum(II) complex with NAC was synthesized by reaction of 5.0×10^{-4} mol of potassium tetrachloridoplatinate (K_2PtCl_4), in aqueous solution (5.0 mL), with 5.0 mL of an aqueous solution of lithium N-acetyl-L-cysteinate, freshly prepared as described earlier [21], containing 1.0×10^{-3} mol of the ligand (molar proportion Pt : NAC of 1 : 2). Synthesis of the complex was carried out with stirring at room temperature. The final volume was 10.0 mL. After 24 h of constant stirring, a solid was obtained from the reaction mixture by precipitation with about 10 mL of ethanol. The bright-yellowish precipitate was collected by filtration, washed with cold ethanol, and dried in a desiccator over P_4O_{10}. Anal. Calcd for $Pt_2(C_5H_8NO_3S)_4 \cdot 3H_2O$ (%): C, 22.0; H, 3.50; N, 5.13; S, 11.7. Found (%): C, 21.0; H, 2.96; N, 5.23; S, 11.0. Yield 62%. No single crystals were obtained, even after several attempts using a mixture of solvents (water : ethanol in different proportions). The complex in aqueous or dimethyl sulfoxide solution was also left to stand at room temperature for 2 weeks, but no crystals formed. The Pt(II)–NAC complex is soluble in water, dimethyl sulfoxide, and methanol, scarcely soluble in ethanol, acetone, and chloroform, and insoluble in hexane.

3. Results and discussion

3.1. *Solution and solid-state NMR spectroscopy*

The structure of NAC with hydrogen and carbon numbering is shown in figure 1. According to published data [21], the chemical shifts for H_2, H_3, and H_5 are 4.58, 2.94, and 2.02 ppm, respectively, while the chemical shifts for carbons from C_1 to C_5 are 174.5, 54.98, 25.35, 173.8, and 21.94 ppm, respectively.

Solution-state ^1H and ^{13}C-{^1H} NMR spectra of the Pt(II)–NAC complex are of poor resolution. Due to the broadening of the ^1H signals in D_2O solution, assignment of the hydrogens was not obtained; a possible decomposition of the complex when dissolved in D_2O needs to be considered. Similar behavior was observed for the Pd(II)–NAC complex [21].

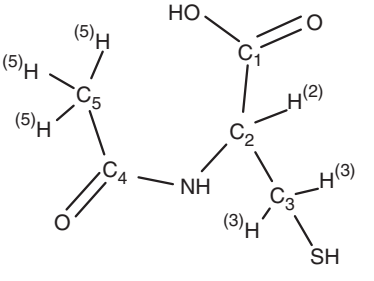

Figure 1. Schematic structure of NAC showing hydrogen and carbon numbering.

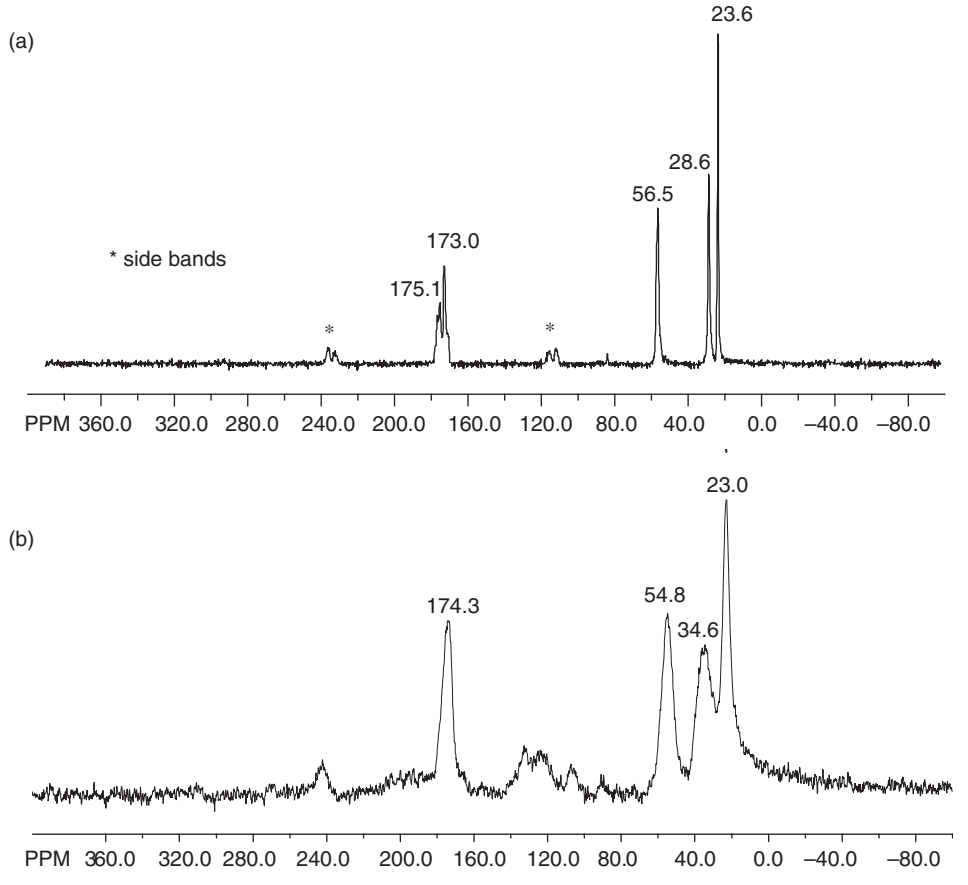

Figure 2. Solid-state ^{13}C NMR spectra for NAC (a) and Pt(II)–NAC (b).

CP-MAS solid-state NMR (SSNMR) was applied to assign the ^{13}C peak positions [23] by comparison to the spectrum of free NAC. The ^{13}C NMR spectra are shown in figure 2.

Sulfur coordination of NAC to Pt(II) is indicated by ^{13}C NMR spectra. The chemical shift for C_3 (bonded to the S atom) in the spectrum of the free ligand is at 28.6 ppm while in the spectrum of the complex it is at 34.6 ppm ($\Delta\delta$ of 6.0 ppm). For the palladium(II) complex with NAC [21], sulfur coordination to Pd(II) was proposed based on a coordination shift of 6.3 ppm. In addition, solid and solution-state ^{13}C NMR spectra of a palladium(II) complex with 2,5,8-trithia-[9](2, 9)-1,10-phenanthrolinophane, showing sulfur coordination, exhibit shifts of the carbon bonded to sulfur by 7.1–12.4 ppm when ligand and complex spectra are compared [24]. For platinum complexes with glutathione, peaks attributed to carbons near the thiol group appeared to be affected most by sulfur coordination [25]. The ^{13}C SSNMR chemical shifts for NAC and Pt(II)–NAC are summarized in table 1.

Possible nitrogen coordination to Pt(II) was also considered by comparing the solid-state ^{13}C NMR spectra of the free ligand and the Pt(II)–NAC complex. The chemical shift for C_2, bonded to the nitrogen atom, appears at 56.5 ppm in the ligand spectrum while for the complex it shifts upfield to 54.8 ppm ($\Delta\delta$ of 1.70 ppm). This minor change

Table 1. ^{13}C chemical shifts for NAC and for Pt(II)–NAC.

	Chemical shifts (ppm)				
Compounds	C1	C2	C3	C4	C5
NAC	175.2	56.5	28.6	173.0	23.6
Pt(II)–NAC	174.3	54.8	34.6	174.3	23.0

suggests that nitrogen is not coordinated. In the Pt(II) complex with 3-hydroxypicolinic acid, nitrogen–platinum coordination produces shifts of the carbon atoms bonded to nitrogen of 3.8–5.0 ppm (solution-state ^{13}C NMR) [26].

The chemical shifts of 175.2 and 173.0 ppm in the spectrum of NAC are assigned to the carbon atoms of the carboxyl and acetyl groups (C_1 and C_4 in figure 1), respectively. In the spectrum of the complex, the chemical shifts for C_1 and C_4 appear at 174.3 ppm. The minor chemical shift differences, 0.9 ppm for C_1 and 1.3 ppm for C_4 indicates that neither nitrogen nor oxygen of the amide coordinates to Pt(II).

3.2. *Infrared and UV-Vis spectroscopic measurements*

The Pt(II)–NAC IR spectrum was analyzed in comparison to the IR spectra of free NAC and lithium N-acetyl-L-cysteinate. The IR spectra of NAC, lithium N-acetyl-L-cysteinate, and Pt(II)–NAC are shown in "Supplementary material".

The IR spectrum of NAC exhibits a strong absorption band at 1718 cm^{-1}, assigned to carboxylic group [27], observed at 1725 cm^{-1} in the Pt(II)–NAC complex evidence that the carboxylic group is not coordinated as proposed by ^{13}C NMR analysis.

The IR spectrum of NAC shows a sharp S–H stretching absorption band at 2548 cm^{-1}. The absence of this band in the Pt(II)–NAC spectrum is a valuable evidence of coordination to Pt(II) through the sulfur atom [28]. The IR spectrum of lithium N-acetyl-L-cysteinate exhibits a weak absorption band at 685 cm^{-1}, assigned to ν(C–S), shifted to 665 cm^{-1} in the complex, additional evidence of coordination of NAC to Pt(II) through sulfur [27, 29].

According to the literature, if coordination occurs through nitrogen, the hydrogen of N–H is most likely lost and the N–H vibration disappears from the IR spectrum of the complex [22, 30]. The N–H vibration mode in the spectrum of the ligand is at 3270 cm^{-1} while in the complex a broad band at 3380 cm^{-1}, further supporting non-coordination through nitrogen. As previously described [21], broadening of the N–H band is likely due to the presence of water, which forms hydrogen bonds in the solid complex [27]. However, the broad band at 3380 cm^{-1} could arise from the O–H stretches of the COOH group and the H_2O molecules and so coordination of NAC to Pt(II) through the nitrogen cannot be ruled out from IR data.

The UV-Vis spectrum of the Pt(II)–NAC complex exhibits a strong absorption with a maximum at 420 nm (23,800 cm^{-1}). Platinum(II) complexes containing S-donor ligands exhibit strong ligand to metal charge-transfer bands (LMCT), assigned to the sulfur $\rightarrow$ platinum(II) transition [31, 32]. For Pt(II)–NAC, broadening of the LMCT

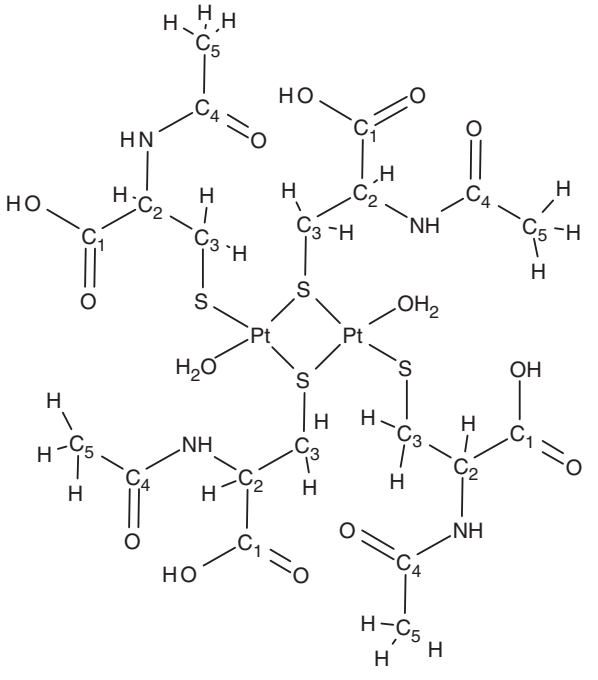

Figure 3. Structural formula proposed for Pt(II)–NAC. Hydration water omitted.

band may be due to the presence of intraligand transitions and weak platinum(II) d–d transitions.

3.3. *Thermal analysis*

Thermogravimetric (TGA) and differential thermal analysis (DTA) curves for the Pt(II)–NAC complex are provided in "Supplementary material". Water molecules are lost at the beginning of heating, below 180°C. Anal. Calcd for loss of H_2O molecules (%): 4.94. Found (%): 4.60. Oxidation of the ligand starts almost simultaneously with the end of water loss, at temperatures near 180°C. The residue formed after the thermal treatment of the Pt(II)–NAC complex at 900°C was identified by powder X-ray diffractometry as metallic platinum [33].

The DTA curve for Pt(II)–NAC complex shows a strong exothermic peak at 322°C and two weak exothermic peaks with maxima at 260 and 360°C. These effects are assigned to ligand oxidation in three steps, leading to the formation of Pt^0 as the final residue of the thermal treatment.

4. Conclusions

The molar composition of the Pt(II)–NAC complex was 1 : 2 (metal : ligand). Water content was confirmed by thermogravimetric analysis. Solid-state ^{13}C NMR, IR, and UV-Vis data support coordination of the ligand to Pt(II) *via* the sulfur. Based on the

chemical and spectroscopic results, a schematic structure for the Pt(II)–NAC complex, with molecular formula $[(NAC\text{-}S)(H_2O)Pt(\mu\text{-}NAC\text{-}S)_2Pt(H_2O)(NAC\text{-}S)]\cdot H_2O$, is presented in figure 3. A Pt(II) dimer with two bridging N-acetyl-L-cysteines is supported by previously published results on $[Pt_2\ \mu\text{-}NAC\text{-}S)_2(bpy)_2]$ (bpy = bipyridine), where the sulfur of NAC bridges two metals [22], and also by the recently published data of a Pd(II) complex with N-(2-mercaptoethyl)-3,5-dimethylpyrazol (Hmed) of composition $[PdCl(med)]_2$, where each Pd(II) is coordinated to a pyrazolic nitrogen, one Cl atom, and two bridging sulfurs [28].

Although this proposed structure with sulfur coordination seems most probable, an alternative formulation with sulfur and nitrogen coordination cannot be completely discarded based on these data.

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