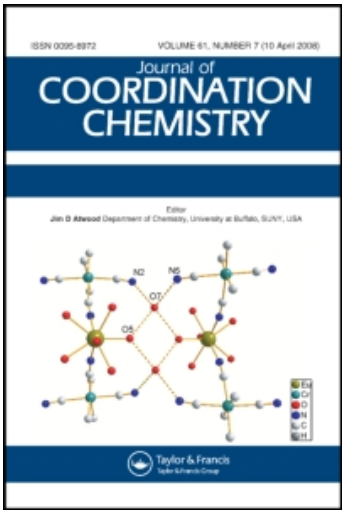

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Chemical and spectroscopic studies of a new palladium(II) complex with N-acetyl-L-cysteine

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Chemical and spectroscopic studies of a new palladium(II) complex with *N*-acetyl-L-cysteine

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Chemical and spectroscopic studies of a new palladium(II) *N*-acetyl-L-cysteine complex are described. Elemental analyses for the solid complex are consistent with the formula $[Pd(C_5H_8NO_3S)_2]\cdot H_2O$ or $[Pd(NAC)_2]\cdot H_2O$. Solid-state ^{13}C nuclear magnetic resonance (NMR), UV–Visible (UV–Vis) and infrared (IR) spectroscopic analyses are consistent with coordination of the ligand to palladium(II) through the nitrogen and sulfur atoms in a square-planar geometry. Thermogravimetric and differential thermal analyses confirmed the composition; final residue was identified as metallic palladium.

Keywords: *N*-acetyl-L-cysteine; Palladium(II); ^{13}C NMR; Infrared spectroscopy; UV–Vis; Thermal analysis

1. Introduction

Metal-based drugs and imaging agents are used in medicine for diagnosis and treatment of different human malignancies [1]. Auranofin, aurothioglucose, gold sodium thiomalate and sanochrysin are examples of gold(I) complexes used in treatment of rheumatoid arthritis [2, 3]. Gadolinium(III) diethylenetriaminepentaacetate, or [Gd(DTPA)], is one of the most common clinically employed contrast agents [3]. Sodium nitroprusside is an iron(II) complex used in medicine for hypertension therapy [3, 4]. More recently, some vanadium complexes have been investigated in the treatment of diabetes [3]. However, cisplatin remains the best example of a metal-based drug used in medicine. Cisplatin, or *cis*-diammindichloridoplatinum(II), is a square-planar platinum(II) complex used as an anticancer drug since 1978, particularly for treatment of bladder, cervical, head, neck and also testicular cancer, for which it has a cure rate of over 90% [5]. Nevertheless, toxic side effects of cisplatin, especially nephrotoxicity, neurotoxicity, ototoxicity and gastrointestinal toxicity, have limited its use in high doses [6–8].

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Interest in developing new complexes active against tumors, but with reduced side effects, has stimulated the synthesis of many new complexes. Second generation compounds based on cisplatin structure have been prepared and tested as anticancer drugs. Carboplatin and nedaplatin are two cisplatin analogues used for treatment of ovarian, head, neck, testicular, bladder and lung cancers [9]. Platinum complexes with amino acids and their palladium analogues have also been prepared and studied as possible anticancer drugs. Complexes of platinum(II) and palladium(II) containing tyrosine, alanine and methionine displayed anticancer activities against some lymphocytic leukemia cells [6]. Studies on structural and kinetic reactivity of platinum and palladium complexes with L-cysteine-derived ligands have also been investigated due to Pt–S bond lability [10].

Recently, new palladium(II) and platinum(II) complexes with deoxyalliin (*S*-allyl-L-cysteine) showing *in vitro* antiproliferative and cytotoxic activities over HeLa tumorigenic cells were prepared in our laboratories [11–13]. In addition, a new palladium(II) complex with methionine sulfoxide showing N, O coordination and molecular formula $[Pd(C_5H_{10}NO_3S)_2]\cdot H_2O$ was also obtained [14]. Preliminary *in vitro* cytotoxic studies showed low activity of this palladium complex against HeLa cells.

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 [15]. The antioxidant effects of NAC in body cells were recently described in the literature [16]. NAC can also be applied as a mucolytic agent in the treatment of respiratory diseases [17]. The protective effect of NAC against the toxicity of paracetamol and acrolein was also described earlier [18]. Moreover, NAC has been studied as a suppressor of fibroblast cell cycle progression in G1 phase [19].

Synthesis, characterization and reactivity of a dinuclear platinum(II) complex with NAC and bipyridine have NAC coordinated to Pt(II) atom through sulfur [20]. The present manuscript describes the synthesis and characterization of a new palladium(II) complex with NAC.

2. Materials and methods

2.1. *Reagents and equipment*

N-Acetyl-L-cysteine and lithium tetrachloropalladate(II) of analytical grade were purchased from Sigma-Aldrich laboratories. Elemental analyses for carbon, hydrogen and nitrogen were performed using 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 nuclear magnetic resonance (NMR) spectra were recorded on a Varian 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 of 2.0 ms and the recycle delay time was of 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 Pd(II)–NAC complex were acquired in deuterium oxide (D_2O). The NMR spectra were recorded on a Varian 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 and at 125.6 MHz. Ultraviolet–visible (UV–Vis) spectrum of the Pd(II)–NAC complex was acquired by diffusion reflectance of the solid complex on a Varian Cary 500 spectrophotometer. Thermal analyses were performed on a Thermoanalyzer TGA/DTA simultaneous SDT Q 600, TA Instruments, in the following conditions: air, flux rate of 50 $cm^3\,min^{-1}$ and heating rate of 10°C min^{-1}, from 40°C to 900°C.

2.2. *Synthesis of the complex*

The palladium(II) complex with NAC was synthesized by reaction of 1.0×10^{-3} mol of lithium tetrachloropalladate (Li_2PdCl_4), in ethanolic solution (20 mL), with a freshly prepared ethanolic solution of lithium *N*-acetyl-L-cysteinate (60 mL) containing 2.0×10^{-3} mol of the ligand (molar proportion Pd : NAC of 1 : 2). Synthesis of the complex was carried out with stirring at room temperature. A yellowish precipitate slowly formed. After 2 h of constant stirring, the complex was filtered, washed with cold ethanol and dried in a desiccator over P_4O_{10}. Anal. Calcd for $PdC_{10}H_{16}N_2O_6S_2 \cdot H_2O$ (%): C, 26.8; H, 4.05; N, 6.24. Found (%): C, 26.0; H, 4.09; N, 5.91. No single crystals were obtained, even after several attempts. The Pd(II)–NAC complex is soluble in water, dimethyl sulfoxide and methanol, slightly soluble in ethanol, acetone and chloroform, and insoluble in hexane.

Lithium *N*-acetyl-L-cysteinate was prepared by reaction of equimolar quantities of lithium hydroxide and NAC at 60°C under stirring for 20 minutes.

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. The ^1H NMR spectrum of NAC in D_2O shows chemical shifts for H_2, H_3 and H_5 at 4.58, 2.94 and 2.02 ppm, respectively. The ^{13}C-{^1H} NMR spectrum of NAC shows chemical shifts from C_1 to C_5 at 174.5, 54.98, 25.35, 173.8 and 21.94 ppm, respectively.

Solution-state ^1H and ^{13}C-{^1H} NMR spectra of the Pd(II)–NAC complex are of poor resolution. Enlargement of the ^1H signals in D_2O solution did not permit an assignment of the hydrogen atoms. Based on these results, decomposition of the complex when dissolved in D_2O at room temperature cannot be discarded.

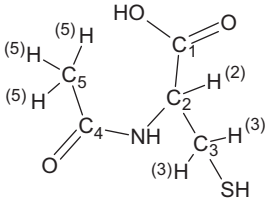

Figure 1. Schematic structure of *N*-acetyl-L-cysteine showing hydrogen and carbon numbering.

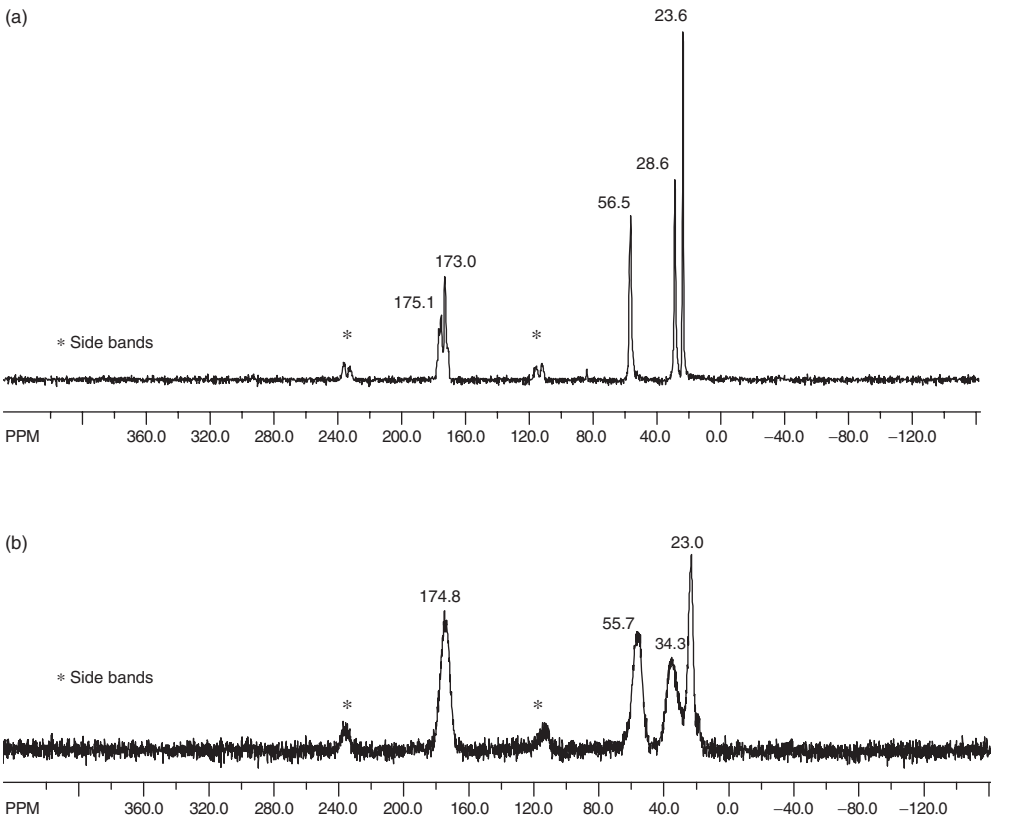

Figure 2. Solid-state ^{13}C NMR spectra for NAC (a) and the Pd(II)–NAC complex (b).

Nuclear magnetic resonance in the solid-state (SSNMR) is a powerful method for determination of molecular structures of different classes of compounds [21]. In the case of NMR studies of metal complexes that exhibit poor spectra or may suffer structural changes when dissolved in solvents, the CP/MAS solid-state NMR experiment is a powerful tool to determine ^{13}C peak positions [22]. CP/MAS ^{13}C NMR spectra of NAC and Pd(II)–NAC were useful for assigning ligand to metal bonding sites. The NMR spectrum of the complex was analyzed in comparison to the spectrum of the ligand. ^{13}C NMR spectra for NAC and for the Pd(II)–NAC complex in the solid-state are shown in figure 2.

The ^{13}C SSNMR spectra indicate coordination of NAC to Pd(II) through the nitrogen and sulfur atoms. According to the ^{13}C NMR data, chemical shifts at 175.2 and 173.0 ppm in the spectrum of NAC are assigned, respectively, to the carbon atoms of the carboxylic and acetyl groups (C_1 and C_4 in figure 1). In the spectrum of the complex the chemical shifts for C_1 and C_4 appear at 174.8 ppm. The shift of carbon C_4 (bonded to nitrogen) by 1.80 ppm in the complex spectrum compared to NAC may result from N–Pd coordination. Indeed, minor changes are also observed for the chemical shift of C_2 in the spectrum of the Pd(II)–NAC complex when compared to the ligand. C_2 which is also bonded to nitrogen, appears at 56.5 ppm in the ligand spectrum while for the complex shifting upfield to 55.7 ppm. These changes reinforce the

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

	Chemical shifts (ppm)				
Compounds	C1	C2	C3	C4	C5
NAC	175.2	56.5	28.6	173.0	23.6
Pd(II)–NAC	174.8	55.7	34.9	174.8	23.0

proposed coordination of NAC to Pd(II) through nitrogen. Because there are limited solid-state ^{13}C NMR data available for palladium(II) complexes with amino acids showing N, S coordination, similar palladium(II) complexes with N, O and N, S donor ligands were used for comparative studies. For the Pd(II) complex with 3-hydroxypicolinic acid, the N–Pd coordination causes isomer shifting of carbon atoms bonded to the nitrogen by 2.9–4.9 ppm (solution-state ^{13}C NMR data) [23]. Moreover, for the Pd(II) complex with 3-hydroxypicolinic acid, coordination of the oxygen atom of the carboxylate group to Pd(II) is attested by the isomer shifting of the carbon atom of this group by 5.1 ppm (solid-state ^{13}C NMR data). The absence of chemical shifting for the carbon atom of the carboxylic group in the NMR spectrum of NAC when compared to the spectrum of the Pd(II)–NAC complex is an indication of the non-coordination of NAC to palladium(II) through the oxygen atom of the carboxylic group [23].

Sulfur coordination of NAC to Pd(II) is also inferred by considering the ^{13}C NMR spectra. The chemical shift for C_3 (bonded to sulfur) in the spectrum of the ligand is at 28.6 ppm, while in the spectrum of the complex the chemical shift is downfield, at 34.9 ppm (see figure 2). In the palladium(II) complex with *S*-allyl-L-cysteine previously described, sulfur coordination to Pd(II) was proposed by observing the chemical shift of the carbon atoms bonded to the sulfur atom by 6.3–8.3 ppm when the ligand and the complex ^{13}C NMR spectra in solution-state are compared [11]. Moreover, solid and solution-state ^{13}C NMR spectra of the palladium(II) complex with 2,5,8-trithia-[9](2,9)-1,10-phenanthrolinophane, showing N, S coordination, exhibit shifts of the carbon bonded to sulfur by 7.1–12.4 ppm when ligand and complex data are compared [24]. ^{13}C SSNMR chemical shifts for NAC and the Pd(II)–NAC complex are summarized in table 1.

3.2. *IR and UV–Vis spectroscopic measurements*

The Pd(II)–NAC IR spectrum was analyzed in comparison to the IR spectrum of lithium *N*-acetyl-L-cysteinate. The amino group involvement in the coordination of NAC to Pd(II) is proposed by the shift of the N–H absorption band from 3270 cm^{-1} in the IR spectrum of lithium *N*-acetyl-L-cysteinate to 3370 cm^{-1} (broad band) in the spectrum of the complex [25]. Enlargement of the N–H band in the spectrum of Pd(II)–NAC is probably due to the presence of water molecules, which form hydrogen bonds with the complex [25].

The spectrum of the Pd(II)–NAC complex exhibits a strong absorption at 1720 cm^{-1}, not observed in the spectrum of lithium *N*-acetyl-L-cysteinate. The band at 1720 cm^{-1} in the spectrum of the complex would be assigned to the un-ionized and uncoordinated

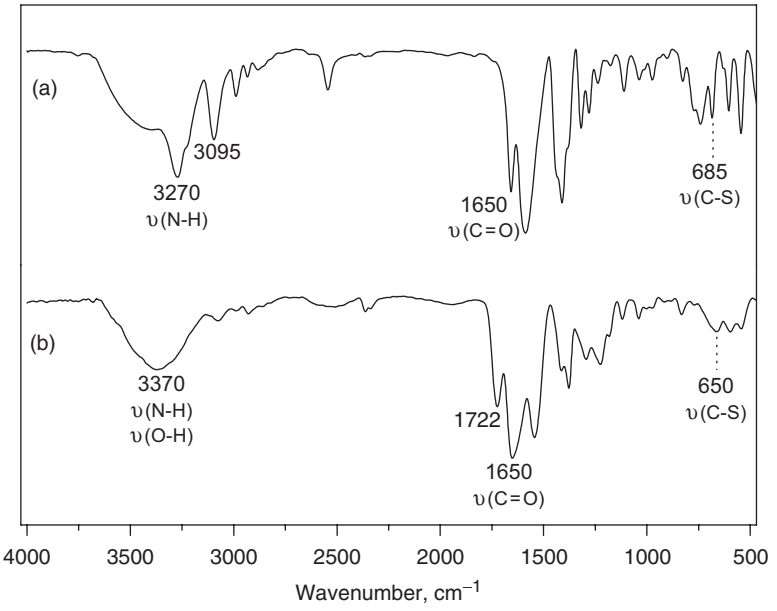

Figure 3. IR spectra of lithium *N*-acetyl-L-cysteinate (a) and the Pd(II)–NAC complex (b).

carboxylic group [24]. The IR spectrum of lithium *N*-acetyl-L-cysteinate also exhibits a weak band at 685 cm^{-1}, assigned to the ν(C–S) vibration. In the spectrum of the complex, this weak band shifts to 650 cm^{-1}, providing additional indication of coordination of NAC to Pd(II) through the sulfur as proposed by ^{13}C NMR spectroscopy [25, 26]. The IR spectra of lithium *N*-acetyl-L-cysteinate and the Pd(II)–NAC complex are shown in figure 3.

UV–Vis spectrum of the Pd(II)–NAC complex exhibits absorption bands at 270 nm (37,000 cm^{-1}) and in the region 330–500 nm (31,300–20,000 cm^{-1}, broad band). According to the literature, complexes containing sulfur donor ligands exhibit strong charge-transfer transitions, which prevent observation of the expected bands. The band with a maximum at 270 nm may be assigned to a combination of sulfur → palladium(II) and nitrogen → palladium(II) charge-transfer, while the broad band is assigned to palladium(II) d–d transitions [27, 28].

3.3. *Thermal analysis*

Thermogravimetric (TGA) and differential thermal analysis (DTA) curves for Pd(II)–NAC are shown in figure 4. According to the thermogravimetric data, the composition of the complex $[Pd(C_5H_8NO_3S)_2]\cdot H_2O$ is confirmed. The water is lost at the beginning of heating, at temperatures not exceeding 150°C. Anal. Calcd for loss of one H_2O molecule (%): 4.03. Found (%): 4.01. 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 Pd(II)–NAC complex at 900°C was identified by powder X-ray diffractometry as metallic palladium [29].

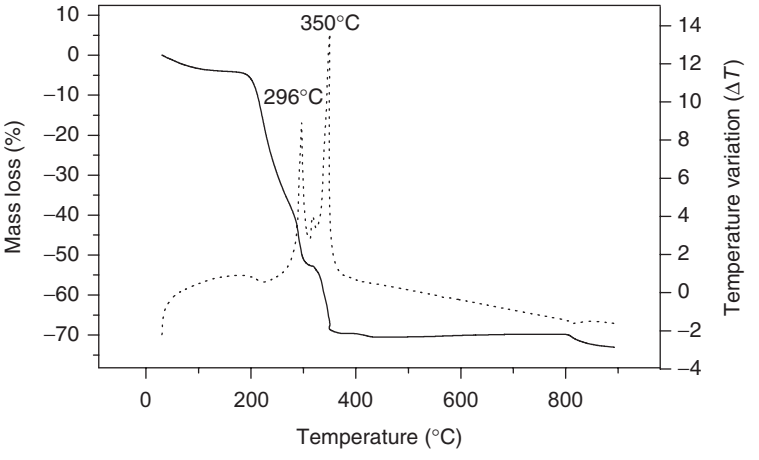

Figure 4. TGA (solid) and DTA (dash) curves for $[Pd(C_5H_8NO_3S)_2] \cdot H_2O$.

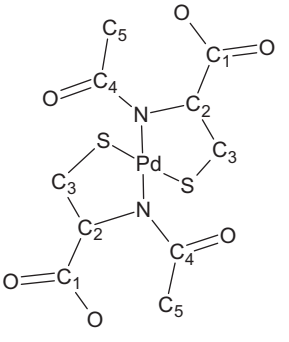

Figure 5. Structural formula proposed for the Pd(II)–NAC complex. Hydrogen atoms were omitted.

The DTA curve of the Pd(II)–NAC complex shows two strong exothermic peaks with their maxima at 296°C and 350°C, assigned to ligand oxidation in two steps, leading to formation of Pd^0 as the final residue of the thermal treatment.

4. Conclusions

Molar composition of the Pd(II)–NAC complex was found to be 1 : 2 (metal : ligand). ^{13}C NMR, IR and UV–Vis data indicate coordination of the ligand to Pd(II) *via* nitrogen and sulfur in a square-planar geometry. Based on the chemical and spectroscopic results, the proposed structure for the Pd(II)–NAC complex is presented in figure 5.

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