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Copper(II), palladium(II) and platinum(II) chloride complexes with 5-amino-2-*tert*-butyltetrazole: Synthesis, characterization and cytotoxicity

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ABSTRACT

Complexes CuL_3Cl_2, PdL_2Cl_2 and PtL_2Cl_2, where L is a novel ligand from the series of 2-substituted 5-aminotetrazoles, namely 5-amino-2-*tert*-butyltetrazole (**1**), have been synthesized by the reaction of metal(II) chlorides with **1** and characterized by IR spectroscopy, thermal and X-ray analyses. The crystallographic structural analysis of these complexes revealed that **1** acts as a monodentate ligand coordinated to the metal *via* endocyclic N4 atom. Platinum complex demonstrates promising cytotoxicity against human cervical carcinoma cells with IC_{50} value average between those of cisplatin and carboplatin.

1. Introduction

5-Aminotetrazole and its derivatives possess a unique combination of properties. They have high nitrogen content and, despite their large positive enthalpies of formation [1], are thermally stable [2]. Therefore, these compounds are of interest as gas generating and blowing agents [2,3]. A range of 5-aminotetrazoles has been reported as biologically active compounds [4]. Moreover, they are valuable precursors in the synthesis of diverse tetrazole derivatives [3], including condensed tetrazoles [5], 5-aminotetrazolium salts [6] and 5-nitroaminotetrazoles [7] possessing useful properties.

In recent years aminotetrazoles have gained more and more attention as ligands in complexes with transition metal salts [8]. In particular, complexes of 5-aminotetrazole [9], its binuclear analog – *N*,*N*-bis(1*H*-tetrazol-5-yl)-amine [10], and 1-substituted derivatives, namely, 5-amino-1-methyltetrazole [11,12], 1,5-diaminotetrazole [13] and 5-aminotetrazole-1-acetic acid [14] have been characterized and some of them have been proposed as "green" pyrotechnics [15], promising low-toxic priming explosives and components of gas generating compositions [11,16], initial compounds for preparation of metallic nanocellular porous materials [17]. Among complexes of 2-substituted 5-aminotetrazoles only silver complexes of 5-amino-2-methyltetrazole have been synthesized and characterized by X-ray analysis [12].

Herein, we report the preparation, IR characterization and single crystal X-ray diffraction analysis of novel ligand in series of 2-substituted 5-aminotetrazoles, namely 5-amino-2-*tert*-butyltetrazole (**1**, Scheme 1) and its complexes with chlorides of copper(II), platinum(II) and palladium(II). Thermal behavior and cytotoxic activity of the complexes have been also investigated.

2. Experimental

2.1. Materials and instrumentation

Copper(II) chloride dihydrate, platinum(II) chloride and palladium(II) chloride dihydrate were purchased from commercial sources and used without further purification. FT-IR spectra were recorded on a Thermo Nicolet Avatar 360 spectrometer. The TG and DSC curves were obtained using a NETZSCH STA429 thermoanalyzer in a dynamic nitrogen atmosphere (heating rate: 10 °C/min, aluminum oxide, mass 1–3 mg and temperature range with in room temperature to 600 °C).

2.2. Synthesis of tetrazole **1**

Compound **1** was synthesized according to a literature procedure [6b]. *tert*-Butyl alcohol (1.2 mL, 13 mmol) was added with stirring to 5-aminotetrazole monohydrate (1.96 g, 12 mmol) dissolved in 70% perchloric acid (5 mL). The obtained solution was kept at room temperature for 1 h. Alkalization of reaction mixture with aqueous NaOH till pH 8–9 and following filtration gave **1**

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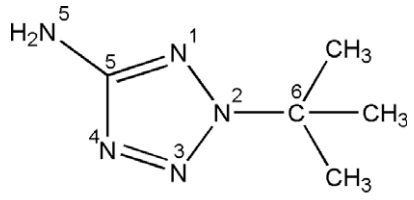

1

Scheme 1. Classical representation and numbering of 5-amino-2-*tert*-butyltetrazole.

(1.3 g, 77%) as white crystals. Mp 115–116 °C (from water). ^{1}H NMR δ (ppm): 5.90 (s, 2H, NH_2), 1.51 (s, 9H, *t*-Bu); ^{13}C NMR δ (ppm): 167.2 (CN_4), 62.6 (CMe_3), 29.2 (Me). FT-IR (cm^{-1}): 3431 (s), 3324 (s), 3232 (s), 3175 (s), 3080 (m), 2988 (s), 2939 (s), 2912 (m), 2876 (m), 1636 (s), 1565 (s), 1539 (s), 1462 (s), 1403 (m), 1373 (s), 1310 (m), 1219 (s), 1196 (s), 1118 (w), 1081 (w), 1037 (w), 1015 (m), 939 (w), 823 (w), 778 (w), 762 (w), 654 (w br), 578 (w), 429 (vw), 315 (m), 262 (w), 192 (m), 142 (s), 111 (w), 92 (m). *Anal.* Calc. for $C_5H_{11}N_5$: C, 42.5; H, 7.8; N, 49.6. Found: C, 42.7; H, 7.6; N, 49.8%.

2.3. Synthesis of CuL_3Cl_2 (**2**)

Copper(II) chloride dihydrate (1 mmol, 0.17 g) was added to a solution of **1** (2 mmol, 0.282 g) in 20 mL of 1,2-dichloroethane. The resulting mixture was stirred at room temperature for 1 h and filtered. Slow evaporation of obtained solution at ambient conditions gave green crystals of complex **2** with quantitative yield (0.37 g). Calc. for $Cu(C_{15}H_{33}N_{15})Cl_2$: Cu 11.39. Found: Cu 11.20%. FT-IR (cm^{-1}): 3436 (s), 3332 (s), 3188 (s), 3071 (w), 2986 (s), 2938 (s), 2911 (w), 2876 (w), 1624 (vs), 1560 (vs), 1458 (s), 1438 (sh), 1404 (m), 1373 (s), 1331 (s), 1305 (m), 1236 (m), 1190 (vs), 1120 (m), 1083 (vw), 1036 (w), 1015 (s), 937 (w), 828 (m), 785 (m), 752 (m), 699 (w), 655 (w br), 576 (m), 429 (m), 354 (s), 322 (m), 312 (m), 274 (w), 241 (m), 194 (m), 173 (s), 143 (s), 134 (w), 128 (m), 123 (m), 96 (s), 68 (w).

2.4. Synthesis of PtL_2Cl_2 (**3**)

Platinum(II) chloride (1 mmol, 0.266 g) was added to the solution of **1** (2 mmol, 0.282 g) in mixture of toluene–THF (2:1). The resulting mixture was stirred at room temperature for 1 h and filtered. Slow evaporation of obtained solution at ambient conditions gave yellow crystals of **3**. Yield (0.47 g, 86%). Calc. for $Pt(C_{10}H_{22}N_{10})Cl_2$: Pt 35.58. Found: Pt 35.23%. FT-IR (cm^{-1}): 3446 (s), 3350 (s), 3165 (w), 3087 (vw), 2987 (s), 2939 (m), 2874 (w), 1618 (vs), 1550 (s), 1455 (s), 1429 (sh), 1403 (m), 1371 (s), 1331 (s), 1299 (s), 1239 (m), 1189 (vs), 1078 (vw), 1034 (w), 1022 (m), 937 (w), 827 (m), 789 (w), 744 (w), 573 (m), 475 (w), 437 (m), 342 (m), 307 (w), 236 (s), 217 (s), 160 (m), 129 (s), 73 (w).

2.5. Synthesis of PdL_2Cl_2 (**4**)

A solution of **1** (2 mmol, 0.282 g) in 20 ml of ethanol was dropped with stirring to a solution of palladium(II) chloride dihydrate (1 mmol, 0.214 g) in 20 ml of 1% hydrochloric acid. The resulting mixture was stirred at room temperature for 20 min. The resulting yellow solid residue was filtered, washed with water, dried and recrystallized from water/ethanol mixture (1/1) to give yellow crystals of **4**. Yield (0.432 g, 94%). Calc. for $Pd(C_{10}H_{22}N_{10})Cl_2$: Pd 23.15. Found: Pd 22.78%. FT-IR (cm^{-1}): 3440 (s), 3414 (s), 3390 (s), 3347 (s), 3158 (w), 3062 (vw), 2987 (s), 2939 (m), 2874 (w), 1612 (vs), 1551 (s), 1453 (s), 1430 (sh), 1403 (m), 1371 (s), 1327 (s), 1299 (s), 1237 (m), 1192 (vs), 1147 (w), 1078 (vw), 1027 (m), 1022 (m), 937 (w), 827 (m), 786 (w), 745 (w), 572 (m), 439 (w), 353 (m), 332 (w), 319 (w), 307 (w), 253 (w), 226 (s), 160 (m), 132 (s).

2.6. X-ray structure determinations

Suitable single crystals for X-ray analysis were picked directly from the reaction products. In the case of palladium complex **4**, single crystals of two polymorphs, marked as **4a** and **4b**, were found. They are triclinic and monoclinic, respectively. Crystal data, data collection and refinement details for the structures reported are summarized in Table 1. X-Ray data were collected on a Nicolet *R*3*m* diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at room temperature. The structures were solved by direct methods (SIR2004 [18]) and refined by full matrix least square technique (SHELXL 97 [19]). In **1**, **2** and **4b**, rotational disorder of the *tert*-butyl groups over two positions was observed. For the disordered groups, bond lengths C–C(*tert*-butyl) and distances C(methyl)···N (where N is the tetrazole ring atom bonded to the *tert*-butyl group) were restrained to be equal, respectively. The amino group H atoms were localized from difference Fourier maps. For **1**, coordinates of amino H atoms were refined freely, whereas for all complexes, bond lengths N–H were restrained to 0.88 Å. U_{iso}(H) values were set to 1.2U_{eq}(N) for all compounds. Molecular graphics was performed with the program PLATON [20].

2.7. Cytotoxicity

In vitro cytotoxicity tests were performed at N.N. Alexandrov National Cancer Centre of Belarus, Minsk, Belarus.

2.7.1. Cell culture

HeLa cells (human cervical carcinoma) were obtained from the cell culture collection of Research Institute for Epidemiology and Microbiology (RIEM, Minsk, Belarus). The cells were cultured as a monolayer in culture flasks covered with 199 medium (RIEM) supplemented with 10% fetal calf serum (RIEM) and 100 μg/mL kanamycin.

2.7.2. Cytotoxicity assay

All the experiments were carried out on exponentially growing cells. Cell monolayer was detached from the culture flasks with 0.02% versen (DIALEK, Belarus), plated at a concentration of 2×10^5 cells/flask and incubated for 24 h at 37 °C. Stock 10^{-2} M solutions of test compounds were freshly prepared in dimethylsulfoxide (DMSO), then dilutions from 10^{-4} to 10^{-6} M in distilled water were made. On the day of the experiment, 50, 100 or 200 μL of drug dilutions were added into the flasks with cell monolayer at final concentrations of 0–50 μM. The cells were incubated in water bath at 37.0 °C for 48 h. Then treated and control cell monolayers were versenized and viable cells were counted using trypan-blue exclusion on a haemocytometer [21]. The mean ± standard deviation was calculated from three experiments. IC_{50} values (drug concentration at which 50% of the cells are viable relative to the control) were determined for each experiment using regression analysis of the data received.

3. Results and discussion

3.1. Preparation of complexes

Tetrazole **1** was found to react smoothly with transition metal(II) chlorides in solutions without heating giving highly crystalline colored complexes CuL_3Cl_2 (**2**), PtL_2Cl_2 (**3**) and PdL_2Cl_2 (**4**) in