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Research paper

Synthesis, DNA and BSA binding of Pd(II) and Pt(II) complexes featuring tetrazolylacetic acids and their esters

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ABSTRACT

Two series of palladium(II) and platinum(II) complexes featuring esters of tetrazol-1-yl and tetrazol-5-ylacetic acids {*trans*-[$PdCl_2L_2$] and *trans*-[$PtCl_2L_2$], L = 5-methyl-1*H*-tetrazol-1-ylacetic acid and its ethyl, butyl, isobutyl esters (**1**–**5**); 2-R-2*H*-tetrazol-5-ylacetic acid and its ethyl esters, R = ^{t}Bu, CH_2CH_2OH (**6**–**10**)} were synthesized and their binding to calf-thymus DNA (CT DNA) and bovine serum albumin (BSA) were studied by means of experimental (CD, UV, viscometry, fluorometric and electrophoretic techniques) and theoretical methods. According to the spectrophotometric data, the interaction of the metal complexes with CT DNA is observed. The significant increase of melting point of CT DNA in the presence of the metal complexes (ΔT_m = 8–13 °C) indicates strong stabilization of the DNA helix. Electrophoretic studies demonstrate the ability of the metal complexes to interact with pBR322 plasmid DNA and to change its mobility. According to the data of the fluorescence quenching technique, binding with constants (K_{bin}) of Pd(II) complexes with BSA are in the range 0.83–4.12 × 10^5 L M^{-1}. The molecular docking studies show the minor groove binding behavior of tetrazole-containing palladium(II) and platinum(II) complexes to DNA ($\Delta G_{binding}$. −5.56 – −6.12 kcal/mol) and effective binding to BSA *via* the favored binding site Trp213 ($\Delta G_{binding}$ −7.2 – −7.56 kcal/mol). The complex *trans*-[$PtCl_2$(2-*tert*-butyl-tetrazol-5-ylacetic acid)$_2$] exhibited noticeable antiproliferative activity in two human cancer cell lines with IC_{50} values of 11.40 μM in HT-29 cells and 11.02 μM in MDA-MB-231 cell line.

1. Introduction

Anticancer agents based on the platinum metal complexes are recognized and widely used in malignancies therapy [1]. A perspective approach in developing of platinum group metal-based drugs with improved efficiency and fewer side effects is introducing various heterocyclic ligands (phenanthroline, imidazole, pyrimidine, purine, etc.) into the structure of the complexes [2]. Tetrazole-containing coordination compounds of platinum group metal ions known to date form a special group of promising compounds exhibiting antitumor activity [3]. For instance, complex [{*cis*-Pt$(NH_3)_2$}$_2$(μ-OH)(μ-5-methyl-tetrazolato-N_2,N_3)]$^{2+}$ was shown to be more cytotoxic than cisplatin in PC-9 (IC_{50} = 0.5 μM) and PC-14 (IC_{50} = 0.2 μM) NSCLC cell lines, and cross-resistance to this complex in the cisplatin-resistant cells was largely circumvented [4]. Also high cytotoxic activity was demonstrated by *cis*-[PtL_2Cl_2].H_2O against HeLa cell line with IC_{50} value of 1.3 μM (for L = 5-amino-1-phenyltetrazole) and 0.9 μM (for L = 5-amino-2-*tert*-butyltetrazole) [5].

Recently, a number of studies have been devoted to different metal complexes bearing tetrazolylcarbonic acids [6]. In preceding papers, we have synthesized and characterized some Pt(II) and Pd(II) complexes featuring derivatives of tetrazol-1-yl and tetrazol-5-ylacetic acids, but the data of their biological activity are limited [7,8]. However, some of these complexes demonstrated noticeable antiproliferative effects: for *trans*-[$PtCl_2$(ethyl 2-*tert*-butyl-tetrazol-5-ylacetate)$_2$], IC_{50} values in HT-29 and MCF-7 human cancer cell lines are 14.2 ± 1.1 and 5.8 ± 1.2 μM, respectively, and are comparable to those of cisplatin [7].

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In this follow-up study, two series of palladium(II) and platinum(II) complexes containing esters of tetrazolylacetic acids as ligands were synthesized and characterized by means of CHN analysis, HRESI-MS, ^{1}H and $^{13}C\{^{1}H\}$ NMR and IR spectroscopies. The structure of the novel *trans*-[$PdCl_2$(butyl 5-methyl-1H-tetrazol-1-ylacetate)$_2$] was established by X-ray diffraction analysis.

DNA is one of the main targets of metal-based drugs and the drug affinity to plasma proteins directly influences the drug concentration in the bloodstream and its biological effect. Therefore, an understanding of the features that determine binding of metal complexes to DNA is very important for the rational design of metal-based chemotherapeutics [9].

In the present study, the interaction of Pd(II) and Pt(II) complexes bearing derivatives of tetrazol-1-yl and tetrazol-5-ylacetic acids with CT DNA was investigated by means of spectroscopic, viscometric and electrophoretic techniques.

On the other hand, drug affinity to plasma proteins directly influences the drug concentration in the bloodstream and its biological effect. Thus, evaluation of the interaction of metal complexes with serum albumins can be useful to predict an efficiency of transfer of a potential drug in the body [10]. In this paper binding constants (K_{bin}) of Pd(II) complexes with BSA were determined by means of the fluorescence quenching technique. Additionally, the molecular docking studies of the tetrazole-containing palladium(II) and platinum(II) complexes with DNA and BSA were carried out. The antiproliferative activity of some metal complexes in human cancer cell lines was determined. The results of these studies are described further in details.

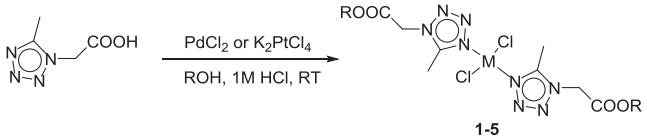
2. Results and discussion

2.1. Structural types, synthesis and characterization

Two principal structural types of the tetrazolylacetic acids ligands have been considered in the present work. The first type comprises derivatives of 5-R-tetrazol-1-ylacetic acid, and the second one includes derivatives of 2-R-tetrazol-5-ylacetic acid. These two types are quite different in their properties and can be synthesized by known procedures, namely *via* alkylation of 5-R-tetrazoles by Cl-acetic acid esters or *via* alkylation of NH-unsubstituted tetrazol-5-ylacetic acid ester by alcohols in strong acidic media [11–13]. Upon interaction with Pt(II) or Pd(II) salts, these ligands allow obtaining water soluble complexes [7,8,12].

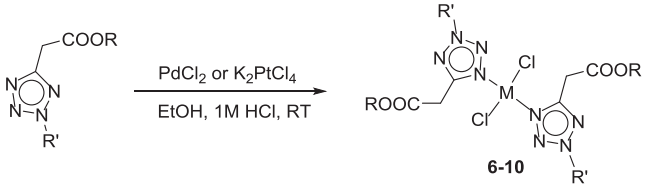
Trans-isomeric palladium(II) and platinum(II) complexes **1**–**5** were obtained by the reaction of 5-methyl-1H-tetrazol-1-ylacetic acid with $PdCl_2$ or K_2PtCl_4 in 1 M HCl in the presence of the corresponding alcohol (Scheme 1). As it has been shown earlier, addition of alcohol to the reaction mixture may result to the esterification of the carboxyl groups of the ligands. The nature and concentration of the alcohol in the reaction mixture affect the composition and the yield of the complexes obtained [8].

Similarly, 2-alkyl-tetrazol-5-ylacetic acids or their ethyl esters were used for the synthesis of complexes **6**–**10** (Scheme 2). Complexes **9** and **10** were synthesized for the first time, while complexes **6**–**8** were obtained as described earlier [7,8].



M = Pd, R = H (**1**), Et (**2**), Bu (**3**), ^{i}Bu (**4**)
M = Pt, R = Et (**5**)

Scheme 1. Synthesis of the complexes *trans*-[MCl_2L_2] (**1**–**5**) featuring 5-methyl-1*H*-tetrazol-1-ylacetic acid and its esters.



M = Pd, R = H, R' = ^{t}Bu (**6**);
M = Pd, R = Et, R' = ^{t}Bu (**7**);
M = Pt, R = Et, R' = ^{t}Bu (**8**);
M = Pd, R = Et, R' = CH_2CH_2OH (**9**);
M = Pt, R = Et, R' = CH_2CH_2OH (**10**)

Scheme 2. Synthesis of the complexes *trans*-[MCl_2L_2] **6**–**10** featuring derivatives of 2-R-2*H*-tetrazol-5-ylacetic acid.

In complexes **1**–**10**, the presence of the tetrazolylacetic fragments and corresponding substituents was confirmed by the characteristic signals in the ^{1}H and $^{13}C\{^{1}H\}$ NMR and IR spectra. Thus, the tetrazole moieties give the characteristic IR bands in the range of 900–1600 cm^{-1} [14]. The carbonyl ν(C=O) stretching bands are observed in the range of 1734–1737 cm^{-1} (ESI† Figs. S33, S34). In the *far*-IR region, *trans* complexes displayed bands associated with the ν(Pd–Cl) stretching vibrations in the range of 280–420 cm^{-1} (for example, at 375.8 cm^{-1} for **4**) (ESI† Fig. S35).

In the $^{13}C\{^{1}H\}$ NMR spectra, the signals of the carbon atoms of the tetrazolyl-1-yl rings were observed at 153.2–154.8 ppm for complexes **1**–**5**, and the signals of the carbon atoms of the tetrazolyl-5-yl rings were observed at 159.5–160.2 ppm for complexes **6**–**10**. The signals of the carbon atoms of the carbonyl groups were observed at 166.4–166.9 ppm. The coordination led to insignificant changes of the chemical shifts of protons and carbon atoms in the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra. Generally, ^{1}H NMR signals in the spectra of the complexes were deshielded in comparison with those in the spectra of uncomplexed tetrazolylacetic acids. For example, in the ^{1}H NMR spectrum of *trans*-[$PdCl_2$(butyl 2-(5-methyl-1H-tetrazol-1-yl)acetate)$_2$] (**3**), the change of 0.1 ppm was observed for the CH_2 group signal (5.40 ppm for 5-methyl-1H-tetrazol-1-ylacetic acid and 5.50 ppm for **3**). On the other hand, majority of $^{13}C\{^{1}H\}$ NMR signals in the spectra of the complexes were shifted upfield. So, $^{13}C\{^{1}H\}$ NMR signals were observed at 8.0 (CH_3), 47.5 (CH_2), and 166.4 (COOBu) ppm for *trans*-[$PdCl_2$(butyl 2-(5-methyl-1H-tetrazol-1-yl)acetate)$_2$] (**3**) and at 8.17 (CH_3), 47.7 (CH_2), 167.8 (COOH) ppm for 5-methyl-1H-tetrazol-1-ylacetic acid. It was noticed that signal of the endocyclic C(5) atom did not shift or shifted upfield insignificantly. Besides, in the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of complexes, signals of atoms of Et, Bu and ^{i}Bu groups are observed.

The ESI(+) mass spectra of complexes **5**, **9** and **10** exhibit the characteristic signals of $[M + Na]^+$ ions (ESI† Figs. S23–25).

2.2. Description of the structures

Molecular and crystal structure of complex **3** was elucidated by X-ray diffraction and shown in Fig. 1 with the atom labeling. The crystals of **3** belong to the orthorhombic system. Table S1 (ESI†) lists the selected bond lengths and bond angles for the studied species.

The compound **3** is molecular complex exhibiting typical square-planar environment of the palladium(II) centers. It should be noted that only the endocyclic N(4) atoms of the tetrazolyl moieties are exclusively involved in coordination with the palladium (II) centers.