Inorganica Chimica Acta 411 (2014) 5–10

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Novel platinum(II) complexes containing diaminocyclohexane and thiourea derivative ligands: Synthesis and X-ray crystal structure of (*trans*-1,2-diaminocyclohexane)dithioureaplatinum(II) nitrate monohydrate

Jing Fang, Xin Wei, John B. Sapp, Yuanjian Deng *

Department of Chemistry, Texas Southern University, 3100 Cleburne Street, Houston, TX 77004, USA

ARTICLE INFO

Article history:
Received 30 September 2013
Received in revised form 7 November 2013
Accepted 13 November 2013
Available online 25 November 2013

Keywords:
Platinum complexes
1,2-Diaminocyclohexane
Thiourea
NMR
X-ray crystal structures

ABSTRACT

Six novel platinum(II) complexes of the form $[Pt(dach)L_2](NO_3)_2$, where dach = *trans*-1,2-diaminocyclohexane, L = thiourea (tu) or its derivatives, including 1-acetyl-2-thiourea, 1-ethyl-2-thiourea, 2-imidazolidinethione, 1,3-dimethyl-2-thiourea and 1,1,3,3-tetramethyl-2-thiourea, have been synthesized and characterized by elemental analysis, IR spectrometry, and NMR (^{1}H and ^{13}C) spectroscopy. The general synthetic procedure involves the reaction of $[Pt(dach)(H_2O)_2](NO_3)_2$, which is formed *in situ* by treating $Pt(dach)I_2$ with silver nitrate, and two equivalents of tu or its derivatives. All the complexes are ionic compounds with nitrate counter ions and thus water soluble. The crystal structure of $[Pt(dach)(tu)_2](NO_3)_2 \cdot H_2O$ is determined using a single crystal X-ray diffraction method. This compound crystallizes in the orthorhombic space group *Pnma* with centrosymmetry.

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1. Introduction

The anticancer activity of the platinum-based first-generation drug cisplatin [*cis*-diamminedichloroplatinum(II)] was discovered in 1969 [1] and its clinical use was approved in 1978 [2]. Since then, thousands of new platinum complexes have been synthesized and evaluated for their anticancer activity [3,4]. The fact that cisplatin possesses considerable adverse side effects that limit its application has stimulated the extensive search for new platinum-based anticancer drugs. In an effort to overcome cisplatin's shortcomings, such as dose-limiting and acquired resistance, the second- and third-generation analogues carboplatin [*cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II)] and oxaliplatin [(1*R*,2*R*-diaminocyclohexane)oxalatoplatinum(II)] have been developed and also approved for clinical use. Studies show that these drugs can reduce renal toxicity in chemotherapy because they tend to react with the sulfur atoms in methionine and cysteine groups of proteins [5–7]. Strong affinity of platinum(II) towards sulfur-containing molecules has long been known. Thus, one modification to the platinum-based anticancer drugs is to use sulfur-containing molecules as carrier ligands along with the nitrogen-containing molecules because the platinum–sulfur interaction would prevent the side effects and improve the transport of the platinum drugs [5]. Commonly used sulfur-containing molecules include dithiocarbamates [8], thiosemicarbazones [9,10], xanthate [11], 2-imidazolidinethione [12], and 1,1,3,3-tetramethylthiourea [13]. In addition to being carrier ligand, some of these sulfur-containing molecules may also be used as protective and rescue agents in platinum-based chemotherapy [5]. Thiourea and its derivatives are of particular interest because of their unique anti-inflammatory, anticancer, and antiproliferative activities [5,14–19]. Both mono- and bi-functional thiourea derivatives have been used as alternative coordinating carrier groups in platinum(II) anticancer complexes [13]. These complexes consist of a cationic platinum(II) complex ion and a counter anion and therefore are soluble in water. Recently, Ma et al. reported that a thiourea derivative ligand, 1-(2-(acridin-9-ylamino)ethyl)-1,3-dimethylthiourea, was released from the inner coordination sphere of ethylenediamineplatinum(II) cation, when this cation reacted with N-acetylcysteine, a derivative of cysteine [20]. Their findings suggested that the platinum–sulfur bond formed with thiourea was weakened when attacked by the cysteine sulfur. To further investigate the relative reactivity between platinum(II)–thiourea complexes and other sulfur-containing model molecules, we have selected *trans*-1,2-diaminocyclohexane (dach) as a carrier ligand because of its ability to form a chelate ring with platinum(II) and thus preventing its replacement by incoming sulfur-containing molecules. Furthermore, the chemistry between oxaliplatin and thiourea derivatives would be of special interest because both have

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* Corresponding author. Tel.: +1 713 313 1917; fax: +1 713 313 7824.
E-mail address: deng_yj@tsu.edu (Y. Deng).

0020-1693/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ica.2013.11.012

demonstrated anticancer activity. To our knowledge, there has been no report on platinum-dach compounds containing dithiourea ligands. Thus, our first goal of research is to synthesize and characterize the dach-platinum-thiourea type complexes. In this paper, we report the preparation and characterization of six novel platinum(II) complexes of the form $[Pt(dach)L_2](NO_3)_2$, where L = thiourea (tu), 1-acetyl-2-thiourea (atu), 1-ethyl-2-thiourea (etu), 2-imidazolidinethione (imt), 1,3-dimethyl-2-thiourea (dmtu), and 1,1,3,3-tetramethyl-2-thiourea (tmtu). Each complex has been characterized by elemental analysis, IR spectrometry, and NMR (^1H and ^{13}C) spectroscopy. All of the complexes are water soluble. The crystal structure of $[Pt(dach)(tu)_2](NO_3)_2{\cdot}H_2O$ is determined using a single crystal X-ray diffraction method.

2. Experimental

2.1. Materials

Potassium tetrachloroplatinate (K_2PtCl_4) was purchased from Johnson Matthey Electronics (Ward Hill, MA). Tu, atu, etu, imt, dmtu, tmtu, dach, and silver nitrate were purchased from Sigma–Aldrich Chemical Co. (St. Louis, MO). Potassium iodide was acquired from Fisher Scientific (Hanover Park, IL). All other chemicals and solvents were obtained from commercial suppliers and used without further purification. Deuterated dimethylsulfoxide (DMSO-d_6) was supplied by Cambridge Isotope Laboratories, Inc. (Andover, MA). 0.20-μm nylon acrodis syringe filters were purchased from Gelman Scientific (Ann Arbor, MI).

2.2. Elemental analysis and spectroscopic measurements

Carbon, hydrogen and nitrogen analyses were carried out by Robertson Microlit Laboratories (Madison, NJ). FTIR spectra were recorded on a Nicolet 380 FTIR spectrometer. NMR spectra (^1H and ^{13}C) were obtained on a JEOL 400 MHz spectrometer. The NMR experiments were conducted in DMSO-d_6 on which signals were locked. Chemical shifts for ^1H and ^{13}C NMR spectra were referenced to the instrument's locked values for the solvent DMSO-d_6 at 2.4662 and 40.0370 ppm, respectively.

2.3. Synthesis of complexes

All six platinum(II) complexes containing dach and tu or its derivatives were synthesized with a similar procedure. The synthesis started with reaction of $Pt(dach)I_2$, which was prepared by a method described by Dhara using the dach ligand instead of the ammine ligand [21], and two equivalents of silver nitrate followed by reacting the appropriate tu derivative. A typical synthetic approach of $[Pt(dach)(tu)_2](NO_3)_2$ is given as an example. For the other five complexes, only their measured data are given.

2.3.1. $[Pt(dach)(tu)_2](NO_3)_2{\cdot}H_2O$

To a 30 mL suspension of $Pt(dach)I_2$ (0.565 g, 1.0 mmol) was added 5 mL of $AgNO_3$ solution (0.330 g, 1.9 mmol). Then a small amount of acetone was added to the suspension. The mixture was stirred at room temperature in the dark for 24 h. Precipitated AgI was then filtered off, and to the filtrate was added 5 mL of tu (0.150 g, 1.9 mmol). Upon stirring at room temperature overnight, the solution was filtered again to remove any insoluble residue, and the solvent was evaporated at 45 °C under reduced pressure. When the volume was reduced to about 5 mL, an off-white precipitate appeared. After the volume was further reduced to about 1 mL, a small amount of acetone was added, resulting in the formation of more precipitate. The solid was then collected by vacuum filtration, washed with two portions of acetone and diethyl ether in sequence, and dried in vacuum oven at 30 °C. Yield, 73% (0.440 g). *Anal.* Calc. for $C_8H_{24}N_8O_7S_2Pt$: C, 15.92; H, 4.01; N, 18.57; S, 10.63. Found: C, 16.52; H, 3.71; N, 18.33; S, 10.39%. IR bands (cm^{-1}): 3381-3131, 2937m, 2856w, 1633s, 1327s, 1169m, 1063s, 824s, 708w, 624w, 590w, 478s.

2.3.2. $[Pt(dach)(atu)_2](NO_3)_2{\cdot}H_2O$

Yield: 53%. *Anal.* Calc. for $C_{12}H_{28}N_8O_9S_2Pt$: C, 20.96; H, 4.10; N, 16.30; S, 9.33. Found: C, 21.10; H, 4.03; N, 15.17; S, 8.06%. IR bands (cm^{-1}): 3500-3078, 2935w, 2864w, 1715s, 1622m, 1564m, 1373w, 1317m, 1294m, 1222s, 1162s, 1041s, 827w, 730br, 596m, 479s.

2.3.3. $[Pt(dach)(etu)_2](NO_3)_2$

Yield: 87%. *Anal.* Calc. for $C_{12}H_{30}N_8O_6S_2Pt$: C, 22.46; H, 4.71; N, 17.47; S, 10.00. Found: C, 22.60; H, 4.56; N, 17.28; S, 9.80%. IR bands (cm^{-1}): 3397-3110, 2947w, 2860w, 1614vs, 1455s, 1322s, 1166s, 1065m, 1039w, 919m, 824s, 695s, 500m, 541s, 466m, 434m.

2.3.4. $[Pt(dach)(imt)_2](NO_3)_2{\cdot}H_2O$

Yield: 75%. *Anal.* Calc. for $C_{12}H_{28}N_8O_7S_2Pt$(%): C, 21.98; H, 4.30; N, 17.10; S, 9.78. Found: C, 21.74; H, 4.14; N, 16.68; S, 9.82%. IR bands (cm^{-1}): 3354-3131, 2930w, 2895w, 1520s, 1484m, 1311s, 1278s, 1192w, 1154m, 1064m, 1034s, 914m, 826m, 709s, 492m.

2.3.5. $[Pt(dach)(dmtu)_2](NO_3)_2$

Yield: 96%. *Anal.* Calc. for $C_{12}H_{30}N_8O_6S_2Pt$: C, 22.46; H, 4.71; N, 17.47; S, 10.00. Found: C, 22.58; H, 4.83; N, 17.31; S, 9.67%. IR bands (cm^{-1}): 3289-3188, 2935m, 2864w, 1588s, 1506m, 1453w, 1372w, 1314s, 1171w, 1149m, 1036s, 826m, 725m, 611br.

2.3.6. $[Pt(dach)(tmtu)_2](NO_3)_2$

Yield: 91%. *Anal.* Calc. for $C_{16}H_{38}N_8O_6S_2Pt$: C, 27.54; H, 5.49; N, 16.06; S, 9.19. Found: C, 27.54; H, 5.44; N, 15.36; S, 8.72%. IR bands (cm^{-1}): 3423-3105, 2934m, 2861w, 1559s, 1498m, 1448m, 1319s, 1259m, 1157m, 1107m, 1059m, 1030w, 876m, 827m.

2.4. X-ray crystallography

Suitable crystals of $[Pt(dach)(tu)_2](NO_3)_2{\cdot}H_2O$ were grown by slow evaporation of an aqueous solution at room temperature. All measurements were made with a Bruker DUO platform diffractometer equipped with a 4 K CCD APEX II detector and an Incoatec 30 Watt Cu microsource with compact multilayer optics. A hemisphere of data (2713 frames at 4 cm detector distance) was collected using a narrow-frame algorithm with scan widths of 0.50 deg in omega and an exposure time of 20 s/frame. The data were integrated using the Bruker-Nonius SAINT program, with the intensities corrected for Lorentz factor, polarization, air absorption, and absorption due to variation in the path length through the detector faceplate. A ψ scan absorption correction was applied based on the entire data set. Redundant reflections were averaged. Final cell constants were refined using 8167 reflections having $I > 10\sigma(I)$, and these, along with other information pertinent to data collection and refinement, are listed in Table 1. The Laue symmetry was determined to be mmm, and from the systematic absences noted the space group was shown to be either *Pna*2(1) or *Pnma*. The asymmetric unit consists of one-half cation situated on a mirror plane, one nitrate anion, and one-half molecule of solvate water also on the mirror plane. The dach ligand is disordered across the mirror, yielding a 50:50 mix of the two different chiralities of this moiety. This is consistent with the racemic mix of dach used in the reaction. Refinement in the non-centrosymmetric space group *Pna*2(1) resulted in a 50:50 merohedral twin indication, again showing a mix of dach chiralities. Laser measurements showed no second harmonic generation, indicating that the true

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