Inorganica Chimica Acta 376 (2011) 574–580

Contents lists available at SciVerse ScienceDirect

Inorganica Chimica Acta

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

Synthesis, characterization and cytotoxic activity of palladium (II) dithiocarbamate complexes with α,ω-diamines

Diego Montagner [a,*], Cristina Marzano [b], Valentina Gandin [b]

[a] Dipartimento di Scienze Chimiche dell' Università, Via Marzolo 1, 35131 Padova, Italy
[b] Dipartimento di Scienze Farmaceutiche dell' Università, Via Marzolo 5, 35131 Padova, Italy

ARTICLE INFO

Article history:
Received 12 May 2011
Received in revised form 12 July 2011
Accepted 20 July 2011
Available online 28 July 2011

Dedicated to Dr. Elena Bertacco, a Ph. D. student of our group recently deceased.

Keywords:
Palladium complexes
Diamines
Dinuclear complexes
Cytotoxicity

ABSTRACT

The polymeric $[PdCl(dithiocarbamate)]_n$ complexes, in which the ligand ion is dimethyldithiocarbamate (DMDT), pyrrolidine dithiocarbamate (PyDT, $(CH_2)_4NCS_2^-$) and sarcosine ethyl ester dithiocarbamate (ESDT, $EtO_2CCH_2N(CH_3)CS_2^-$), have been reacted with chelating diamines, like ethylenediamine (en) or 1,3-diaminopropane (dap) and long chain diamines, like 1,4-diaminobutane (dab) or 1,7-diaminoheptane (dah). The reaction products depend on either diamine chain length or molar ratio. By operating at PdCl(dithiocarbamate)/diamine molar ratio 1:1 chelating diamines yielded the ionic [Pd(dithiocarbamate)(diamine)]Cl species (diamine = en or dap), whereas with long chain diamines species of the type $[Pd(dithiocarbamate)(diamine)]_nCl_n$ (diamine = dab or dah) were obtained, in which each Pd(dithiocarbamate)$^+$ unit binds to the NH_2 group of two different molecules, in a network of bridging diamines. At molar ratio 1:0.5, the long chain diamines yielded the binuclear $[Pd_2Cl_2(dithiocarbamate)_2(diamine)]$ complexes (diamine = dab or dah), whereas exchange reactions take place generally in the presence of en or dap. The reaction trend is described on the basis of IR and proton NMR spectra. The new dithiocarbamate complexes were preliminarily tested for their cytotoxicity on human cancer cells.

1. Introduction

Recent advances on platinum-based drugs concern the improvement of the antitumour properties of cisplatin and carboplatin by appropriate changes in either leaving or N-donor groups, which could influence DNA interactions and drug metabolism [1]. Several series have been synthesized, in which the non-leaving ligands are generally mono- or diamines, the leaving groups being chloride ions or carboxylates, whereas reports on the palladium analogues are scanty. The main purpose of several researches is to overcome toxicity and cross resistance induced by cisplatin and analogues. Small changes in ligand substituents can influence the biological activity of the complexes, as for the chain length in *N*-alkyl-ethylenediamine derivatives of the type $[cis\text{-}PtCl_2\{H_2NCH_2CH_2NH(CH_2)_nCH_3\}]$ (n = 8–15) and $[\{cis\text{-}PtCl_2(H_2NCH_2CH_2NH)\}_2(CH_2)_n]$ (n = 6–12), the latter containing a bridging aliphatic chain between the $PtCl_2N_2$ centres [2]. Propanediamine derivatives of the type $[PtCl_2(N\text{-benzyl-1,3-propanediamine})_2]$ have been reported as potential antitumour agents [3], whereas platinum complexes with 2,2′-bipyridines, in which have been inserted acridine tails, allow to examine the combination of covalent attack to DNA (through the $PtCl_2N_2$ moiety) and intercalation effect (by the tail chromophore) [4]. Kinetics of ligand replacement by ethylenediamine in palladium complexes containing either 2,2′-bipyridine and substituted ethylenediamines depends on the alkyl groups at the N-atom, which influence the hydrogen bond network with water oxygen [5].

Dinuclear species like $[M_2(diamine)(triazolopyrimidinato)_2]^{2+}$ (M = Pd or Pt; diamine = 2,2′-bipyridil or 1,10-phenantroline) contain two nearly parallel $[M(diamine)]^{2+}$ units, the M atoms being linked by two nitrogen atoms of each bridging pyrimidinato anion [6]. Binuclear and trinuclear platinum complexes are actually under study as potent second generation drugs, whose interaction with DNA differs from that of cisplatin and depends on geometry, leaving groups and bridging ligands, generally polyamines [7]. Polyamines are present in human cells and in tumours, and they can influence RNA expression through polyamine-dependent protein [8,9]. The trinuclear complex $[Pt(NH_3)_2Cl\{NH_2(CH_2)_6NH_2\}Pt(NH_3)_2\{NH_2(CH_2)_6NH_2\}Pt(NH_3)_2Cl]^{4+}$, which contains three *trans*-diaminoplatin units linked by two diaminohexane molecules, is now in clinical trial, owing to the ability to overcome cisplatin resistance [10]. In order to enhance the therapeutic index, dinuclear complexes in which the bridging ligands are spermidine, or analogues containing carbamato groups, have been studied, obtaining species of remarkable activity [11]. Substitution of ammonia with pyridine or picolines in dinuclear alkyldiamine platinum complexes causes lower cytotoxicity, notwithstanding a DNA binding kinetics superior to cisplatin [12]. Attempts toward more effective

* Corresponding author. Tel.: +39 49 8275172; fax: +39 49 8275161.
E-mail address: diego.montagner@unipd.it (D. Montagner).

0020-1693/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ica.2011.07.031

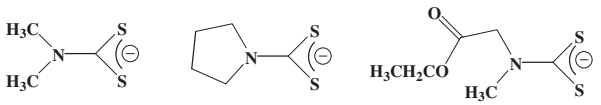

Chart 1.

polynuclear drugs consist in the insertion of functionalized groups in bridging polyamines, as amido-residues in bimetallic palladium and platinum complexes [13].

As a general remark, the interaction mode of polynuclear complexes with DNA could follow a different way than cisplatin, whose attack occurs preferentially between the N7 atom of two adjacent guanine residues. The fact that many S-donor sites are also present could suggest competition among N and S sites as determinant in drug behaviour, metal coordination to sulfur inducing possibly the formation of a drug reserve in the cell [14]. Sulfur donors, generally thiols, are administered in combination with cisplatin, in order to reduce renal damages [15–20]. The chemoprotective action of sulfur containing molecules explains the attention to their effect on Pd–N and Pt–N bonds. Glutathione has been found to be the strongest nucleofile toward palladium complexes with tridentate N-donors, whereas diethyldithiocarbamate was the most effective rescue agent against cisplatin in respect to thiourea, thiosulfate or glutathione [21,22].

An alternative way to modulate activity and toxicity of platinum-based drugs concerns the design of new molecules containing both N and S donor sites [23–25]. As regards dithiocarbamates, the mixed complexes $[M(S_2CNEt_2)(L)]NO_3$ (M = Pd or Pt; L = 2,2′-bipyridil or 1,10-phenantroline) were found active toward leukemic cells [26]. In this line we reported various palladium and platinum complexes containing either dithiocarbamate and amine moieties, of general formula [MCl(dithiocarbamate)(amine)] and [M(dithiocarbamate)(amine)$_2$]Cl [27,28]. Among them, some species in which dithiocarbamate was ESDT ($EtO_2CCH_2(CH_3)NCS_2^-$) (Chart 1), an ion containing the sarcosine moiety, gave interesting results when tested against human cancer cells [29], the most efficacy being the [PtCl(ESDT)(pyridine)] complex [30,31]. This compound has shown cytotoxic efficacy, ability to overcome cisplatin resistance and low toxicity [30,31] whereas $[PdCl(ESDT)]_n$ was toxic and scarcely active [30]. We thought then of interest to extend the study to polynuclear diamino-bridged complexes containing MCl(dithiocarbamate) residues. As a first study, this paper reports the interaction of the polymeric $[PdCl(dithiocarbamate)]_n$ species with diamines. Dithiocarbamate ions were $Me_2NCS_2^-$ (DMDT), $(CH_2)_4NCS_2^-$ (PyDT) and $EtO_2C(CH_2)N(CH_3)CS_2^-$ (ESDT) and the amines were ethylenediamine (en), 1,3-diaminopropane (dap), 1,4-diaminobutane (dab) and 1,7-diaminoheptane (dah).

Although recent studies are focused on the interaction of multinuclear platinum complexes linked by flexible diamino alkanes, mixed platinum and palladium complexes of the type $[\{trans\text{-}PtCl(NH_3)_2\}_2\text{-}\mu\text{-}\{trans\text{-}Pd(NH_3)_2\text{-}(H_2N(CH_2)_nNH_2)_2\}]Cl_4$ (n = 4–7) have been found to exhibit significant anticancer activity against ovarian cancer cell lines [32–35]. Those species contain a central *trans*-$Pd(NH_3)_2$ unit, which is bound to two *trans*-$Pt(NH_3)_2$ units by bridging diamines, the trinuclear complex assuming a +4 charge. For this reason either neutral or ionic species, containing dithiocarbamate and chelating or bridging diamines, were evaluated for their cytotoxicity on human tumour cell lines.

2. Experimental

Elemental analyses were carried out on a Fisons EA1108 CHNS-O microanalyser. IR spectra were recorded on Nicolet 5SXC FT-IR and 20F Far-IR spectrometers, as either Nujol mulls between KBr and polyethylene discs or KBr pellets. NMR spectra were measured using a Bruker DRX 300 (ppm; internal standard, TMS). Thermogravimetric data in air were obtained on Netzsch STA 449 thermoanalytical equipment (flux rate, 50 $cm^3\,min^{-1}$; heating rate, 5 °C min^{-1}; reference material Al_2O_3). The weight of the samples in the crucible was about 15–25 mg.

2.1. Reagents

Palladium chloride, NBu_4Cl, ethylenediamine (en), 1,3-diaminopropane (dap), 1,4-diaminobutane (dab), and 1,7-diaminoheptane (dah) and DMSO-d_6 were used as supplied (Aldrich products).

2.2. Starting materials

The $[PdCl(ESDT)]_n$ complex (ESDT = $EtO_2CH_2N(CH_3)CS_2^-$) was prepared by thermal degradation of solid samples of $[PdCl_2(ESDTM)]$ (ESDTM = $EtO_2CH_2N(CH_3)CS_2CH_3$) in oil bath (120 °C) under reduced pressure [36,37]. The $[PdCl(PyDT)]_n$ analogue was obtained by heating the parent $[PdCl_2(PyDTM)]$ species (PyDTM = $(CH_2)_4NCS_2CH_3$) in oil bath at 210 °C [38]. Evolution of methyl chloride takes place, the orange initial product turning into a pink powder, the colour being common to all the examined intermediates. The $[PdCl(DMDT)]_n$ intermediate was prepared either by thermal degradation of $[PdCl_2(DMDTM)]$ (DMDTM = $(CH_3)_2NCS_2CH_3$; oil bath at 150–170 °C) [39], or by reaction of $PdCl_2$ with DMDTB (DMDTB = $(CH_3)_2NCS_2$-Ph) in dichloromethane [38].

The $[PdCl_2(dap)]$ complex has been prepared by reacting $PdCl_2$ (1.0 mmol) and dap (1.0 mmol) in $CH_3CN/CHCl_3$ (3:1 vol/vol, 1 day with stirring). Yield, 61%. The pale yellow solid was filtered, washed with $CHCl_3$ and dried under reduced pressure. The $[Pd(dap)_2]Cl_2$ species has been prepared by reaction of $PdCl_2$ (1.0 mmol) with dap (4.0 mmol) in $CHCl_3$ (15 cm^3; 8 days). Yield, 95%. The white solid was washed with $CHCl_3$ and *n*-pentane and dried *in vacuo*.

The $NBu_4[PdCl_2(DMDT)]$ salt was prepared by reaction of $[PdCl(DMDT)]_n$ (0.5 mmol) with NBu_4Cl (0.55 mmol) in CH_2Cl_2 (5 cm^3). An orange solution formed initially, which, on standing (8 h), separated an orange solid. The compound was filtered, washed with CH_2Cl_2 and dried under reduced pressure. Yield, 88%. The $NBu_4[PdCl_2(PyDT)]$ complex synthesis was reported previously in Ref. [38].

2.3. Synthesis of the en complexes

The [Pd(PyDT)(en)]Cl complex was prepared by reaction of $[PdCl(PyDT)]_n$ (0.8 mmol) and en (0.93 mmol) in $CHCl_3$ (8 cm^3) with vigorous stirring (24 h). The pink suspension turned into a pale yellow solid, which was filtered, washed with $CHCl_3$ and *n*-pentane and dried under reduced pressure. Yield, 83%. The [Pd(ESDT)(en)]Cl and [Pd(DMDT)(en)]Cl analogues were prepared by reaction of the appropriate $[PdCl(dithiocarbamate)]_n$ intermediate with en, as reported in Refs. [28,40]. The [Pd(DMDT)(en)][$PdCl_2$(DMDT)] complex was obtained by reaction of $[PdCl(DMDT)]_n$ (1.1 mmol) with en (0.55 mmol) in $CHCl_3$ (5 cm^3; 2 days with vigorous stirring). The beige solid was separated by centrifugation, washed with $CHCl_3$ and *n*-pentane and dried under reduced pressure. Yield, 72%. By operating in the same conditions, the reaction of $[PdCl(PyDT)]_n$ with en at molar ratio 1:0.5 yielded a mixture of [Pd(PyDT)(en)][$PdCl_2$(PyDT)], [$Pd(PyDT)_2$] and [$PdCl_2$(en)]. Physical data, elemental analyses, IR and NMR data of the products are collected in Tables 1, 2 and 3, respectively.