Inorganica Chimica Acta 443 (2016) 141–150

Contents lists available at ScienceDirect

Inorganica Chimica Acta

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

Addition of tetraethylthiuram disulfide to antimony(III) iodide; synthesis, characterization and biological activity

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ARTICLE INFO

Article history:
Received 2 November 2015
Received in revised form 18 December 2015
Accepted 28 December 2015
Available online 4 January 2016

Keywords:
Antimony(III) complexes
Crystal structures
N,N-diethylcarbamodithioic acid
Cytotoxicity
Structure Activity Relationship (SAR)

ABSTRACT

Three new antimony(III) iodide complexes with the N,N-diethylcarbamodithioic acid of formulae $\{[(SbI(Et_2DTC)_2)(I_2)]_n\}$ (**1**), $\{[(Sb(Et_2DTC)_2)_4\ (SbI_6)\ (I_3)]_n\}$ (**2**) and $\{[SbI(Et_2DTC)_2]_2\}$ (**3**), (Et_2DTCH: N,N-diethylcarbamodithioic acid, $C_5H_{11}NS_2$) were synthesized from the reaction of antimony(III) iodide with tetraethylthiuram disulfide in 1:1 stoichiometry. The complexes **1**–**3** were characterized by melting point, elemental analysis, FT-IR spectroscopy, Raman spectroscopy, ^1H, ^{13}C NMR spectroscopy and Thermal Gravimetry–Differential Thermal Analysis (TG–DTA). Moreover, crystal structures of complexes **1**–**3** were determinated with single crystal X-ray diffraction analysis. Complexes **1**–**3** derived from ligand reduction with concomitant degradation of the tetraethylthiuram disulfide to dithiocarbamates. Complexes **1** and **2** are polymer but complex **3** is dimmer. Complex **1** consists of two residues, $[SbI(Et_2DTC)_2]$ and $[I_2]$, while **2** consists of three residues, four cationic $[Sb(Et_2dtc)_2]^+$, one $[SbI_6]^{3-}$ and one $[I_3]^-$ counter anion.

Complexes **1**–**3** were evaluated for their *in vitro* cytotoxic activity against human breast adenocarcinoma (MCF-7) and human cervix adenocarcinoma (HeLa) cells. Structure Activity Relationship (SAR) studies reveal that the high activity of the complexes is positively correlated with the low H-all atoms intermolecular contacts.

1. Introduction

The medicinal applications of antimony can be traced back to the sixteenth century when it was used as an emetic drug [1]. Nowadays there is an increasing interest in medicinal application of antimony, and significant progress has been made [2]. At present, antimony complexes are clinically used for the treatment of Leismaniasis [3]. Recently, the antitumor activity of antimony compounds is also reported [4–6]. Antimony(III) compounds were tested, *in vitro*, for their inhibitory effects on the proliferation of cancerous cell lines, with different tissues such as, leimyosarcoma (LMS), human breast adenocarcinoma (MCF-7), murine leukemia (L1210), murine mammary (FM3A), human T-lymphocyte (Molt4/C8, CEM) and human cervix (HeLa) cells. Antimony(III) halide complexes were found to exhibit strong antiproliferative activity against HeLa, LMS and MCF-7 cell lines [5,7].

Thiuram disulfides are a class of organic disulfides and they are the thiocarbamoyl esters of dialkyldithiocarbamic acids [8]. The general formula of thiuram disulfides are shown in Scheme 1. Tetraalkylthiuram disulfide compounds, known as disulfiram are bioactive materials, which possess applications as fungicides, agents of alcoholism therapy and as arrestors of human immunodeficiency virus infections such as AIDS [8–11].

Three different kinds of products were obtained from the reaction of thiuram disulfides: (a) adducts; (b) thiuram oxidation products and (c) ligand reduction with concomitant degradation to dithiocarbamate and/or thiocarboxamide ligands [11]. Example of thiuram disulfide adducts include the $[Hg(Et_4tds)I_2]$ (Et_4tds: Tetraethylthiuram disulfide) complex [12]. Besides, five membered dicationic cyclic derivatives which are neutralized by metal halides counter anions may obtained; e.g. $[Et_4biit\text{-}3]^{2+}[Hg_2I_6]^{2-}$ (Et_4biit-3: 3,5-bis (N,N′diethylammonium)-1,2,4-trithiolane) [13a], $[Et_4biit\text{-}3]^{2+}2[FeCl_4]^-$ and $[Bu_4biit\text{-}3]^{2+}[Cu_2X_6]^{2-}$ (Bu_4biit-3: 3,5-bis(N, N′dibutylammonium)-1,2,4-trithiolane, X:Cl, Br) [13b]. In the case

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http://dx.doi.org/10.1016/j.ica.2015.12.028
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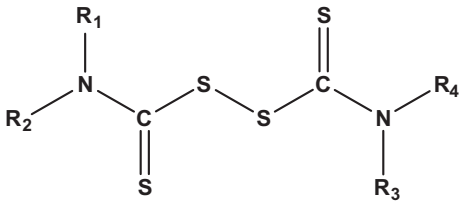
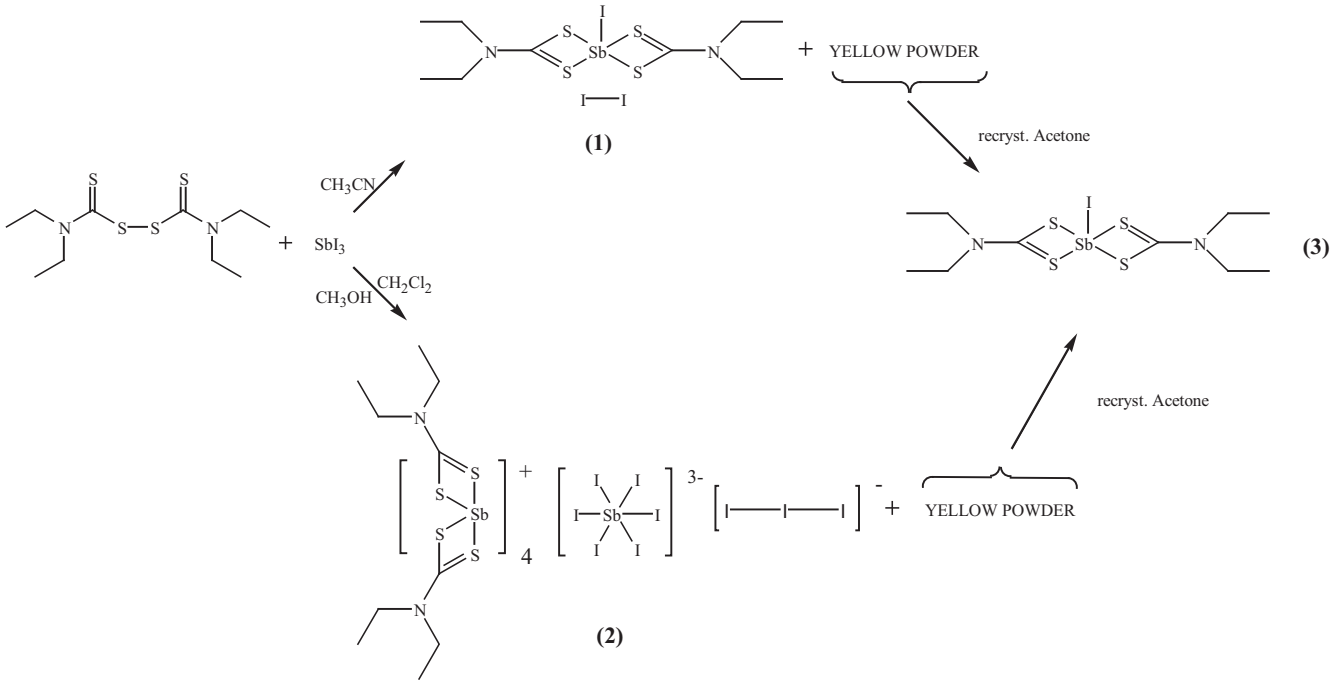


Scheme 1. General structure of thiuram disulfides ($R_2NC(S)S_2C(S)NR_2$).

of ligands degradation, the S–S bonds are cleaved resulting in the formation of dithiocarbamate and/or thiocarboxamide fragments. These fragments can then coordinate to metal ions. Examples of ligand reduction with simultaneous ligand degradation include: $[Cu(Et_2dtc)]_4$, $[Cu\{(i\text{-}Pr)_2dtc\}Br_2]$ [14], $Tl(Me_2dtc)_3$ [15a], $[Me_3Sb(dtc)_2]$ [15b], $[V_2(\mu\text{-}S_2)_2(Et_2dtc)_4]$ [15c], $[Mo(R_2dtc)_4]$ (R: Me, Et, Ph) [15d–f], $\{[SbX(Me_2dtc)_2]_n\}$ (X: Cl, Br or I) [7], $\{[Bi(Et_2dtc)_3]_2\}$ [7].

Reactions of antimony(III) or bismuth(III) containing species with thiuram sulfides are characterized by the oxidizing properties of the thiuram [7]. Reduction of the ligand and cleavage of the S–S bond results in the coordination of the dithiocarbamate fragments into the antimony or bismuth coordination sphere [7]. Dithiocarbamates coordinate strongly with a variety of metal ions especially with antimony(III) and bismuth(III) [16,17]. Dithiocarbamates, already play an important role in medicine [18]. Metal-dithiocarbamate complexes have been investigated for their anti-cancer potential, most notably with platinum(IV), palladium(II), tin(IV) and gold(I/III) [18]. Diethyldithiocarbamates can inhibit tumor induction caused by benzo[a]pyrene [18]. In recent studies, the bismuth diethyldithiocarbamate complex $Bi(Et_2dtc)_3$ inhibits *in vitro* seven human cancer cell lines (A498 (renal), MCF-7 (breast), EVSA-T (breast), H226 (non-small cell lung), IGROV (ovarian), M19 MEL (melanoma), WIDR (colon)) [18].

In the progress of our studies on the design and development of new metallotherapeutics containing elements of the group 15 [4,5,7], we have synthesized and characterized new antimony(III) iodide complexes with the ligand tetraethylthiuram disulfide (Et_4tds). Reactions of tetraethylthiuram disulfide with antimony (III) iodide lead to the ligand degradation with the simultaneous



Scheme 2. Reaction scheme for the synthesis of **1–3**.

Table 1
Chemical shifts (ppm) of the resonance signals observed in ^1H and ^{13}C NMR spectra of starting compound (Et_4tds) and complexes **1–3** in DMSO-d_6.

Compounds	^1H NMR chemical shifts (ppm)	^{13}C NMR chemical shifts (ppm)
Et_4tds	1.17–1.20, t, 6H, (CH_3— of Et_4tds) 1.38–1.40, t, 6H, (CH_3— of Et_4tds) 3.94–4.00, q, 8H, (—CH_2— of Et_4tds)	11.18, (CH_3— of Et_4tds) 13.29, (CH_3— of Et_4tds) 47.25, (—CH_2— of Et_4tds) 51.52, (—CH_2— of Et_4tds) 190.85, (C=S of Et_4tds)
1	1.23–1.27, t, 12H, (CH_3— of 2) 3.75–3.82, q, 8H, (—CH_2— of 2)	12.05, (CH_3— of 1) 48.83, (—CH_2— of 1) 194.14, (C=S of 1)
2	1.23–1.27, t, 12H, (CH_3— of 2) 3.75–3.82, q, 8H, (—CH_2— of 2)	12.06, (CH_3— of 2) 48.84, (—CH_2— of 2) 194.11, (C=S of 2)
3	1.22–1.27, t, 12H, (CH_3— of 3) 3.75–3.82, q, 8H, (—CH_2— of 3)	12.03, (CH_3— of 3) 48.79, (—CH_2— of 3) 194.56, (C=S of 3)