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Antiproliferative activities of trithiolato-bridged dinuclear arene osmium complexes

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ABSTRACT

Trithiolato-bridged arene osmium complexes of the general formula $[(p\text{-cymene})_2Os_2(\mu\text{-SR})_3]^+$ (R = C_6H_5, [**1**]$^+$; C_6H_4-*p*-Me, [**2**]$^+$; C_6H_4-*p*-OMe, [**3**]$^+$; C_6H_4-*p*-Pr^i, [**4**]$^+$; C_6H_4-*p*-Bu^t, [**5**]$^+$; $CH_2C_6H_5$, [**6**]$^+$; $CH_2CH_2C_6H_5$, [**7**]$^+$; $CH_2C_6H_4$-*p*-Bu^t, [**8**]$^+$) were synthesized in ethanol by reacting the *p*-cymene osmium dimer $[(p\text{-cymene})_2Os_2(\mu\text{-Cl})_2Cl_2]$ with the corresponding thiol (RSH). The complexes were isolated as their chloride salts, and fully characterized by spectroscopic methods. The single-crystal X-ray structure analysis of the salt [**6**]Cl is also presented. These osmium complexes were found to be highly cytotoxic towards several cancerous cell lines (A2780, A549, B16F10, HeLa) with IC_{50} values comparable or even better to those found for doxorubicin.

1. Introduction

Research on piano-stool complexes has traditionally focused on their applications in catalysis [1], although piano-stool complexes are now receiving considerable attention in medicinal chemistry [2]. Among these piano-stool complexes, arene osmium complexes show relevant anticancer activity [3], but are generally less well explored compared to their ruthenium analogs [4], and to a lesser extent to the related half-sandwich rhodium and iridium complexes [5].

Recently, it was shown that the trithiolato-bridged dinuclear arene ruthenium complexes were highly cytotoxic against human ovarian cancer cells, with IC_{50} values in the nanomolar range [6]. Among the tested derivatives, the most active compound was the *tert*-butyl *para*-substituted thiophenolato-bridged *p*-cymene ruthenium salt $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)_2Ru_2(\mu\text{-}SC_6H_4\text{-}p\text{-}Bu^t)_3]Cl$ with an IC_{50} of 30 nM [7]. A later study also demonstrated that the analogous trithiolato-bridged half-sandwich Rh(III) and Ir(III) complexes possess a similar activity [8]. Unfortunately, these highly cytotoxic dithiolato- and trithiolato-bridged dinuclear half-sandwich complexes have showed, so far, low or modest selectivity for cancerous (A2780, A2780cisR, MCF-7, B16F10, A549) over non-cancerous (CRL2115, CRL2120, HEK293) cell lines [7,8].

Herein we present the missing family of thiolato-bridged dinuclear half-sandwich complexes based on osmium. Dinuclear arene osmium complexes bridged by thiolato ligands are extremely rare in the literature. Indeed, to the best of our knowledge only one complex has been reported so far, a neutral dithiolato-bridged complex of the formula $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)_2Os_2(\mu\text{-}SC_6H_4\text{-}p\text{-}Me)_2(SC_6H_4\text{-}p\text{-}Me)_2]$ [9]. Therefore, together with the synthesis and characterisation of eight trithiolato-bridged *p*-cymene osmium complexes, the antiproliferative activity of these new dinuclear arene osmium complexes against the cancerous A2780, A549, B16F10, HeLa and noncancerous CRL2115, CRL2120, HEK293 cell lines are presented.

2. Results and discussion

Reaction of the dinuclear dichlorido-bridged complex $[(p\text{-cymene})_2Os_2(\mu\text{-Cl})_2Cl_2]$ with three equivalents of thiol derivatives in ethanol under reflux led to the formation of the cationic trithiolato-bridged complexes of the general formula $[(p\text{-cymene})_2Os_2(\mu\text{-SR})_3]^+$ (R = C_6H_5, [**1**]$^+$; C_6H_4-*p*-Me, [**2**]$^+$; C_6H_4-*p*-OMe, [**3**]$^+$; C_6H_4-*p*-Pr^i, [**4**]$^+$; C_6H_4-*p*-Bu^t, [**5**]$^+$; $CH_2C_6H_5$, [**6**]$^+$; $CH_2CH_2C_6H_5$, [**7**]$^+$; $CH_2C_6H_4$-*p*-Bu^t, [**8**]$^+$). All complexes were isolated in good yield as chloride salts (Fig. 1). These compounds were sparingly soluble in polar solvents and insoluble in non-polar solvents. They were also moderately soluble in water.

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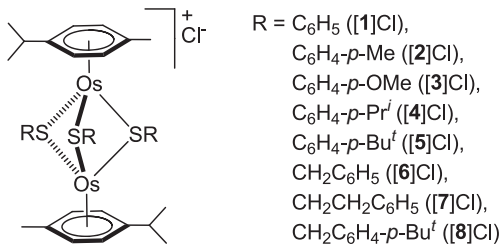

Fig. 1. Molecular structures of the trithiolato-bridged complexes [**1**]Cl–[**8**]Cl.

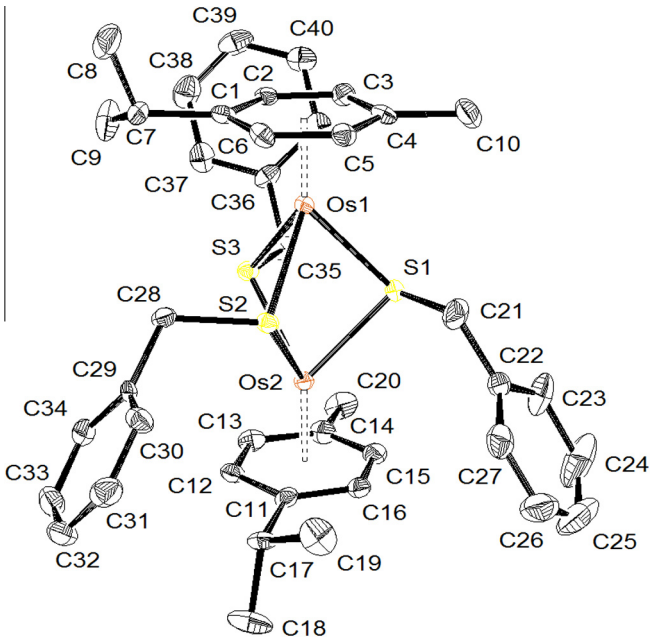

Fig. 2. Molecular structure of [**6**]$^+$ with ellipsoids at the 50% probability level; H atoms, Cl^- and CH_2Cl_2 molecules omitted for clarity. Selected bond lengths (Å) and angles (°): Os1–S1 2.4073(14), Os1–S2 2.4118(12), Os1–S3 2.3980(13), Os2–S1 2.4049(13), Os2–S2 2.4157(13), Os2–S3 2.4032(13), S1–C21 1.843(6), S2–C28 1.848(5), S3–C35 1.846(5); S1–Os1–S2 74.91(4), S1–Os1–S3 75.60(4), S2–Os1–S3 74.19(4), S1–Os2–S2 74.88(4), S1–Os2–S3 75.55(4), S2–Os2–S3 74.03(4), S1–C21–C22 114.2(4), S2–C28–C29 112.0(4), S3–C35–C36 110.9(4).

All complexes were characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy, mass spectrometry, and elemental analysis (see Section 4). The ^1H NMR spectra of complexes [**1**]Cl–[**8**]Cl showed an important shielding of the signals associated to the *p*-cymene ligands after coordination to the osmium atoms. On the other hand, the resonances of the thiolato-bridging ligands are observed at lower frequencies than those of the uncoordinated thiols. Additionally, the aromatic protons of the *p*-cymene ligands were observed as four doublets suggesting a low symmetry for these dinuclear complexes.

The electro-spray ionization (ESI) mass spectra of compounds [**1**]Cl–[**8**]Cl, obtained in a positive mode, showed the expected peak of the cationic complex $[(p\text{-cymene})_2Os_2(\mu\text{-SR})_3]^+$ at $m/z = 976.2$ ([**1**]Cl), 1018.3 ([**2**]Cl), 1066.2 ([**3**]Cl), 1103.0 ([**4**]Cl), 1144.3 ([**5**]Cl), 1018.3 ([**6**]Cl), 1060.2 ([**7**]Cl) and 1187.0 ([**8**]Cl), respectively. Moreover, the isotopic patterns of these parent peaks were all consistent with the presence of $(p\text{-cymene})_2Os_2(\mu\text{-SR})_3$ cores. Finally, the molecular structure of [**6**]Cl was established by single-crystal X-ray structure analysis.

2.1. Molecular structure of [6]Cl

Crystals suitable for single-crystal X-ray structure analysis were obtained for [**6**]Cl. The molecular structure of the cation [**6**]$^+$ was presented in Fig. 2. The salt crystallized in the monoclinic space group $P2_1/c$ with two molecules of dichloromethane per asymmetric unit. The molecular structure of the cation showed a closed trigonal bipyramid Os_2S_3 framework, with each metal being coordinated to a *p*-cymene ligand and three sulfur atoms. The Os–S bond distances [ranging from 2.398(1) to 2.416(1) Å] were comparable to those found in analogous trithiolato-bridged half-sandwich complexes [6–8]. However, the Os–S–Os angles [ranging from 90.51(4)° to 91.15(4)°] were more obtuse than the Ru–S–Ru angles of related trithiolato-bridged arene ruthenium complexes [6,7]. These more obtuse angles were consistent with the longer Os···Os distance observed [3.4288(3) Å], in comparison to the corresponding Ru···Ru separation [3.3576(5) Å] [6]. This Os···Os distance was also much longer than the Os···Os separation observed in the trichlorido-bridged dinuclear complex $[(p\text{-cymene})_2Os_2(\mu\text{-Cl})_3]^+$ (3.236(1) Å) [10], and the trimethoxido-bridged complex $[(p\text{-cymene})_2Os_2(\mu\text{-OMe})_3]^+$ (3.078(2) Å) [11].

The molecular structure of [**6**]$^+$ showed that two of the three benzyl groups were pointing away from the third one, thus providing in the solid state different environments for the *p*-cymene ligands. As emphasized in Fig. 3, two benzyl groups formed a small pocket in which a *p*-cymene unit sat perfectly, while the remaining benzyl group was positioned next to an edge of the other *p*-cymene ligand. Despite such a tight packing in the solid state, in solution the benzyl groups were free to rotate, showing in the ^1H NMR spectrum of [**6**]Cl, a singlet at 3.79 ppm integrating for 6 protons for the $C\mathbf{H}_2$ group.

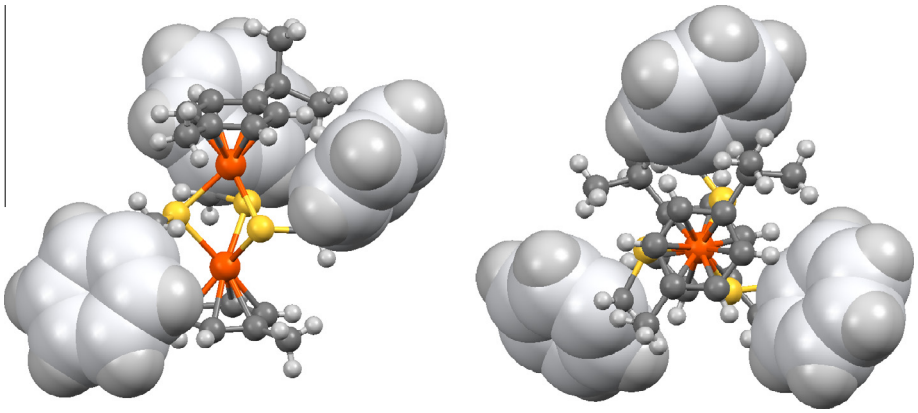

Fig. 3. Space-filling views of the benzyl groups in [**6**]$^+$, showing the entrapment of a *p*-cymene ligand between two benzyl groups.