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Highly water soluble trithiolato-bridged dinuclear arene ruthenium complexes

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ABSTRACT

Water soluble arene-functionalised trithiolato-bridged ruthenium complexes of general formula $[(\eta^6\text{-}C_6H_5OCH_2CH_2OH)_2Ru_2(\mu\text{-}SR)_3]^+$, where 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**) and $CH_2C_6H_4$-*p*-Bu^t (**8**), were prepared from the reaction of $[(\eta^6\text{-}C_6H_5OCH_2CH_2OH)_2Ru_2(\mu\text{-}Cl)_2Cl_2]$ with the corresponding thiol, RSH. Complexes [**1**]Cl–[**8**]Cl were isolated in good yields as their chloride salts and they were fully characterised using spectroscopic and analytical techniques and the structures of [**1**]Cl, [**3**]Cl and [**4**]Cl were determined in the solid-state by single-crystal X-ray diffraction. The antiproliferative activity of [**1**]Cl–[**8**]Cl was evaluated against human ovarian cancer (A2780, A2780cisR) and non-cancerous (HEK293) cells with [**4**]Cl and [**5**]Cl being more active than cisplatin on the cancer cells and also more selective.

1. Introduction

The anticancer properties of ruthenium complexes are well established [1] and, of these, arene ruthenium compounds are currently under intensive investigation [2]. Two key compounds comprise $[(\eta^6\text{-}p\text{-cymene})Ru(en)Cl]^+$ [3] and $[(\eta^6\text{-}p\text{-cymene})Ru(pta)Cl_2]$ (pta = 1,3,5-triaza-7-phosphaadamantane) [4], that not only represent amongst the earlier studied, but also those studied in most detail. The former compound exerts an anticancer effect that may be related to its in vitro cytotoxicity [3] whereas $[(\eta^6\text{-}p\text{-cymene})Ru(pta)Cl_2]$ exerts antimetastatic behaviour [5] and anti-angiogenic effects [6] that can lead to a reduction in the growth of primary tumours [7]. The different biological effects of these two compounds have been tentatively related to differences in binding to chromatin, with $[(\eta^6\text{-}p\text{-cymene})Ru(en)Cl]^+$ preferentially binding to the DNA and $[(\eta^6\text{-}p\text{-cymene})Ru(pta)Cl_2]$ to the histone core [8].

The majority of studies have been performed on compounds with the *p*-cymene ring although complexes with other arene ligands, e.g. benzene, toluene, durene and hexamethylbenzene have also been studied [9] as have compounds with cyclopentadienyl-type ligands [10]. Furthermore, arene ligands with functional groups have been shown to modify the physico-chemical properties of arene ruthenium complexes leading to altered biological function [9]. For example, extended arene ligands such as biphenyl or tetrahydroanthracene increase the cytotoxicity of the $[(\eta^6\text{-arene})Ru(en)Cl]^+$ complex (en = ethylenediamine), whereas the $[(\eta^6\text{-}C_6H_5COOCH_3)Ru(en)Cl]^+$ analogue was poorly active [3,11]. Similarly, the cytotoxicity and the uptake of the $[(\eta^6\text{-arene})Ru(pta)Cl_2]$ (pta = 1,3,5-triaza-7-phosphaadamantane) complex can be optimised by the introduction of functionalised arene ligands [5] including those with substituents that can participate in hydrogen-bonding [12]. Arene ruthenium complexes with η^6-bound arenes functionalised with bioactive groups have also been reported [9,13], with a system derivatised with ethacrynic acid having been studied in some detail [14]. Other functional groups covalently linked to the η^6-arene ligand include intercalators [15] and chiral appendages [16].

Recently, we observed that the trithiolato-bridged dinuclear *p*-cymene ruthenium [17] and *p*-cymene osmium [18] complexes are highly cytotoxic to cancerous cells; the most active compound being the ^{t}butyl derivative $[(\eta^6\text{-}p\text{-cymene})_2M_2(\mu\text{-}SC_6H_4\text{-}p\text{-}Bu^t)_3]^+$ with IC_{50} values in the nanomolar range. Indeed, transition metals bridged by thiolato ligands are ubiquitous in nature being found in the active site of certain enzymes [19]. While the substituent group on the bridging thiolato ligand has been extensively varied, to date very little effort has been directed towards variation of the η^6-arene ring. Herein, we used a functionalised arene ruthenium derivative, which is soluble in water and has the potential to form hydrogen bonds, to prepare trithiolato-bridged dinuclear ruthenium complexes, in order to evaluate the impact of the arene ligand on the antiproliferative activity.

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2. Results and discussion

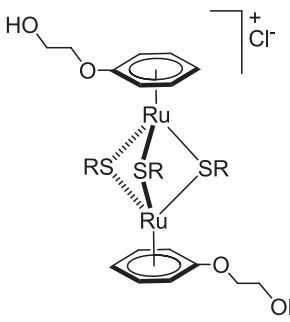
The reaction of the known arene-functionalised ruthenium dimer $[(\eta^6\text{-}C_6H_5OCH_2CH_2OH)_2Ru_2(\mu\text{-}Cl)_2Cl_2]$ [20] with three equivalents of thiols (RSH) leads to the formation of the cationic trithiolato-bridged complexes $[(\eta^6\text{-}C_6H_5OCH_2CH_2OH)_2Ru_2(\mu\text{-}SR)_3]^+$ with R = C_6H_5 (**1**), R = C_6H_4-*p*-Me (**2**), R = C_6H_4-*p*-OMe (**3**), R = C_6H_4-*p*-Pr^i (**4**), R = C_6H_4-*p*-Bu^t (**5**), R = $CH_2C_6H_5$ (**6**), R = CH_2CH_2-C_6H_5 (**7**) and R = $CH_2C_6H_4$-*p*-Bu^t (**8**) (Fig. 1), isolated as their chloride salts. Complexes [**1**]Cl–[**8**]Cl are stable in air and are sparingly soluble in polar solvents such as dichloromethane, chloroform, acetone and acetonitrile, insoluble in non-polar solvents including hexane and diethylether, but highly soluble in water. The complexes were fully characterised by elemental analysis, UV–Vis, ^{1}H and ^{13}C NMR spectroscopy and electrospray ionisation mass spectrometry (see the Section 4 for full details).

The ^{1}H NMR spectra of [**1**]Cl–[**8**]Cl in $CDCl_3$ at 25 °C show, as compared to the free thiols, a downfield shift of the signals associated to the protons of the thiolato-bridged ligands. The aromatic protons of the functionalised arene groups in these complexes shift upfield relative to those of the starting dimer $[(\eta^6\text{-}C_6H_5OCH_2CH_2OH)_2Ru_2(\mu\text{-}Cl)_2Cl_2]$. For example, the aromatic protons of the starting dimer were observed in the range of 6.2–5.4 ppm, and upon formation of the cationic trithiolato complexes, the corresponding signals were shifted upfield to between 5.6 and 4.4 ppm. Electrospray ionisation mass spectra of [**1**]Cl–[**8**]Cl were obtained in acetonitrile in positive ion mode providing clean molecular ion peaks corresponding to the intact cations $[\mathbf{1}]^+$–$[\mathbf{8}]^+$ corroborating the expected structures.

The electronic absorption spectra of complexes [**1**]Cl–[**8**]Cl (10^{-5} M concentration in water with 5% DMSO) in the range 225–500 nm are shown in Fig. 2. The spectra are characterised by the presence of an intense ligand-localised or intra-ligand π–π^* transition in the ultraviolet region and of a lower intensity band in the visible region corresponding to a metal-to-ligand charge transfer (MLCT) transition. These transitions are commonly observed in arene ruthenium complexes [21]. The stability of these complexes was confirmed following incubation at 37 °C corresponding to the cell proliferation conditions. The absorption spectra recorded after 3 and 24 h had the same profile as those recorded for the freshly prepared samples at room temperature.

2.1. Solid-state structures of [1]Cl, [3]Cl and [4]Cl

Crystals suitable for single crystal X-ray diffraction analysis were obtained for [**1**]Cl, [**3**]Cl and [**4**]Cl. Crystals of [**1**]Cl·$2CH_2Cl_2$·$CHCl_3$ were obtained from slow diffusion of hexane into a dichloromethane-chloroform solution of [**1**]Cl, crystals of [**3**]Cl·H_2O·$CHCl_3$ were grown by slow diffusion of pentane into a wet



R = C_6H_5 ([**1**]Cl),
C_6H_4-*p*-Me ([**2**]Cl),
C_6H_4-*p*-OMe ([**3**]Cl),
C_6H_4-*p*-Pr^i ([**4**]Cl),
C_6H_4-*p*-Bu^t ([**5**]Cl),
$CH_2C_6H_5$ ([**6**]Cl),
$CH_2CH_2C_6H_5$ ([**7**]Cl),
$CH_2C_6H_4$-*p*-Bu^t ([**8**]Cl)

Fig. 1. Structures of complexes [**1**]Cl–[**8**]Cl.

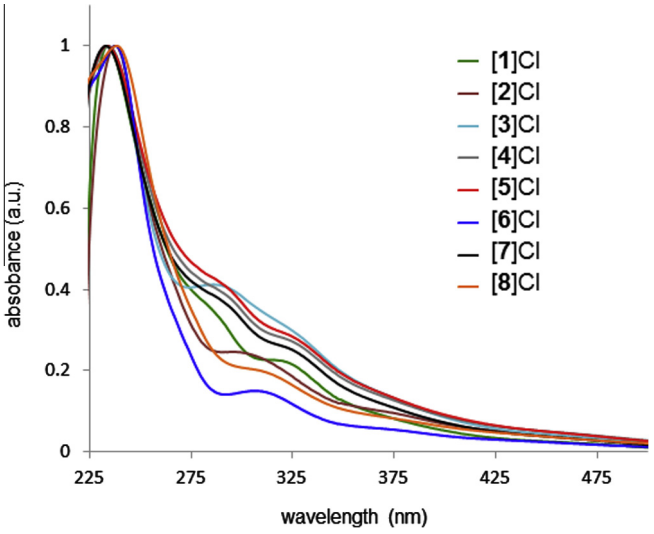


Fig. 2. Normalised absorption spectra of [**1**]Cl–[**8**]Cl (10^{-5} M in H_2O containing 5% DMSO) recorded at room temperature.

chloroform solution of the complex, and crystals of [**4**]Cl were obtained by slow diffusion of ether into a dichloromethane solution of [**4**]Cl. The molecular structures of the cations, $[\mathbf{1}]^+$, $[\mathbf{3}]^+$ and $[\mathbf{4}]^+$, are shown in Figs. 3–5, respectively. Selected bond lengths and angles are listed in Table 1.

The structures of the three complexes are essentially as expected. The Ru–Ru distance in the cations, $[\mathbf{1}]^+$, $[\mathbf{3}]^+$ and $[\mathbf{4}]^+$, is >3.3 Å suggesting no direct metal–metal bond is present. Similar Ru–Ru separations have been observed in analogous trithiolato-bridged dinuclear *p*-cymene ruthenium complexes [22]. Notably, these structures show that the hydroxyl groups of the arene ligands are directed away from the dinuclear core and form hydrogen bonds with the counter anion, solvate molecules or neighbouring complexes. Similar orientation of the hydroxyethanol arms have been observed in complexes incorporating the same arene ligand, $[(\eta^6\text{-}C_6H_5OCH_2CH_2OH)Ru(\eta^2\text{-}N,O\text{-}L)Cl]$ (LH = 2-{(propylimino)methyl}phenol) [23] and $[(\eta^6\text{-}C_6H_5OCH_2CH_2OH)_2Ru_2(\mu\text{-}Cl)_2\{P(OPh)_3\}_2]$ [24].

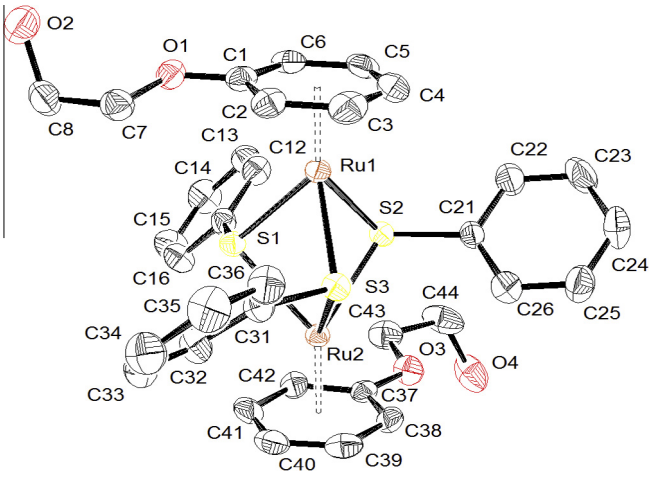


Fig. 3. Ortep drawing of $[\mathbf{1}]^+$ at 50% probability level ellipsoids with hydrogen atoms omitted for clarity.