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Novel rhenium(V) nitride complexes with dithiocarbimate ligands – A synchrotron X-ray and DFT structural investigation

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This paper is dedicated to Professor Ionel Haiduc on the occasion of his 80th birthday.

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ABSTRACT

The application of rhenium complexes as therapeutic agents in nuclear medicine has propelled research into the chemistry of these compounds. In our effort to develop and investigate new therapeutic radiopharmaceuticals based on the complexes of rhenium we have investigated the nitride core, $[ReN]^{2+}$. This work looks at the behavior of sulfonamide based dithiocarbimates towards the rhenium(V) nitride core. The aim here was to prepare anionic complexes with aromatic as well as fluorescent aromatic groups in the sulfonamide substituent located on the dithiocarbimate backbone. We envisaged that the polar sulfonamide and dianionic charge would confer solubility in water. Here we report the reactions of the dithiocarbimate ligands towards the rhenium(V) precursors: $[ReNCl_2(PPh_3)_2]$ and $[ReNCl_2(PMe_2Ph)_3]$. These reactions proceeded with bis-substitution by the dithiocarbimate ligand, resulting in the formation of a dianionic rhenium(V) complex, of the type $[ReN(S\text{-}S)_2]^{2-}$, where (S-S) denotes the sulfonamide-tagged dithiocarbimato unit. Spectroscopic characterization data, as well as the synchrotron X-ray diffraction structure of the metal complex with the phenyl sulfonamide backbone shed light into the structural features of this interesting class of ligands and opens up opportunities for further studies in molecular imaging and therapeutic arenas.

1. Introduction

Despite significant progress made in the development of diagnostic radioisotopes for medical imaging techniques such as single photon emitted computed tomography (SPECT) or positron emission tomography (PET), the availability of therapeutic radioisotopes with matching radiochemistry, half-lives and wide accessibility at reasonable costs remains the holy-grail for applications in nuclear medicine, particularly for oncology. The development of rhenium compounds as therapeutic radiopharmaceuticals remains a matter of interest for chemists and nuclear imaging specialists both in academic and in clinical settings.

To date, the most widespread use of rhenium complexes in major clinical applications is that involving ReHEDP (hydroxyethane bisphosphonate) for uses in bone targeting in terminal cancer patients [1]. The research area has been reviewed: the chapters in Comprehensive Coordination Chemistry on Technetium by Alberto [2] and Rhenium by Abram, [3] are detailed. Extensive reviews have covered the recent chemistry aspects of both $^{186/188}$Re and ^{99m}Tc chemistry across a whole range of available oxidation states and coordination numbers in aqueous and non-aqueous media [4,5]. Our recent book Chapter also gives an overview of the development of the coordination chemistry of Tc and Re relevant to nuclear medicine with an emphasis on key ligand systems and imaging agents [4].

The strong π-donating characteristics of the trianionic nitride-group make a major contribution to the stability of high oxidation state Tc and Re nitrides. The presence of an additional negative charge on "nitride" compared to "oxo" opens up a series of complexes with different co-ligands, or overall charges, to those of the ubiquitous Re-oxo complexes. Tc or Re nitride syntheses were first carried out by Chatt et al. who showed that $[ReNCl_2(PPh_3)_2]$ and $[ReNCl_2(PMe_2Ph)_3]$ could be synthesized using hydrazine or azide as the source of nitride [6,7]. This work was extended to ^{99}Tc and ^{99m}Tc: Baldas and co-workers reported extensively on

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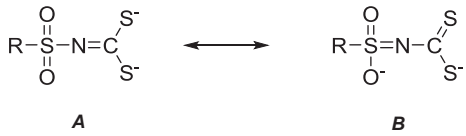
nitride complexes and proposed that the nitride core could be used in ^{99m}Tc based radiopharmaceuticals [8–14]. The paramagnetic Tc (VI) species $[TcNCl_4]^-$ emerges from the reaction between pertechnetate and azide in acid solution. Its substitution and redox chemistry (by the same synthetic route) was applied to the synthesis of $[ReNCl_4]^-$ [15]. The coordination chemistries and spectroscopic properties of the $[TcN]^{2+}$ and $[ReN]^{2+}$ cores were highlighted by Abram et al. and some representative examples of this work are shown in Fig. 1 (**A**–**C**) [16–18,15,19]. In the nitride complexes research space, Duatti and co-workers showed that neutral dithiocarbamato-Tc nitrides act as promising heart imaging agents. Particularly, the bis(N-ethoxy, N-ethyl dithiocarbamato)nitrido technetium(V), *TcNOET* (Fig. 1, compound **D**) entered clinical trials despite the fact that myocardial tissue retention remains unclear [20–22].

The hydrazine derivative $MeSCSNMeNH_2$ and its variants led to the formation of both $[TcN]^{2+}$ and $[ReN]^{2+}$ cores directly from the corresponding tetroxometallates in high yields [23,24]. No intermediates could be isolated with the Tc core but the $[ReO(NHNMeCSSMe)_2]^+$ species emerged from the reaction of $[ReO_4]^-$ with the *N*-methylated hydrazine in the presence of HCl, followed by addition of a dithiocarbimate (dtc) to give $[ReN(dtc)_2]$ [25]. To incorporate the nitride core, it is of interest to synthesize complexes with a mixed ligand system analogous to a [3 + 2] systems, which have been shown to be effective for oxo complexes. The same approach for the nitrides gives mixtures of compounds, however, it has been shown that the stereochemistry and stoichiometry of the Tc or Re nitride cores can be controlled using tridentate SNS or PNP donors. In the case of PNP ligands, the π-acceptor P donors favor a *trans* geometry [26]. The halide ligands are placed in a *cis* position and they can readily be substituted by bidentate monoanionic or dianionic ligands [27]. This control level can be achieved with bidentate nitrogen ligands (i.e. bipy, phenanthroline) that allow the isolation of the cyanonitrido complexes [28]. The use of bulky thiolate ligands demonstrated stabilizing effect on the rhenium nitride, arylimido and nitrile cores [29].

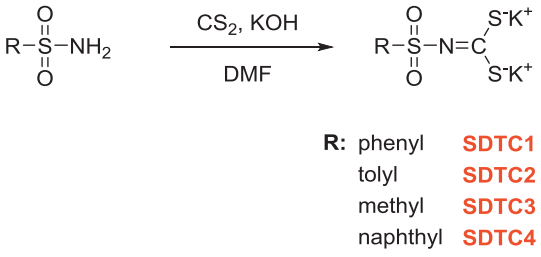
The structure of the Re dichloride (compound **E**) and the cationic dithiocarbamate derivative bis[(dimethoxypropylphosphanyl) ethyl]ethoxyethylamine N,N′-bis(ethoxyethyl)dithiocarbamato nitrido technetium(V), Tc-*N*-DBDOC (compound **F** which shows promise as a cardiac imaging agent *in vivo*) are shown in Fig. 1 [30]. A choice of bidentate ligands with bioorthogonal functionalization can lead to conjugation to a range of biomolecules as well as hig kinetic stabilities [31–35].

Rhenium has two beta-emitting radioisotopes, ^{186}Re and ^{188}Re, and through careful ligand design these can be encapsulated and then targeted to cancer cells where the beta-radiation emitted destroys the cancer cells. Both of these species are reactor-produced radioisotopes which are attractive for a variety of therapeutic applications. Thus far, Re-186 is unavailable from a generator system, and must therefore be directly produced in a nuclear reactor. However, Re-188 can be eluted as perrhenate from an alumina-based ^{188}W/^{188}Re generator, and although it has a much shorter half-life of 16.9 h, this is still compatible with most *in vivo* imaging and therapy requirements as it emits a beta-particle with a much higher energy (2.12 MeV and a 155 keV gamma photon, 15%) which would be also suitable for the coupled SPECT imaging.

To date, the majority of research into rhenium based therapeutic agents design has centered around the rhenium(V) oxo core. Our approach in this study was to investigate the coordination of a series of sulfonyl-dithiocarbimate ligands to the rhenium(V) nitride, $[Re{\equiv}N]^{2+}$ core. This work focuses on the synthesis and coordination behavior of sulfonamide based dithiocarbimates (Scheme 2, **SDTC 1**–**4**) towards the rhenium(V) nitride core. The aim here is to functionalize the dithiocarbimate backbone by incorporating both fluorescent and non-fluorescent aromatic groups in the sulfonamide substituent. This will enable observation of the behavior of these complexes at the cellular level. To date, the only related rhenium compounds reported in the literature are neutral and involve the diethyldithiocarbamate ligand [36,37].



Scheme 1. Proposed resonance forms for dithiocarbimate-based ligands.



Scheme 2. General synthesis for dithiocarbimate ligands studied hereby.

A measure of water solubility is a prerequisite for metal complexes to be used in biomedical applications. A commonly adopted approach is to add polar groups containing carboxylate, hydroxy or sulfonate groups to the ligand backbone. Here, we have adopted an alternate approach by using sulfonyl substituted dithiocarbimate ligands. Dithiocarbimate ligands have been relatively little studied and there have been just a couple of X-ray structures reported of Re complexes, readily prepared from sulfonamides and CS_2 in the presence of a base [38,39]. They have two possible resonance forms as shown in Scheme 1. In form *B*, one negative charge resides on a sulfonyl oxygen giving a charged group closely related to the sulfonic acids (RSO_3^-). We anticipate that such complexes could be water-soluble and this would be enhanced by a negative charge on the complex.

The substituents on the sulfonyl backbone of the ligands, methyl, phenyl, tolyl and naphthyl groups, have been carefully chosen in the work reported hereby to improve kinetic stabilities and modulate the lipophilicities. To enhance the understanding of the behavior of these compounds in cells across a range of conditions and concentration domains, a fluorescent ligand tag (e.g. naphthyl based) is desirable as it would allow the monitoring of the *in vitro* behavior of the compound. The design and synthesis of a series of ligands and of their novel complexes are here reported. Currently there are no reports in the literature regarding X-ray structures of Re complexes with this ligand. New species were characterized in solution and in the solid state, and their UV–Vis spectroscopy behavior in solution was investigated. The fluorescence spectra of a new naphthyl-tagged ligand and investigations into its corresponding Re(V) complex are also reported. A stability study of the tolyl complex, $[ReN(SDTC2)_2]^{2-}$, in the presence of water over a period of 6 h was also conducted showing promising kinetic stability compatible with its intended pre-clinical aims. The complex proved to be stable in the presence of H_2O, with the UV–Vis spectra showing little change over this period.

2. Results and discussions

The synthesis of the sulfonamide dithiocarbimate ligands was adapted from literature procedures [36,37] and successfully employed for all starting materials with alkylic and arylic backbones. The addition of carbon disulfide to the sulfonamides in a