Crown Thioether Chemistry: Bis(1,4,7-Trithiacyclononane)rhenium(II), the First Homoleptic Thioether Complex of Rhenium

Simba O. C. Matondo,[a] Philip Mountford,[a] David J. Watkin,[b] William B. Jones[a] and Stephen R. Cooper*[a†]

[a] *Inorganic Chemistry Laboratory, University of Oxford, Oxford, UK OX1 3QR*
[b] *Chemical Crystallography Laboratory, University of Oxford, Oxford, UK OX1 3PD*
† *Current address: Mallinckrodt Medical Inc., 675 McDonnell Blvd. PO Box 5840, St. Louis, Missouri 63134 USA*

FAB-MS, magnetic susceptibility, CV and X-ray diffraction establish $[Re(9S3)_2]^{2+}$ (9S3 = 1,4,7-trithiacyclononane) as the first homoleptic thioether complex of Re, a compound of potential utility in cancer therapy.

Recent proposals to use the γ-emitting isotopes $^{186,188}Re$ in cancer radiotherapy[1] focus attention on complexes suitable for delivery of these isotopes *in vivo*. Crown thioethers have great promise for this application. In addition to resisting aerial oxidation, hydrolysis and protonation, they coordinate more strongly than acyclic analogues[2] typically to form homoleptic thioether complexes. Mazzi[3] has recently stressed the utility in nuclear medicine of such homoleptic complexes.

Despite this motivation and the dramatic development of crown thioether chemistry in the last ten years,[4,5,6] the coordination chemistry of Re with thioethers (cyclic or otherwise)[2] includes only two examples involving crown thioethers.[7,8] We report here the synthesis, characterisation and structure of $[Re(9S3)_2]^{2+}$, the first homoleptic thioether complex of Re and we point out the opportunity to control biodistribution of Re through redox tuning mediated by 9S3 and analogous crown thioethers.

Reaction of ReO_4^- and 9S3 in glacial acetic acid in the presence of Sn^{II} and $HBF_4{\cdot}Et_2O$ affords deep-red solutions of $[Re(9S3)_2]^{2+}$ [λ_{max} 429 nm (1674 $dm^3\,cm^{-1}\,mol^{-1}$) and 361 nm (567 $dm^3\,cm^{-1}\,mol^{-1}$)] as its BF_4^- salt. FAB-MS study of this material (nitrobenzyl alcohol matrix) shows a peak at 634 *m*/*z*, corresponding to $\{[Re(9S3)_2](BF_4)\}^+$. Solid-state magnetic measurements give μ_{eff} = 1.6 μ_B at 300 K, decreasing to 1.46 μ_B at 20 K, indicative of an $S = \frac{1}{2}$ low-spin d^5 system with the substantial orbital contribution expected for a third-row element thereby substantiating formation of Re^{II}.

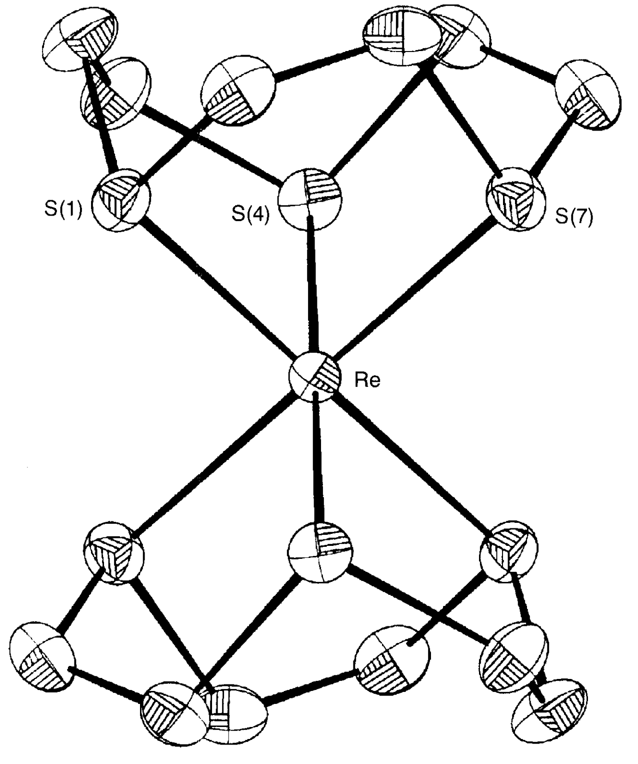

Fig. 1 Thermal ellipsoid drawing of $[Re(9S3)_2](PF_6)_2{\cdot}2CH_3NO_2$. Bond distances: Re(1)–S(1) 2.366(1) Å, Re(1)–S(4) 2.374(2) Å, Re(1)–S(7) 2.375(2) Å. Atomic numbering follows IUPAC convention [S(1), C(2), C(3), S(4)].

X-Ray diffraction measurements on the analogous PF_6 salt confirm synthesis of the first example of a homoleptic $Re(thioether)_6$ core,‡ with two 9S3 rings coordinated to the metal ion in tridentate fashion at an average Re–S distance of 2.37 Å (Fig. 1). Strong M–L interactions manifest themselves in the Re–S bond lengths [2.366(1)–2.375(2) Å], the shortest reported for any Re–thioether complex. They fall substantially short of those in, *e.g.* $[ReBr_3(tetrahydrothiophene)_3]$ [2.396(4)–2.425(5) Å],[9] $[Re(1,4,8,11\text{-tetrathiaundecane})(L)(PPh_3)]$ (L = NNCOPh, $NNCO_2Me$) [2.404(4)–2.483(5) Å],[10] $[Re(CO)_3(9S3)]^+$ [2.457(3)–2.467(3) Å],[7] or $[ReO_3(9S3)]^+$ [2.564(4)–2.585(5) Å].[8] Comparison with the analogous Ru^{II} ($Ru\text{–}S_{ave}$ 2.34 Å)[11–14] complex shows that M–S (M = Ru^{II}, Re^{II}) bond lengths differ roughly in accord with the expected difference in ionic radii. As is typical of 9S3 complexes[4] the coordinated ligand reflects practically no conformational change from the free form,[15] a major factor in the stability of 9S3 complexes.

Preparation of the first homoleptic crown thioether complexes of Re may have important implications for ^{186}Re-based radiotherapy. CV (MeCN, glassy carbon) shows that $[Re(9S3)_2]^{2+}$ undergoes reduction to Re^I in a range commensurate to that found *in vivo*. The couples occur at E_f = +0.47 and −0.43 V relative to Fc^+/Fc; 1.02 and 0.12 V *vs.* NHE corresponding to the $Re^{III/II}$ and $Re^{II/I}$ couples respectively. Different crown thioether ring sizes have been shown to shift redox potentials in the $Rh^{III/II/I}$-*n*S3 (*n* = 9–12) system,[16] a series of complexes all containing the MS_6 core.[16] Because redox potentials strongly influence biodistribution of radiopharmaceutical chelates,[17,18] such redox 'tuning' may permit the deliberate localisation of Re in hypoxic tumours or other oxygen deficient pathologies through a bioreductive trapping mechanism. Work directed toward this goal is in progress.

We are grateful to Mallinckrodt Medical, Inc. for support of this research, and to the Cliff Foundation for a scholarship for S. O. C. M.

Received, 5th October 1994; Com. 4/06086E

Footnotes

‡ *Crystal data* for $Re(9S3)_2(PF_6)_2.2MeNO_2$: $C_{16}H_{30}F_{12}N_2O_4P_2ReS_6$, *M* = 958.89, monoclinic, space group $P2_1/c$, *a* = 10.641(1) Å, *b* = 15.141(2) Å, *c* = 9.622 Å, β = 100.00(1)°, *V* = 1526.7 Å³, *F*(000) = 938, *Z* = 2, D_c = 2.09 g cm^{-3}, μ(Cu-Kα) = 132.9 cm^{-1}, *T* = 293 K, R_{merge} = 0.049, $R(F^2)$ = 0.045, $R_w(F^2)$ = 0.053. An irregular red crystal of $Re(9S3)_2(PF_6)_2.2MeNO_2$ measuring 0.10 × 0.15 × 0.25 mm was sealed in a Lindemann glass capillary. Diffraction data were collected on an Enraf-Nonius CAD4 diffractometer fitted with a graphite-monochromated Cu-Kα radiation (λ = 1.54056). A total of 4121 reflections with 2θ = 2–150° were collected, of which 3136 were unique. The rhenium atom position was determined from a Patterson synthesis and subsequent difference Fourier syntheses revealed the positions of all other non-hydrogen atoms. The isotropic model was applied to the unmerged reflection data corrected only for Lp effects

and with systematically absent reflections removed. Equivalent reflections were then merged and the model refined by blocked-matrix least-squares procedures on 2315 data with $I > 3\sigma$ for 195 variables with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms attached to the methylene carbons of the 9S3 fragment were located from a Fourier difference synthesis and refined riding on their supporting carbon atoms with equivalent isotropic thermal parameters for each pair of CH_2 hydrogens. Hydrogen atoms for the $MeNO_2$ molecule were placed in calculated positions, C–H = 0.96 Å. The PF_6^- anion was refined subject to soft restraints. Crystallographic calculations were carried out using the CRYSTALS suite of programs on a Micro Vax 3800 computer. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

1 P. Blauenstein, *New J. Chem.*, 1990, **14**, 405.
2 S. G. Murray and F. R. Hartley, *Chem. Rev.*, 1981, **81**, 365.
3 U. Mazzi, *Polyhedron*, 1989, **13**, 1683.
4 S. R. Cooper and S. C. Rawle, *Struct. Bond.*, 1990, **72**, 1.
5 A. J. Blake and M. Schröder, *Adv. Inorg. Chem.*, 1990, **35**, 1.
6 S. R. Cooper, *Acc. Chem. Res.*, 1988, **21**, 141.
7 C. Pomp, S. Drüeke, H. J. Küppers, K. Wieghardt, C. Krueger, B. Nuber and J. Z. Weiss, *Z. Naturforsch., Teil B*, 1988, **43**, 299.
8 H. J. Küppers, B. Nuber, J. Weiss and S. R. Cooper, *J. Chem. Soc., Chem. Commun.*, 1990, 979.
9 I. M. Gardiner, M. A. Bruck, P. A. Wexler and D. E. Wigley, *Inorg. Chem.*, 1989, **28**, 3688.
10 T. Nicholson and J. Zubieta, *Inorg. Chem.*, 1987, **26**, 2094.
11 S. C. Rawle and S. R. Cooper, *J. Chem. Soc., Chem. Commun.*, 1987, 308.
12 S. C. Rawle, T. J. Sewell and S. R. Cooper, *Inorg. Chem.*, 1987, **26**, 3769.
13 M. N. Bell, A. J. Blake, M. Schröder, H. J. Küppers and K. Wieghardt, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 250.
14 M. N. Bell, A. J. Blake, A. J. Holder, T. I. Hyde and M. Schröder, *J. Chem. Soc., Dalton Trans.*, 1990, 3841.
15 R. S. Glass, G. S. Wilson and W. N. Setzer, *J. Am. Chem. Soc.*, 1980, **102**, 5068.
16 S. R. Cooper, S. C. Rawle, R. Yagbasan and D. J. Watkin, *J. Am. Chem. Soc.*, 1991, **113**, 1600.
17 E. Deutsch, A. R. Ketring, K. Libson, H. R. Maxon and J. L. Vanderheyden, *Nucl. Med. Biol.*, 1986, **13**, 465.
18 M. J. Clarke and L. Podbielski, *Coord. Chem. Rev.*, 1987, **78**, 253.