Crown Thioether Chemistry. The First Homoleptic Thioether Complex of Technetium and Its Potential Application in Tumor Imaging

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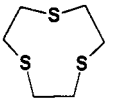
Despite the rapid development of crown thioether coordination chemistry with transition metal ions in recent years,[1-3] crown thioether complexes of Tc are conspicuous by their absence. This oversight is surprising given the central role of ^{99m}Tc-based imaging in nuclear medicine.[4-6] Myocardial imaging in particular requires complexes of low charge,[7,8] and consequently monocationic complexes (such as $[Tc(isonitrile)_6]^+$)[9] now see extensive use. Dicationic species are in demand, but their preparation under clinically feasible conditions has proven elusive. Because crown thioethers stabilize low oxidation states, typically to produce 2+ and 1+ complexes, and they have high chemical robustness, they have evident application to ^{99m}Tc imaging. We report here the synthesis, characterization, and structure of $[Tc(9S3)_2]^{2+}$ (where



9S3

9S3 = 1,4,7-trithiacyclononane), the first homoleptic thioether complex of this element, and we point out the possibility of controlling ^{99m}Tc biodistribution through redox tuning mediated by 9S3 and analogous crown thioethers.

Synthesis of $[^{99}Tc(9S3)_2]^{2+}$ was undertaken from $^{99}TcO_4^-$ because of the ubiquity of this starting material (as $^{99m}TcO_4^-$) in a clinical context. Reaction of NBu_4TcO_4 (12.5 mg, 31 μmol) with 9S3 (17 mg, 92 μmol) in refluxing CH_3CN in the presence of $SnCl_2{\cdot}2H_2O$ (7 mg, 31 μmol) and HBF_4/Et_2O (85% w/v; 70 μL) deposits $[Tc(9S3)_2]^{2+}$ as a dark brown microcrystalline precipitate of its BF_4^- salt. Recrystallization from hot CH_3CN gives the product solvated with two molecules of solvent, one of which is lost under vacuum. Anal. Calc (found) for $[Tc(9S3)_2](BF4)_2{\cdot}CH_3CN$: C, 24.3 (24.9); H, 3.9 (4.0); N, 1.7 (2.0); S, 28.1 (28.5). Of especial importance in the medical context, the bis complex results (albeit more slowly) under the same conditions without addition of Sn(II) or other reducing agent, but rather the excess ligand serves as a sacrificial reductant. Most importantly for clinical application, the synthesis can also be carried out in an analogous manner in physiological saline solution.

Formulation of the product as $[Tc(9S3)_2]^{2+}$ is indicated by FAB MS (monothioglycerol matrix), which exhibits peaks at

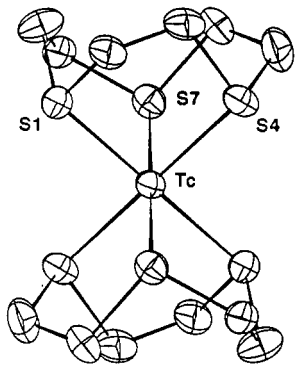


Figure 1. SNOOPI diagram of $[Tc(9S3)_2]^{2+}$. Bond distances: Tc(1)–S(1) = 2.379 (3), Tc(1)–S(4) = 2.372 (3), Tc(1)–S(7) = 2.381 (3) Å. Atomic numbering follows IUPAC convention (S1, C2, C3, S4).

m/z of 546 and 459 amu, corresponding to $\{[Tc(9S3)_2](BF_4)\}^+$ and $\{[Tc(9S3)_2]\}^+$, respectively. Magnetic susceptibility determined in solution by the NMR method indicates an $S = {}^1/_2$ system, with a magnetic moment of 1.8 μ_B at 310 K, consistent with that expected for a low-spin d^5 system with minimal orbital contribution. Electronic spectroscopy shows band maxima of the Tc(II) complex (λ_{max} (ϵ, M^{-1} cm^{-1}) 466 nm (2330), 387 nm (250), 340 nm (150), and 307 nm (140)), while infrared spectroscopy confirms the absence of the Tc=O functional group.

Cyclic voltammetry of $[Tc(9S3)_2]^{2+}$ at a Pt electrode in CH_3CN reveals quasireversible processes at +0.05 and +1.4 V (vs SCE; –0.38 and +0.87 V vs Fc^+/Fc), corresponding to the Tc(II/I) and Tc(III/II) couples, respectively. Controlled-potential electrolysis at a potential greater than +1.4 V vs SCE affords the analogous pale yellow Tc(III) complex with λ_{max} (ϵ) 452 nm (1190) and 384 nm (1320), while at potentials less than –0.2 V vs SCE the cherry-red air-stable Tc(I) complex with λ_{max} (ϵ) 488 nm (5180) and 368 nm (2710) is formed. Both products appear stable under the electrochemical conditions, and their isolation is currently underway.

Structural characterization by X-ray diffraction establishes the existence of a TcS_6 core arising from two 9S3 ligands coordinating facially in a tridentate fashion (Figure 1), with Tc–S bond lengths averaging 2.38 Å.[10] Only two structures containing Tc–thioether bonds have been reported, but neither provides a relevant comparison since both involve oxo species of Tc(V). Comparison with the analogous Ru(II) complex ($Ru-S_{av}$ = 2.34 Å)[11] shows that M–S (M = Tc(II), Ru(II)) bond lengths differ roughly in line with the difference in estimated ionic radii.[12]

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(10) A single crystal (0.2 × 0.3 × 0.7 mm) of $[Tc(9S3)_2](BF_4)_2{\cdot}2MeCN$ was sealed in the mother liquor in a glass capillary. Diffraction data were collected at 20 °C on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). A total of 2251 reflections with 2θ = 2–44° were collected, of which 1670 were unique. Calculations were performed with the CRYSTALS suite of programs on a VAX 11/750 computer, with atomic scattering factors from the usual source. Crystal data: $C_{16}H_{30}N_2B_2F_8S_6Tc$, MW = 715.34, monoclinic, space group $P2_1/c$, Z = 2; a = 10.961 (4) Å, b = 15.284 (3) Å, c = 8.554 (1) Å, β = 104.70 (2)°, V = 1386 Å^3, D_c = 1.951 g/cm^3. Full-matrix least-squares refinement based on 962 data with $F^2 > 2\sigma(F^2)$ converged to R = 0.057 (R_w = 0.056) for 151 parameters.
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Torsional angles of 9S3 itself indicate minimal perturbation from those found in the free ligand,[13] a correspondence that typifies 9S3 complexes with few exceptions.[1]

Extension of crown thioether chemistry to Tc raises intriguing possibilities in nuclear medicine. Deutsch et al.[15] and Clarke and co-workers[4] have recently emphasized the crucial role of redox potential in influencing biodistribution of radiopharmaceutical chelates. Recent work has shown how the choice of different crown ring sizes influences redox potentials within the context of a conserved MS_6 coordination sphere.[14] Redox tuning such as that successfully achieved in the Rh(III/II/I)–*n*S3 (n = 9–12) system[14] may cause localization of ^{99m}Tc in tumors or other hypoxic tissues through a bioreductive trapping mechanism. Work directed toward this goal is in progress.

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Supplementary Material Available: Tables of atomic coordinates, bond angles, bond lengths, anisotropic thermal parameters, hydrogen atomic positions, and crystallographic details (4 pages). Ordering information is given on any current masthead page.

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