The Synthesis of Technetium(V) Complexes Containing Sterically Bulky Thiolate Ligands. The Molecular Structure of Tetrabutylammonium Oxotetrakis(2,4,6-trimethylbenzenethiolato)technetate(V)

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Abstract

The reactions between $[TcOCl_4]^-$ and the sterically bulky thiols ArSH (Ar = 2,4,6-$Me_3C_6H_2$, 2,4,6-$Pr^i{}_3C_6H_2$ and 2,6-$Ph_2C_6H_3$) in methanol afford complexes of formula $[TcO(SAr)_4]^-$ which may be isolated as salts with bulky organic cations. The molecular structure of $[Bu^n{}_4N][TcO(2,4,6\text{-}Me_3C_6H_2S)_4]$ was determined by X-ray diffraction methods. The Tc(V) centre was found to adopt the expected square pyramidal geometry in which an oxo group occupies the apical site and the four thiolate sulphurs the basal sites. The Tc–O distance is 1.659(11) Å and the average Tc–S distance 2.38(2) Å. The average *cis* S–Tc–S, *trans* S–Tc–S and O–Tc–S angles are respectively 82.7(6)°, 138.4(3)° and 110.8(4)°.

Introduction

The γ-emitting radionuclide ^{99m}Tc is widely used as an imaging agent in diagnostic nuclear medicine. The biodistribution of ^{99m}Tc following administration to the patient may be controlled by incorporating it in a coordination or organometallic compound. Both the nature of the ligand and the Tc oxidation state are important in determining the physical properties of the product complex and thus its biodistribution. In turn, the type of ligand used is important in controlling the final Tc oxidation state in the product complex. Ligands have been developed which allow ^{99m}Tc to be used for imaging bone, liver, kidney, heart and brain, among other applications [1–6]. The success of existing ^{99m}Tc radiopharmaceutical agents, has stimulated the search for new ligand systems which may improve on existing materials or offer new applications.

In preparing radiopharmaceuticals for administration to a patient a solution of TcO_4^- is usually treated with a reducing agent in the presence of the ligand. The most commonly used reducing agent at present is $SnCl_2$ which is effective in producing Tc(V). A well established class of Tc(V) compounds contains the TcO^{3+} core coordinated by four additional donor atoms to give a square pyramidal geometry at the Tc centre. Many complexes of this type have now been characterised of which most are anionic, although some examples of neutral or cationic complexes are known. Among such species the thiophenolate complex $[TcO(SPh)_4]^-$ has been reported but not structurally characterised [7]. The report that lipophilic rhenium thiolate complexes $[ReO(ArS)_4]^-$ (Ar = Ph, 2,4,6-$Me_3C_6H_2$, 2,4,6-$Pr^i{}_3C_6H_2$ or 2,6-$Ph_2C_6H_3$) could be prepared using sterically bulky thiolate ligands [8, 9] prompted us to investigate the parallel chemistry of technetium. Recently the synthesis of the related complex $[AsPh_4][Tc(V)O(2,3,5,6\text{-}Me_4C_6HS)_4]$ has been reported by Davison *et al.* [10] along with a structural study of $[Tc\{2,3,5,6\text{-}Me_4C_6HS\}_3(MeCN)_2]$ which adopts a trigonal bipyramidal structure having axial acetonitrile ligands.

Experimental

Synthetic Studies

Reagents were used as received and solvents were dried by standard techniques before use. $[Bu_4N]^+$-$[^{99}TcOCl_4]^-$ was prepared according to a previously described method [11]. The precautions necessary for the handling of ^{99}Tc have been described elsewhere [12]. Infra red and ^{1}H NMR spectra were recorded on PE 297 and Jeol GX 270 instruments respectively. These compounds crystallise as solvates with hydrocarbon solvents and the NMR spectra also contained signals attributable to solvent. Elemental analyses were performed by Butterworths Laboratories.

$[Bu^n{}_4N][TcO\{2,4,6\text{-}Me_3C_6H_2S\}_4]$

To a solution of $[Bu_4N]^+[TcOCl_4]^-$ (85 mg, 0.17 mmol) in dry methanol (30 ml) was added 2,4,6-$Me_3C_6H_2SH$ (0.5 ml, 3.4 mmol) and NEt_3 (0.2 ml). The reaction mixture was stirred at room temperature for 12 h. The volume of the mixture was then

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reduced by evaporation to *ca.* 15 ml and Et_2O and hexane were added to precipitate a purple coloured solid. This was collected by filtration, washed with Et_2O and recrystallised from CH_2Cl_2/hexane mixtures to afford the product as red–brown needles (60 mg, 37%). *Anal.* Found: C, 64.0; H, 8.1; N, 1.3. Calc. for $C_{52}H_{80}NOS_4Tc$: C, 64.9; H, 8.3; N, 1.4%. Infra red ν(TcO) 940 cm^{-1}. ^1H NMR δ(TMS) 1.00 (12m) $N\{(CH_2)_3CH_3\}_4$; 1.2–1.6 (16m) $N\{CH_2(CH_2)_2CH_3\}_4$; 2.05 (12s), 2.18 (12s), 2.30 (12s) $\{SC_6H_2(CH_3)_3\}_4$; 2.70–2.98 (8m) $N\{CH_2(C_3H_7)\}_4$; 6.79 (8s, br) $\{SC_6H_2Me_3\}_4$.

$[Ph_4P][TcO\{2,4,6\text{-}^iPr_3C_6H_2S\}_4]$

$[Bu_4N]^+[TcOCl_4]^-$ (68 mg, 0.13 mmol) and 2,4,6-$^iPr_3C_6H_2SH$ (0.6 ml, 2.7 mmol) were dissolved in dry methanol (30 ml) and the mixture stirred at room temperature for 70 h. The volume of the mixture was then reduced by evaporation to *ca.* 5 ml prior to filtration. The filtrate deposited a brown solid on standing and this was dissolved in toluene and slow evaporation caused a brown solid to separate. This was redissolved in CH_2Cl_2 and treated with Ph_4PBr (0.2 g, 0.54 mmol). On slow evaporation a mixture of white powder and black crystals was deposited. Washing with methanol removed the white solid leaving the black crystalline material which was recrystallised from CH_2Cl_2/hexane mixtures (65 mg, 34%). *Anal.* Found: C, 71.1; H, 8.0; P, 2.6. Calc. for $C_{84}H_{112}OPS_4Tc$: C, 72.3; H, 8.7; P, 2.2%. Infra red ν(TcO) 940 cm^{-1}. ^1H NMR δ(TMS) 0.88 (12d, J_{HH} 6Hz), 0.97 (12d, J_{HH} 7Hz), 0.99 (12d, J_{HH} 7Hz), 1.19 (24d, J_{HH} 7Hz), 1.31 (12d, J_{HH} 6Hz) $\{SC_6H_2(CHMe_2)_3\}_4$; 2.80 (4m), 3.38 (4m) and 4.20 (4m) $\{SC_6H_2(CHMe_2)_3\}_4$; 6.85 (8d, J_{HH} 5Hz) $\{SC_6H_2(CHMe_2)_3\}_4$; 7.43–7.95 (20m) PPh_4.

$[Bu^n{}_4N][TcO\{2,6\text{-}Ph_2C_6H_3S\}_4]$

$[Bu_4N]^+[TcOCl_4]^-$ (0.1 g, 0.2 mmol) and 2,6-$Ph_2C_6H_3SH$ (0.3 g, 1.2 mmol) were dissolved in dry ethanol (25 ml) and the mixture stirred for 10 min. Triethylamine (0.2 ml) was then added and the mixture stirred for a further 3 h at room temperature. A brown solid separated and was collected by filtration, washed with Et_2O then redissolved in CH_2Cl_2. A solution of $Bu^n{}_4NBr$ (47 mg) in methanol (1.5 ml) was next added and the mixture allowed to stand at −5 °C for 3 days. After this time the black solid which separated was collected by filtration and recrystallised from CH_2Cl_2/hexane mixtures (39 mg, 14%). *Anal.* Found: C, 70.7; H, 5.9; N, 0.8. Calc. for $C_{88}H_{88}ONS_4Tc$: C, 71.8; H, 6.1; N, 1.0%. Infra red ν(TcO) 960 cm^{-1}, ^1H NMR δ(TMS) 1.00 (12m) $N\{(CH_2)_3CH_3\}_4$; 1.2–1.7 (16m) $N\{CH_2(CH_2)_2CH_3\}_4$; 3.0 (8m) $N\{CH_2(C_3H_7)\}_4$; 6.4–7.4 (52m) $\{SC_6H_3(C_6H_5)_2\}_4$.

Structural Study of $[Bu_4N]\{TcO(2,4,6\text{-}Me_3C_6H_2S)_4\}$

A crystal 0.4 × 0.5 × 0.6 mm was mounted on an Enraf-Nonius CAD-4 diffractometer; cell dimensions and intensities were measured by $\omega/2\theta$ scans with graphite-monochromated Mo Kα radiation. 8114 reflections were scanned within the range $2° < \theta < 23.5°$. Of these 4468 were unique (merging $R_{Int} = 0.068$). Two standard reflections measured every 2 h showed a drop in intensity of approximately 4% during the period of data collection and appropriate scaling factors were applied. 1957 structure amplitudes with $I > 3\sigma(I)$ were considered observed and used in the analysis. The structure was determined by Patterson and Fourier methods. The anionic complex is disordered about the centre of symmetry at (¼, ¼, 0) and the tetrabutylammonium counter ion is sited on the twofold axis (0, y, ¼). Thus in Fig. 1, which depicts the complex, the primed atoms are centrosymmetrically related to the corresponding unprimed ones; the two orientations of the complex coincide at all atoms except technetium and oxygen (and possibly some of the hydrogen atoms). Tc and O were included in the calculations with site occupancies of 0.5, and with only one of their two possible positions shown in Fig. 1. The cation is also affected to some extent by disorder. Two sites could be found for each carbon atom, with site occupancies of 0.62(1) and 0.38(1), respectively.

Positional and anisotropic thermal parameters were refined by least-squares for the heavier atoms of the complex. The positions of the atoms of the tetrabutylammonium moiety were fixed at the coordinates located from difference maps; only isotropic temperature factors and the site occupancies were refined. Hydrogen atoms were placed in calculated positions 'riding' on their respective bonded C atoms. Those of the minor orientation of the tetrabutylammonium ion were, however, not included. The weighting scheme used in the least-squares refinement was $w = 1/(\sigma^2(F) + 0.001F^2)$ and the refinement converged to $R = 0.073$, $R_w = 0.100$. The residual electron density in the final difference map was within the range 0.64 to −0.37 e Å^{-3}.

Computations were carried out on the University of Birmingham Honeywell computer and on the CDC 7600 at the University of Manchester Regional Computer Centre with the SHELX [13] and PLUTO [14] programs.

Crystal data

$C_{36}H_{44}OS_4Tc^-C_{16}H_{36}N^+$, $M = 962.4$, space group $C2/c$, $a = 21.909(6)$, $b = 17.366(5)$, $c = 14.348(7)$ Å, $\beta = 100.67(3)°$, $V = 5365$ Å^3, $Z = 4$, $D_c = 1.19$ g cm^{-3}, $F(000) = 2056$, Mo Kα radiation ($\lambda = 0.71069$ Å), $\mu = 0.44$ mm^{-1}.

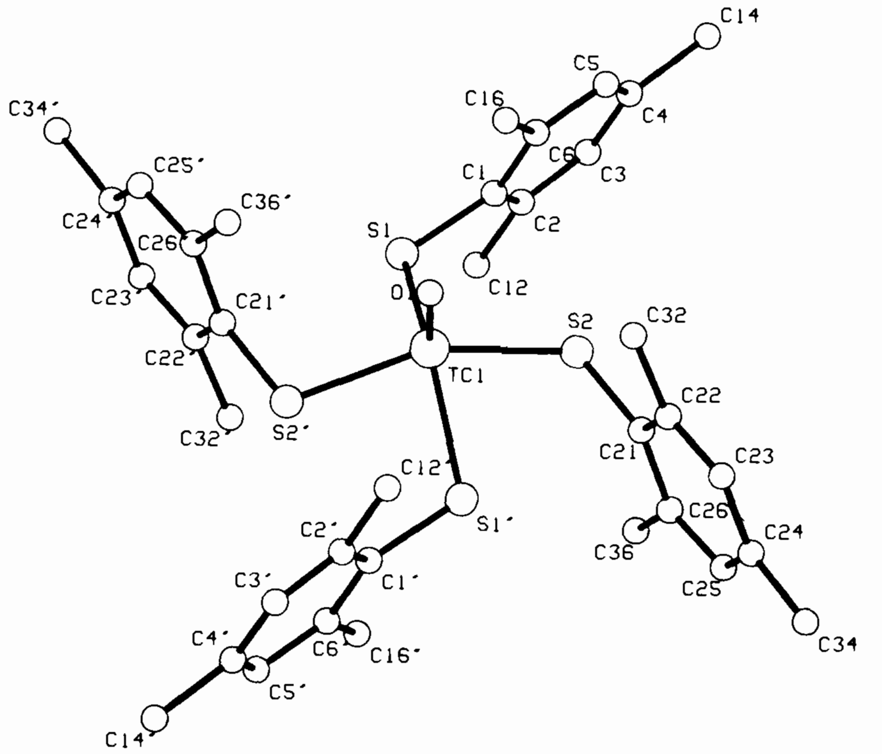

Fig. 1. The structure of the $[TcO(2,4,6\text{-}Me_3C_6H_2S)_4]^-$ ion showing the atom labelling.

Discussion

The rhenium complexes $[ReO(SAr)_4]^-$ were prepared from the reaction between excess ArS^- and $[ReOCl_3(PPh_3)_2]$ [8]. In the case of technetium we have found that $[TcOCl_4]^-$ reacts smoothly with excess ArSH to produce anionic complexes which could be isolated in crystalline form as salts of large cations such as $Bu^n{}_4N^+$ or Ph_4P^+. The infra red spectra of these compounds exhibited bands attributable to the cation, the arylthiolate ligand and the TcO moiety. The ^1H NMR spectra also exhibited signals attributable to the cation and the ligand ArS. The spectral data and elemental analyses for the new complexes were consistent with their formulation as five coordinate species $[TcO(ArS)_4]^-$. In the case of $[TcO\{2,4,6\text{-}^iPr_3C_6H_2S\}_4]^-$ the methyl groups in the isopropyl substituents gave rise to six doublets in the ^1H NMR spectrum. This would be consistent with the complex having an approximately square pyramidal structure like the analogous rhenium compound. Similarly in the complex $[TcO(2,4,6\text{-}Me_3C_6H_2S)_4]^-$ three methyl environments were observed in the ^1H NMR spectrum. This is in accord with the two methyl groups *ortho* to the sulphur on the aryl ring being in different environments, that is *syn* and *anti* to the technyl oxo group.

In order to provide a more detailed structural comparison with the rhenium compounds, the complex $Bu^n{}_4N[TcO(2,4,6\text{-}Me_3C_6H_2S)_4]$ was selected for an X-ray structural study. The final atomic coordinates are listed in Table I and selected bond distances and angles for the anion are presented in Table II. The structure of the anion $[TcO(2,4,6\text{-}Me_3C_6H_2S)_4]^-$ is illustrated in Fig. 1. The coordination geometry about technetium is essentially square pyramidal. The four sulphur atoms constituting the base of the pyramid must of necessity be accurately coplanar because of the symmetry imposed by the disorder. The thermal parameters of these atoms are, however, quite normal, so that there is no reason to believe that the averaged positions of the atoms of the two orientations of the complex differ significantly from the actual positions. The technetium atom is displaced by 0.846 Å from the basal plane towards the apical oxygen, which lies 2.50 Å from this plane.

Comparison with the structure of the corresponding rhenium complex in crystals of the triethylammonium salt [9] shows that its coordination geometry is quite similar, although the square pyramid is somewhat flatter (Re displaced by 0.71 Å from basal plane) and deviates to a greater extent from four-fold symmetry. Thus the O–metal–S angles range from 103.1 to 113.3, mean 107.7°, in the rhenium complex compared with the much narrower range, 109.7–111.7, mean 110.8°, in the technetium complex. The Re–S distances average

TABLE I. Fractional Atomic Coordinates (× 10^4) and Isotropic Temperature Factors ($Å^2 \times 10^3$)

	x	y	z	U
Tc(1)	2581(1)	2943(1)	238(1)	a
S(1)	3095(1)	2006(2)	1271(2)	a
S(2)	1663(1)	2364(2)	674(2)	a
C(1)	2704(5)	1724(6)	2204(6)	a
C(2)	2547(5)	955(6)	2283(7)	a
C(3)	2293(6)	710(7)	3031(9)	a
C(4)	2181(6)	1221(10)	3707(8)	a
C(5)	2319(5)	1977(8)	3622(7)	a
C(6)	2601(5)	2241(6)	2892(7)	a
C(12)	2665(6)	383(6)	1562(9)	a
C(14)	1907(7)	932(9)	4537(8)	a
C(16)	2796(7)	3074(6)	2829(9)	a
C(21)	986(5)	2760(6)	−30(7)	a
C(22)	823(5)	3516(7)	97(7)	a
C(23)	277(7)	3812(9)	−438(9)	a
C(24)	−114(6)	3354(12)	−1086(10)	a
C(25)	53(7)	2624(11)	−1222(9)	a
C(26)	579(7)	2321(7)	−727(9)	a
C(32)	1238(6)	4049(6)	772(8)	a
C(34)	−673(7)	3708(10)	−1707(11)	a
C(36)	765(7)	1521(7)	−943(9)	a
O(1)	2691(6)	3816(7)	709(8)	a
N(1)	0	1955(6)	2500	81(3)
C(N1)	519	1412	2193	67(5)[b]
C(N2)	300	858	1461	96(6)[b]
C(N3)	787	348	1233	125(8)[b]
C(N4)	886	−317	1776	149(10)[b]
C(N5)	312	2385	3325	99(7)[b]
C(N6)	705	2933	3212	157(10)[b]
C(N7)	1034	3394	4193	226(15)[b]
C(N8)	1400	4010	4357	189(13)[b]
C(N1′)	83	1617	1674	135(14)[c]
C(N2′)	600	879	1906	188(20)[c]
C(N3′)	368	285	1183	223(24)[c]
C(N4′)	795	−422	1002	107(12)[c]
C(N5′)	566	2636	2633	216(23)[c]
C(N6′)	701	3045	3639	275(32)[c]
C(N7′)	1005	3688	3526	176(20)[c]
C(N8′)	729	4164	3505	235(28)[c]

e.s.d.s given in parentheses. [a] Refined using anisotropic thermal parameters. [b] Site occupancy 0.62(1). [c] Site occupancy 0.38(1).

2.334 Å compared with 2.380 Å for Tc–S; the metal–O distances, however, agree to within 0.009 Å.

The S–C bond lengths are typical of those between sulphur and sp^2-hybridised carbon and there is, therefore, apparently no significant conjugation between sulphur and the aromatic systems. The steep angle between the aromatic rings and their respective Tc–S–C(phenyl) planes, 60.3 and 68.8°, also supports this conclusion. Adjacent phenyl rings are close to perpendicular, the interplanar angle being 95.6°. The steep inclination of the aromatic rings can be considered to be a necessary consequence of the steric effect of the two *ortho* methyl substituents in each ring. The relatively large bond angles at sulphur, mean 112.4°, may also be due to this steric effect, rather than an electronic effect.

The overall geometry of the $TcOS_4$ grouping is similar to those in oxo-bis(thiomercaptoacetato)-technetium(V) [15], oxo-bis(1,2-dithiolatoethane)-technetium(V) [16] and in a bimetallic Tc(V) complex [17], although small but significant differences do occur. Thus the technetium to basal-plane distances in these compounds, 0.79 [15], 0.76 [16] and 0.74, 0.80 Å [17] are smaller than the corresponding distance, 0.846 Å, in the title compound, and the Tc–S distances, mean 2.320 [15], 2.300 [16] and 2.386 (bridging), 2.266 Å (non-bridging) [17] are generally shorter than the Tc–S distances in the title compound (mean 2.380 Å). The Tc–O distances, 1.671 [15], 1.636 [16] and 1.662, 1.659 Å [17] are in good agreement with our value of 1.659 Å.

The structural data show that the rhenium complex exhibits a significantly larger distortion from square pyramidal towards trigonal bipyramidal with an equatorial oxo-group than does the technetium complex.

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TABLE II. Selected Bond Lengths (Å) and Angles (°) in $[TcO(2,4,6\text{-}Me_3C_6H_2S)_4]^-$

Tc–S(1)	2.344(3)	Tc–S(1′)	2.388(3)
Tc–S(2)	2.432(3)	Tc–S(2′)	2.354(3)
S(1)–C(1)	1.786(10)	S(2)–C(21)	1.772(11)
Tc–O	1.659(11)		
S(1′)–Tc–S(1)	138.1(1)	S(2)–Tc–S(2′)	138.6(1)
S(2)–Tc–S(1)	82.7(1)	S(2′)–Tc–S(1′)	83.5(1)
S(2)–Tc–S(1′)	81.1(1)	S(2′)–Tc–S(1)	83.6(1)
O–Tc–S(1)	111.1(4)	O–Tc–S1′	110.8(4)
O–Tc–S(2)	109.7(5)	O–Tc–S2′	111.7(5)
Tc–S(1)–C(1)	115.1(3)	Tc–S(1′)–C(1′)	112.8(3)
Tc–S(2)–C(21)	109.8(3)	Tc–S(2′)–C(21′)	111.8(3)

arylthiolate ligands, to A.E.R.E. Harwell Laboratory for providing a sample of $NH_4{}^{99}TcO_4$ and to Mr C. D. Bush for experimental assistance.

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