Symmetric bis-substituted and asymmetric mono-substituted nitridotechnetium complexes with heterofunctionalized phosphinothiolate ligands†

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The mixed bidentate ligand 2-(dicyclohexylphosphino)-ethanethiol (HL) reacts with labile nitrido-Tc precursors to afford a rare example of an asymmetric monosubstituted species [TcN(L)Cl(PPh$_3$)], 1, along with the symmetric bis-substituted complex [TcN(L)$_2$], 2. The latter compound, as assessed by TLC and HPLC chromatography, was found to possess the same molecular structure as the agent produced at the 'non carrier added' level utilizing the ^{99m}Tc nuclear isomer.

Nitrido-Tc(v) chemistry is receiving growing attention in the last few years owing to the recent availability of a standard method for producing the $[Tc{\equiv}N]^{2+}$ moiety at 'non carrier added' level utilizing the ^{99m}Tc nuclear isomer.[1] In this connection, the first ^{99m}Tc radiopharmaceutical carrying the nitrido group, namely [^{99m}TcN(NOEt)$_2$] (NOEt = *N*-ethyl-*N*-ethoxydithiocarbamate), has been proposed as a myocardial perfusion agent[2] and is now under phase III clinical trials. The proposed co-ordination of the [TcN(NOEt)$_2$] complex is square pyramidal with the terminal nitrogen group at the apex and the two substituted dithiocarbamate ligands at the base of the pyramid, as previously assessed for the related diethyldithiocarbamato (dedc) compound [TcN(dedc)$_2$],[3] which exhibits a trigonality index τ of 0.02 ($\tau = 0$ for ideal square-pyramidal geometry and $\tau = 1$ for ideal trigonal-bipyramidal geometry[4]). A geometry approaching trigonal bipyramidal ($\tau = 0.76$) is instead exhibited by [Tc(L′)$_2$(O=L′)], a Tc(III) complex containing the bidentate 2-(diphenylphosphino)ethanethiol (HL′) ligand, in which two phosphorus atoms are located at the apexes and the three thiolate sulfur atoms are equatorial, leaving the oxidized phosphorus atom of the third ligand dangling outside the co-ordination sphere.[5] These phosphino-thiolato Tc(III) complexes are generated *via* reduction-substitution reactions starting from $[TcO_4]^-$ and an excess of the relevant phosphinothiol. The formation of intermediate oxo-Tc(v) species was not detected, even when using a stoichiometric amount of the ligand, indicating that if these Tc(v) adducts were formed, they rapidly underwent further reduction to the thermally stable Tc(III) species. However, similar reduction-substitution reactions, conducted at the 'non carrier added' level starting from [^{99m}TcO$_4$]$^-$ in the presence of a nitrido source such as hydrazine or substituted hydrazines and an excess of phosphinothiol, evidenced the existence of novel species having different retention times when compared to those exhibited by the related Tc(III) species. Moreover, these new derivatives have shown promising heart uptake when injected in rats and primates.[6] We were consequently stimulated to elucidate the molecular structure of these agents at the macroscopic level by utilizing the ^{99g}Tc isotope.

The understanding that the nitrido group is much more resistant toward reduction than the corresponding oxo group in Tc(v) complexes,[7] directed our investigation on the reactivity of labile pre-reduced nitrido-Tc precursors with representative P,S ligands. Reaction of $[Tc^{VI}NCl_4]^-$ with a three-fold molar excess of 2-(dicyclohexylphosphino)ethanethiol (HL) in CH_2Cl_2–EtOH (2 : 1 v/v) afforded a yellow–brown solution from which an orange–yellow powder of **2** was isolated upon removal of the solvent. The IR spectrum exhibits a medium intensity stretching vibration at $\nu = 1045$ cm^{-1} indicating the retention of the terminal nitrido group, as well as vibrations characteristic of the cyclohexyl rings. Elemental analysis is in agreement with the presence of two phosphinothiolate ligands, and the singlet in the ^{31}P NMR indicates the magnetic equivalence of the P nuclei. Recrystallization from CH_2Cl_2–MeOH gave pale yellow plates suitable for X-ray determination. In spite of some disorder (see Experimental), the co-ordination about Tc in **2** is well established (Fig. 1), and is best described as intermediate between square pyramidal and trigonal bipyramidal ($\tau^1 = 0.49$ and $\tau^2 = 0.60$ for the two types of molecules). In the trigonal-bipyramidal description the nitrido group and two thiolate sulfur atoms occupy the equatorial sites with the phosphine phosphorus at the apexes of the bipyramid. The twist-envelope five-membered chelate rings of both phosphinothiolato ligands are virtually perpendicular to the S(1)N(1)N(1A) plane and form an angle of 40.4° to each other. The cyclohexyl rings adopt a chair conformation (D_{3d}) and make a dihedral angle of 56.5° to each other.

The mono-substituted complex [TcN(L)Cl(PPh$_3$)], **1**, was produced by reaction of [TcNCl$_2$(PPh$_3$)$_2$] with a slight excess of HL in CH_2Cl_2–EtOH (2 : 1 v/v) mixtures. The ^{31}P NMR spectrum of **1** displays two broad signals at room temperature. On lowering the temperature the signals become narrower, and the appearance of two doublets at 250 K ($^2J_{PP} = 162$ Hz) indicates the existence of two magnetically inequivalent *trans*-positioned P donors. The IR spectrum shows vibrations characteristic of both the cyclohexyl rings and of co-ordinated triphenylphosphine, along with the typical medium intensity band of the terminal nitrido group at $\nu = 1066$ cm^{-1}. The X-ray analysis confirmed a five-co-

† Supplementary material available: HPLC traces for **2** and **2m**. Available from BLDSC (No. SUP 57578, 2 pp.). See Instructions for Authors, 1999, Issue 1 (http://www.rsc.org/njc).

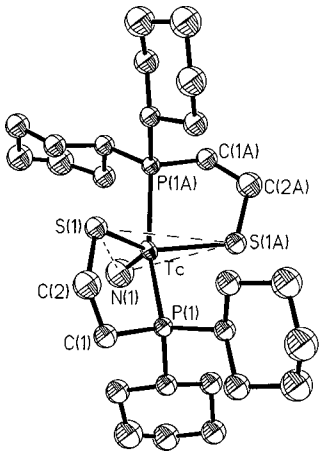

Fig. 1 View of structure **2** showing the numbering scheme adopted. Thermal ellipsoids are drawn at the 40% probability level. Selected bond lengths (Å) and angles (°) [in square brackets for the molecule generated by a pseudo-mirror plane]: Tc–S(1) 2.362(6) [2.46(1)], Tc–P(1) 2.389(5) [2.38(1)], Tc–N(1) 1.64(3) [1.63(6)], S(1)–C(2) 1.82(2) [1.87(3)], P(1)–C(1) 1.85(2) [1.80(4)]; S(1)–Tc–S(1A)* 129.2(3) [124.1(5)], S(1)–Tc–P(1) 82.2(2) [81.5(3)], P(1)–Tc–P(1A)* 158.5(3) [160.1(7)], S(1)–Tc–N(1) 115.4(2) [117.9(3)], P(1)–Tc–N(1) 100.8(2) [99.9(3)], Tc–S(1)–C(2) 110.5(8) [107(1)], Tc–P(1)–C(1) 106.1(7) [108(2)]. * At $-x, y, \frac{1}{2} - z$.

ordiate structure (Fig. 2) approaching the square-pyramidal environment ($\tau = 0.28$) with the nitrido group at the apex and the remaining PSPCl donors at the base of the pyramid. In the square-pyramidal description the Tc atom is displaced by 0.65 Å from the mean equatorial plane toward the nitrido nitrogen atom and the four basal donors are displaced by ± 0.16 Å as well. However, if we use the trigonal-bipyramidal desription the Tc ion is virtually within the S(1)N(1)Cl plane (deviation of only 0.005 Å) and the twist-envelope five-membered chelate ring of the phosphinothiolate ligand is orthogonal to this plane. The cyclohexyl rings behave as in **2** and make a dihedral angle of 65.8° to each other. The three phenyl groups of the triphenylphosphine ligand are almost orthogonal to each other, making dihedral angles of 79.0, 86.5 and 110.1°.

2 and the corresponding agent prepared utilizing ^{99m}Tc, **2m**, have shown identical chromatographic profiles, available as supplementary material, confirming the existence of nitrido-Tc(v) species containing phosphinothiolato ligands at the 'non carrier added' level. As expected from the relative ^{99m}Tc/ligand concentrations, no trace of the mono-substituted complexes has been detected at the 'non carrier added' level.

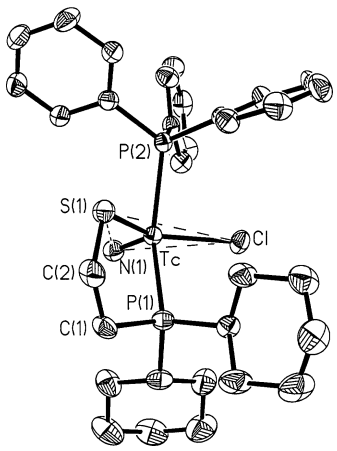

Fig. 2 View of structure **1** showing the numbering scheme adopted. Thermal ellipsoids are drawn at the 40% probability level. Selected bond lengths (Å) and angles (°); Tc–Cl 2.377(2), Tc–P(1) 2.387(2), Tc–P(2) 2.430(2), Tc–S(1) 2.303(2), Tc–N(1) 1.590(5), P(1)–C(1) 1.817(6), C(1)–C(2) 1.471(9), S(1)–C(2) 1.817(6); P(1)–Tc–P(2) 156.4(1), N(1)–Tc–S(1) 109.0(2), N(1)–Tc–Cl 111.4(2), S(1)–Tc–P(1) 82.9(1), Cl–Tc–S(1) 139.6(1), Tc–P(1)–C(1) 105.8(2), Tc–S(1)–C(2) 110.1(2).

Experimental

Syntheses

Ligand 2-(dicyclohexylphosphino)ethanethiol (HL). This ligand was prepared by Argus Chemicals according to the method previously described by Chatt *et al.* for the synthesis of 2-(diphenylphosphino)ethanethiol.[8] Dicyclohexylphosphine and 2 M *n*-BuLi were used instead of diphenylphosphine and methyl lithium.

[Tc(N)(L)Cl(PPh$_3$)], 1. Solid [$TcNCl_2(PPh_3)_2$] (0.085 g, 0.129 mmol) was suspended in CH_2Cl_2 (5 cm^3) and HL (0.064 g, 0.249 mmol) dissolved in EtOH (5 cm^3) was added. The mixture was stirred at reflux for 1 h until a clear orange–yellow solution appeared. After cooling the solvent was removed by a gentle stream of dinitrogen and the residue was treated with EtOH (5 cm^3). A yellow precipitate was collected by filtration, washed with Et_2O (2 × 10 cm^3) and dried under vacuum (yield 72%). Anal. found (calcd. for $C_{32}H_{41}P_2SNClTc$): C, 56.97 (57.52); H, 6.36 (6.18); N, 2.31 (2.10); S, 5.31 (5.22)%. FT IR (KBr pellets, cm^{-1}): 1066 (ν[Tc≡N]). ^{1}H NMR ($CDCl_3$) δ: 7.95–7.30 (Ph_3P, 15 H), 3.05–3.08 (Cy_2P, SCH_2CH_2P, 26 H). ^{31}P NMR ($CDCl_3$, 250 K) δ: 86.3 (d, Cy_2P, $^2J_{PP} = 162$ Hz), 39.3 (d, Ph_3P, $^2J_{PP} = 162$ Hz).

[Tc(N)(L)$_2$], 2. Solid [$AsPh_4$][$TcNCl_4$] (0.082 g, 0.129 mmol) was suspended in CH_2Cl_2 (10 cm^3) and HL (0.100 g, 0.387 mmol) dissolved in EtOH (5 cm^3) was added. The mixture was stirred at room temperature for 1 h until the solution became clear and brown coloured. The solvent was then removed by a gentle stream of dinitrogen and the residue was treated with EtOH (5 cm^3). A pale yellow solid was collected by filtration, washed with Et_2O (2 × 10 cm^3) and dried under vacuum (yield 91%). Anal. found (calcd. for $C_{28}H_{52}P_2S_2NTc$): C, 52.99 (53.56); H, 8.41 (8.35); N, 2.32 (2.24); S, 11.01 (10.21)%. FT IR (KBr pellets, cm^{-1}): 1045 (ν[Tc≡N]). ^{1}H NMR ($CDCl_3$) δ: 2.87 (m, SCH_2–, 4 H), 2.75–1.10 (Cy_2P, PCH_2–, 48 H). ^{31}P NMR ($CDCl_3$, 298 K) δ: 85.9 (s).

[^{99m}Tc(N)(L)$_2$], 2m. In a 5 cm^3 borosilicate vial containing 1 mg of *N*-methyl-*S*-methyldithiocarbazate and tin chloride (0.1 mg) dissolved in water (0.1 cm^3), ethanol (0.75 cm^3) and [^{99m}Tc]pertechnetate solution (0.5 cm^3, 5 mCi) were added. The solution was left to react at room temperature for 30 min, after which the pH was adjusted to 8 by means of a 0.5 M carbonate buffer (0.1 cm^3). Then 0.25 cm^3 of a 0.01 M HL ethanolic solution was added. The vial was quickly capped and placed into an oil bath at 100 °C for 30 min. The reaction mixture was left to cool at ambient temperature; the vial was then opened and aliquots of the reaction mixture were analyzed by HPLC, giving the desired product of radiochemical purity: 88–94%.

Chromatography

HPLC. ODS-C_{18} column (Beckman) equipped with a C_{18} guard column. Isocratic elution methanol–water 90 : 10 at a flow rate of 1 mL min^{-1}.

TLC. Silica gel 60 F_{254} plates (Merck). Elution with an ethanol–chloroform–benzene 0.5 : 2.0 : 1.5 mixture gave r_f values of 0.7 for both **2** and the corresponding ^{99m}Tc agent **2m**.

Crystallography

Crystal data for $C_{32}H_{41}P_2SNClTc$ 1. $M = 667.1$, monoclinic, $P2_1/n$, $a = 12.437(4)$, $b = 13.441(4)$, $c = 19.060(6)$ Å, $\beta = 102.05(3)°$, $U = 3116(2)$ Å, Mo-Kα radiation: $\lambda = 0.71073$ Å, $Z = 4$, $T = 294$ K, μ(Mo-Kα) = 7.40 cm^{-1}. 4563 absorption corrected reflections (Ψ scans,[9] $I = 0.452$–0.763), 4320 unique ($R_{int} = 0.038$). Structure solution and refinement on F^2 using SHELXTL/PC and SHELXTL-93 program packages,[10] with application of anisotropy only to the heavy atoms. At final convergence, $R_1 = 0.043$, $wR_2 = 0.099$, $S = 1.027$ for 339 parameters and 3107 reflections with $I > 2\sigma(I)$ using the following weighting scheme: $w = 1/[\sigma^2(F_0^2) + (0.0678P)^2 + 0.0486P]$, $P = (F_0^2 + 2F_c^2)/3$. Difference electronic density features lie within the range 0.70 to −0.66 e $Å^{-3}$.

Crystal data for $C_{28}H_{52}P_2S_2NTc$ 2. $M = 626.8$, monoclinic, $C2/c$, $a = 10.528(9)$, $b = 11.731(9)$, $c = 24.25(2)$ Å, $\beta = 95.32(9)°$, $U = 2982(4)$ $Å^3$, Mo-Kα radiation: $\lambda = 0.71073$ Å, $Z = 4$, $T = 294$ K, μ(Mo-Kα) = 7.48 cm^{-1}. 2718 Absorption corrected reflections (ψ scans, $I = 0.563$–0.813), 1409 unique ($R_{int} = 0.056$). Unfortunately, the diffracting ability of some samples mounted on the diffractometer fell off rapidly with increasing Bragg angle, and much of the higher angle data were flagged as weak and bore negative intensity. As a consequence, the data collection was restricted to $2\Theta_{max} = 40°$. In addition, the refinement of the structure was relatively difficult due to the siting of the atoms; in fact, the Patterson map and subsequent observed Fourier synthesis showed a double image of the molecule: the atoms of one molecule at *x*, *y*, *z* (major component) together with the others at *ca.* *x*, *y*′, *z* (minor component). They were refined with occupancies of 2/3 and 1/3, and only Tc and Tc′ were assigned anisotropic thermal parameters. No attempt was made to include hydrogen atoms. Refinement, performed with the same procedure used for **1**, converged at $R_1 = 0.078$ and $wR_2 = 0.203$ with 144 parameters. In the difference electron density map the largest peak and hole were 0.58 and −0.62 e $Å^{-3}$, respectively. Some caution is required in considering the metrical data of **2** because of the pseudo-symmetry, which caused some difficulties in refinement, leading to high estimated standard deviations.

CCDC reference number 440/121. See http://www.rsc.org/suppdata/nj/1999/807/ for crystallographic files in .cif format.

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