Nitrido–Technetium(V) Complexes with Amino Acids: Preparation and X-ray Crystal Structure of the L-Cysteinate Ethyl Ester Technetium(V) Complex

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Technetium-99m is the radionuclide of choice in diagnostic nuclear medicine due to its ideal photon energy of 140 keV and half-life of 6 h.

Neutral, stable, and lipophilic technetium complexes with diamino dithiol ligands (DADT) have been widely studied as potential brain perfusion agents[1] and a ^{99m}Tc complex of *N,N'*-1,2-ethylenediylbis(L-cysteine diethyl ester) (L,L-ECD) has been proposed as a marker of regional cerebral blood flow.[2] It crosses the blood brain barrier (BBB) and is retained in the brain owing to enzymatic hydrolysis of one ester group yielding to a more polar species.[2] More recently, a ^{99m}Tc–cysteine complex has been evaluated in animal distribution studies for tumor diagnosis, but its chemical structure has not been determined.[3] A large number of transition metal complexes with amino acids and peptides have been synthesized and structurally characterized[4] to understand their interactions with proteins and antibodies, as well as biocatalitic processes, but only a limited number of rhenium[5] and technetium[2a,3,6] compounds have been reported. Up to now, the only technetium complex to be characterized by X-ray analysis that contains amino acids as ligand is [TcO(L,L-ECD)].[2a] Our interest in the nitrido–technetium chemistry is due to the discovery of a new method for preparing radiopharmaceuticals containing the $[^{99m}Tc{\equiv}N]^{2+}$ core.[7] In this comunication we report the synthesis and characterization of nitrido–technetium complexes with L-cysteine ethyl ester (CYS-OEt), L-cysteine (CYS) and cysteamine (CSA) and the first X-ray crystal structure of a $[TcN]^{2+}$–amino acid complex.

A preliminary study on the synthesis of the corresponding $^{99m}Tc{\equiv}N$ complexes and their biodistribution is also described. The complexes [TcNCl(CYS-OEt)(PPh_3)] (**1**), [TcNCl(CYS)-(PPh_3)] (**2**), and [TcN$(CSA)_2$] (**3**)were prepared as follows:[8] the complex [$TcNCl_2(PPh_3)_2$] (0.2 g, 0.28 mmol) was dissolved in CH_2Cl_2/MeOH (3:1, 40 mL) and heated until the temperature was 40 °C. An excess of the appropriate ligand dissolved in MeOH was added to the pink solution of the starting technetium complex. After a few minutes the solution became light yellow and heating was turned off after 30 min. Yellow crystals of the final compounds were obtained by slow evaporation of the solvent in air, then washed with EtOH, and dried with Et_2O. They are air stable and yield ≥90%. These compounds were also obtained with the same procedure starting from [$AsPh_4$][$TcNCl_4$] and in the presence of PPh_3 in order to reduce the core $[Tc{\equiv}N]^{3+}$ to $[Tc{\equiv}N]^{2+}$.

The formulation of the complexes was supported by elemental analysis[9], IR spectra[10] and X-ray analysis for complex **1**. Their IR spectra showed the Tc≡N absorption in the range 1060–1090 cm^{-1} comparable with those reported for other technetium nitrido complexes,[1c,11] and the stretching observed at 1728 and 1734 cm^{-1} for the complexes **1** and **2**, respectively, denote that the carboxylic group is not coordinated to the metal.[4b] Magnetic susceptibility measurements reveal that they are diamagnetic. All these data suggest a square pyramidal geometry for all the complexes with the Tc≡N group in apical position.

ORTEP[12] view of the molecule is shown in Figure 1 .[13] The complex presents a distorted square pyramidal geometry where the Tc atom is displaced from the mean plane defined by Cl, P, S, and N(2) toward the N(1) atom by 0.594(1) Å. The Tc–N(1) distance of 1.605(3) Å is indicative of a strong triple bond and is typical of all nitrido compounds of technetium(V).[13] All other

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(8) ^{99}Tc is a weak β^- emitter (0.292 keV, $t_{1/2} = 2.12 \times 10^5$ y) and all manipulations were carried out in a laboratory approved for low-level radioactivity. Normal radiation safety procedures must be used at all times to prevent contamination.

(9) Anal. Calcd for $C_{23}ClH_{25}N_2O_2PSTc$ (**1**): C, 49.4; H, 4.5; N, 5.0; S, 5.7. Found: C, 49,5; H, 4.5; N, 4.9; S, 5.6. Calcd for $C_{21}ClH_{21}N_2O_2PSTc$ (**2**): C, 47.5; H, 4.0; N, 5.3; S, 6.0. Found: C, 47.3; H, 4.1; N, 5.2; S, 5.8. Calcd for $C_4H_{12}N_3S_2Tc$ (**3**): C, 18.1; H, 4.6; N, 15.8; S, 24.1. Found: C, 18.0; H, 4.6; N, 15.7; S, 23.8.

(10) IR data for (**1**): ν(Tc≡N) 1080, ν(PPh_3) 1097, ν(CO) 1728, ν(NH) 3242, 3285; (**2**): ν(Tc≡N) 1076, ν(PPh_3) 1097, ν(CO) 1734, ν(NH) 3241, 3287; (**3**): ν(Tc≡N) 1064, ν(NH) 3082–3217.

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(13) Crystal data: $a = 9.785(1)$ Å, $b = 10.123(1)$ Å, $c = 12.897(2)$ Å, $\beta = 108.73(1)°$, $V = 1209.8(3)$ Å^3, space group $P2_1$, $Z = 2$, $D_{calc} = 1.532$ g·cm^{-3}, (Mo Kα) = 0.710 69 Å, $T = 25$ °C. Of the 3691 unique measured reflections, 3383 with $I \geq 3\sigma(I)$ were used in the refinement. R(on F) = 0.024 and $R_w = 0.031$.

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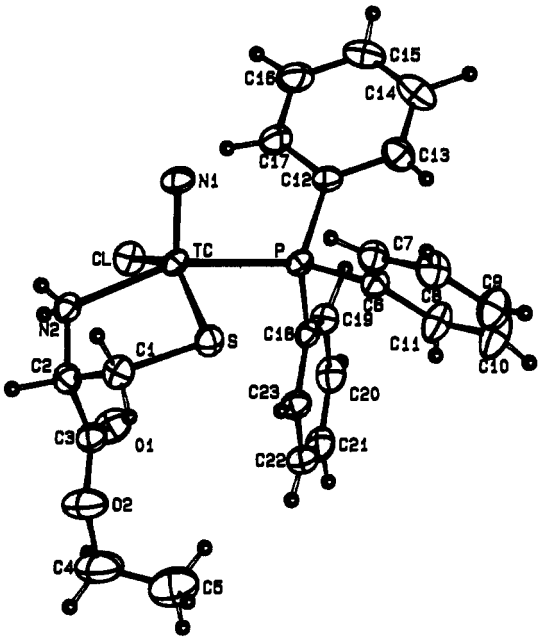

Figure 1. ORTEP drawing (30% probability thermal ellipsoids). Selected bond lengths (Å) and angles (deg) are as follows: Tc–Cl = 2.430(1), Tc–S = 2.327(1), Tc–P = 2.429(1), Tc–N(1) = 1.605(3), Tc–N(2) = 2.176(3); Cl–Tc–S = 144.19(3), Cl–Tc–P = 90.78(3), Cl–Tc–N(2) = 82.4(1); S–Tc–P = 90.09(3), S–Tc–N(2) = 82.6(1), P–Tc–N(2) = 156.1(1).

Tc–X distances are in perfect agreement with those found in this class of compounds.

The ligand assumes a conformation where the oxygen O(1), belonging to the ethyl ester chain, is located in approximately *trans* position to the Tc–N(1) bond at a van der Waals distance Tc---O(1) of 3.352(3) Å, and forming an angle N≡Tc---O(1) of 160.9(3)°.

Since the molecule is chiral in a noncentrosymmetric space group two independent refinements of the two enantiomers were carried out in order to determine the absolute configuration. Unfortunately, the agreement factors R did not show any significant difference in the two cases. Owing to the impossibility to determine the chirality of the molecule we have chosen to refine the enantiomer having the L-cysteine ethyl ester ligand in the same configuration as L-cysteine. The nitrido complexes of ^{99m}Tc were prepared as follows: after completion of the procedure for the preparation of the [^{99m}Tc≡N] intermediate species,[7] the pH of the solution was adjusted to 7.4 using HCO_3^-/CO_3^{2-} buffer (0.5 M), an aqueous solution of the ligand (10 mg mL^{-1}) was added to the vial, and the temperature was raised to 70 °C for 15 min. The chromatographic analysis revealed the formation of products which were different if compared to those obtained at the ^{99}Tc level.

Scintigraphic studies in rats demonstrated a high renal uptake with gradually increasing activity in the urinary bladder. A detailed discussion on the synthesis and characterization of ^{99m}Tc≡N–amino acid complexes and biodistribution studies will be reported elsewhere.

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Supplementary Material Available: Text giving crystal data and details of refinement, tables giving atomic positional parameters, anisotropic thermal parameters, and bond distances and angles, and a figure showing the unit cell and its contents (9 pages). Ordering information is given on any current masthead page.