

SYNTHESIS AND X-RAY STRUCTURE DETERMINATION OF
N,N'-BIS-L-(1-CARBOXY-2-MERCAPTOETHYL)ETHYLENEDIAMINE,
OXOTECHNETIUM (V), [TcO(EC)].

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SUMMARY

The complex of N,N'-bis-l-(carboxy-2-mercaptoethyl)ethylene-diamine (EC) labelled with reduced Tc-99m was proposed as a new agent in renal tubular secretion studies. Here we present the synthesis and single-crystal X-ray structure determination of the N,N'-bis-l-(1-carboxy-2-mercaptoethyl)ethylene-diamine oxotechnetium(V) complex, [^{99m}TcO(EC)]. Crystals are orthorhombic, space group P2₁2₁2₁, with a=19.570(1), b=10.080(1), c=6.300(1)Å, Z=4 and R=0.0294. The technetium is hexacoordinated being bonded to oxygen (1.657(3)Å), the two N atoms and the two deprotonated S atoms. The sixth site, trans to the oxo-group is occupied by one deprotonated carboxylate group. The infrared spectra is also presented.

Keywords: Renal, Technetium, [TcOEC], X-Ray, EC.

INTRODUCTION

The coordination chemistry of technetium has been intensively investigated recently and a variety of complexes have been synthesized and characterized.

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Considerable work was focused in studying the chemistry of oxotechnetium(V) complexes with ligands containing nitrogen and sulfur donor atoms, due to their extensive use nowadays as radiopharmaceuticals in diagnostic Nuclear Medicine.

An important group of technetium diagnostic agents containing the TcO_3^+ core is complexes designed to mimic the tubular secretion of radioiodinated Hippuran.

The design of a novel class of tetradentate bisamide bithiol ligands led to the development of ^{99m}Tc -N,N'-bis-(mercapto-acetyl)ethylene diamine ^{99m}Tc -DADS, which in animals is characterized by active tubular secretion(1-3). Modification of ligand structure by carboxyl group substitution generated the technetium complex ^{99m}Tc -CO₂-DADS which exhibited, in biological species, more favorable renal characteristics (4-7). Further research work on new ligand systems resulted in the development of a triamide NaS technetium complex, ^{99m}Tc -MAGa (mercapto-acetyl triglycine), applied in renal function studies as a potential replacement of Hippuran (8-12).

Recent work on a diamine dithiol technetium complex ^{99m}Tc -EC, where EC is N,N'-bis-1-(1-carboxy-2-mercaptoethyl)ethylene diamine, (13) demonstrated a similar distribution pattern to ^{99m}Tc -MAGa and was proposed as an alternative agent in renal studies.

This paper addresses the structure determination of oxotechnetium(V)-EC complex, synthesized at technetium carrier level.

$[^{99}TcO(EC)]$ complex was prepared by ligand exchange reaction of $^{99}Tc(V)$ -gluconate precursor with the N,N'-bis-L-(1-carboxy-2-mercapto)ethylenediamine.

The complex was also synthesized at tracer level (^{99m}Tc) in order to relate the species formed at tracer level with the complex formed at carrier level. Synthesis of the ^{99m}Tc -complex was accomplished by using either a ligand exchange or

a direct method similar to those reported previously (19), (13).

EXPERIMENTAL

Materials and equipment

All laboratory chemicals were of reagent grade. Solvents for HPLC were HPLC grade and were degassed before use.

L-thiazolidine-4-carboxylic acid was commercially available and was used without further purification. The dimerization reaction proceeded in liquid ammonia and sodium metal, as previously described (14).

^{99}Tc was purchased as ammonium pertechnetate from Oak Ridge National Laboratory. The impure black solid was purified prior to its use by treatment overnight with oxygen peroxide and ammonium hydroxide in methanol. Evaporation of the solvent gave a white powder.

IR spectra were obtained from KBr pellets using a Perkin-Elmer 1600 FT-IR spectrophotometer. Elemental analysis was performed on a Perkin-Elmer 2400 CHNS/O automatic analyser. High performance liquid chromatography (HPLC) was performed on a Waters chromatograph equipped with the 600E solvent delivery system, the 991 photodiode array spectrophotometric detector (PDA) and a μ Bodapack C-18 RP column, fitted with a gradient profile of 100% phosphate buffer pH 2.5 (0.0125M) reaching 91% phosphate buffer: 9% ethanol after 10 minutes. UV-Vis spectra of the eluting complexes were recorded on the photodiode array detector. A Beckman 171 Radioisotope detector was also used.

X-Ray Diffraction Studies

Collection and reduction of intensity data

The complete crystal and intensity collection data are reported in Table 1. Space group $P2_12_12_1$ was recognised from preliminary oscillation and Weissenberg photographs. Unit cell

Table 1. Summary of Crystal and Intensity Collection Data.

| | |
|---|--|
| Formula | $C_8H_{13}N_2O_6S_2Te$ |
| fw | 379.33 |
| a (Å) | 19.570(1) |
| b (Å) | 10.080(1) |
| c (Å) | 6.300(1) |
| V (Å ³) | 1242.76 |
| Z | 4 |
| D _{calc} (Mg m ⁻³) | 2.027 |
| D _{meas} (Mg m ⁻³) | 3.00 |
| Space group | P2 ₁ 2 ₁ 2 ₁ |
| Cryst. dimens (mm) | 0.15 X 0.24 X 0.38 |
| Radiation | Mo/K α 0.71073 |
| μ (cm ⁻¹) | 3.82 |
| Max. Abs. correction factor | 1.32 |
| Scan speed (deg/min) | 6.0 |
| Scan range (deg) | 2.5 + ω 12 separation |
| 2 θ limit (deg) | 50 |
| Data collected | 2938 |
| Data unique | 2175 |
| Data used | 2061 |
| F _o > | 5 σ (F _o) |
| R _{int} | 0.0391 |
| Range of h | -23 to 23 |
| Range of k | 0 to 11 |
| Range of l | -7 to 0 |
| Weighting scheme | 1/w= σ^2 (F _o)+0.00050F _o ² |
| F(000) | 760 |
| No of refined params | 215 |
| Δ / σ _{max} | 0.051 |
| ($\Delta\rho$) _{max} (eÅ ⁻³) | 1.236 |
| ($\Delta\rho$) _{min} (eÅ ⁻³) | -0.973 |
| GOF(1) | 2.47 |
| R(2)/R _w ² (observed) | 0.0294 / 0.0370 |
| R(2)/R _w ² (all data) | 0.0324 / 0.0395 |

$$(1) \text{ GOF} = [\sum w(|F_o| - |F_c|)^2 / (N - P)]^{1/2}$$

P = No of parameters, N = No of observed reflections.

$$(2) R = \sum (|F_o| - |F_c|) / \sum |F_o|$$

$$(3) R_w = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$$

parameters were derived from a least-squares refinement of the setting angles of 28 automatically centered intermediate 2 θ reflections on Syntex P2₁ diffractometer controlled by the Crystal Logic software. The intensities of three standards monitored after 100 reflections were stable, with a scatter of less than 3% from their respective means. Lorentz polarization and ψ -scan absorption corrections were applied.

Solution and refinement of the structure

The structure was solved by SHELXS86 (15) refined with SHELX76 (16) using the full-matrix least-squares method. H-atoms were

located from difference Fourier map and were refined isotropically. Atomic scattering factors were taken from International Tables for X-Ray Crystallography (17). The alternative model with all coordinates changed in sign refined to $R=0.0316$ and $R_w=0.0413$.

Synthesis

N,N'-bis-1-(1-carboxy-2-mercaptoethyl)ethylenediamine, EC.

Synthesis of EC was performed in a manner similar to that previously described (14). L-thiazolidine-4-carboxylic acid was reduced in liquid ammonia with sodium metal. After reaction, ammonia was evaporated to dryness and the remaining solid was dissolved in water. The pH was adjusted to 2 with conc. HCl to give crude EC compound. The solid was purified by dissolution at pH 9 and reprecipitation at pH 2.0-2.5. Yield 44 %. m.p. 251-252 °C dec; Lit. 251-253 °C. IR. cm^{-1} : 3100-2200 $\nu(\text{NH}_2^+)$, 1590 $\nu(\text{COO}^-)$, 1550 sh $\delta(\text{NH}_2^+)$.

$^{99\text{Tc}}(\text{V})$ -gluconate.

Synthesis of Tc(V)-gluconate was based on the method reported previously (18). Thus, to a solution of 200 mg of sodium gluconate in 4 ml water, 36.2 mg (0.2 mmol) $\text{NH}_4^{99\text{Tc}}\text{O}_4$ and 0.1 ml $^{99\text{Tc}}\text{O}_4^-$ generator eluate (1-2 mCi) were added as a tracer. After dissolution, 45 mg of SnCl_2 diluted in 1.5 ml of HCl 1N were added dropwise. Reduction of pertechnetate was controlled by ITLC SG, using methylethylketone or saline as solvent systems. After the reaction was completed, the pH of the resultant red-brown Tc(V)-gluconate solution was adjusted to 11.5 with NaOH 1N.

$[^{99\text{Tc}}\text{O}(\text{EC})]$

An aqueous alkaline solution of 65mg(0.25mmol) EC, was added under stirring to the Tc(V)-gluconate solution prepared as

described above. The resultant brown-green solution was stirred for 2 more hours at room temperature and the pH was then adjusted to 2.5 with HCl 1N. During the pH adjustment the solution colour turned green. After this solution was allowed to stand at room temperature for several days, dark green crystals were isolated. Single crystals of the complex suitable for X-ray crystallography were obtained by recrystallization from water. The recrystallization was accomplished by dissolution of the product in a large volume of water followed by acidification at pH 2.5 and slow evaporation of the resultant solution. Yield 70%. Elemental analysis: Anal. Calc. for $\text{CaH}_{12}\text{N}_2\text{S}_2\text{O}_6\text{Tc}$: C, 25.26; H, 3.43; N, 7.37; S, 16.26. Found: C, 25.31; H, 3.55; N, 7.35; S, 16.05. IR. cm^{-1} (KBr): 952 $\nu(\text{Tc}=\text{O})$, 1568 $\delta(\text{NH}^+)$ and $\nu(\text{C}=\text{O})$ coordinated, 1708 $\nu(\text{C}=\text{O})$ free acid, 3171 $\nu(\text{NH}^+)$. Samples of the crystals were analyzed by HPLC as previously described (19), using a gradient phosphate pH 2.5, ethanol solvent system and a single peak was detected at 14.2 min.

Labelling of EC with $^{99\text{m}}\text{Tc}$

A. Exchange labelling:

$^{99\text{m}}\text{Tc}$ -gluconate precursor was prepared using the method for the $^{99\text{Tc}}$ analog scaled down as follows: 200 mg sodium gluconate was dissolved in 3-5 ml $^{99\text{m}}\text{TcO}_4^-$ generator eluate (5-10mCi) and a stannous chloride solution (0.2 mg SnCl_2 in HCl 0.05N) was added dropwise to the reaction mixture until all pertechnetate was reduced (checked by ITLC). The pH of the resultant solution was adjusted to 11.5.

$^{99\text{m}}\text{Tc}$ -EC complex was formed by the addition of 0.5 ml alkaline solution of EC (1mg/ml) to 1ml $^{99\text{m}}\text{Tc}$ -gluconate solution prepared as described above. The mixture was vortexed for 1 min and after a 15 min incubation period at room temperature, the pH of the solution was adjusted to 7.5 with H_3PO_4 0.05N.

b. Direct labelling:

Direct labelling of EC was performed by a method similar to that reported previously (13). To a solution of the ligand (1 mg) were added successively 200 μg of SnCl_2 in 0.05N HCl (50 μl) and 0.5 ml $^{99\text{m}}\text{TcO}_4^-$ generator eluate (1-2 mCi). After a 20 min incubation period the pH was adjusted to 7.5 with H_3PO_4 0.05N.

The formation of $^{99\text{m}}\text{Tc}$ -complex was determined by HPLC using the same conditions as for analysing the analog ^{99}Tc -complex. A single peak was detected in both exchange and direct labelling preparations eluted at 14.2 min.

RESULTS AND DISCUSSION

$\text{TcO}(\text{N,N}'\text{-bis-1-(1-carboxy-2-mercaptoethyl)ethylenediamine}$, $[\text{TcO}(\text{EC})]$, was synthesized by ligand exchange reaction from the Tc(V) -gluconate precursor in aqueous alkaline solution at room temperature. The complex is isolated as dark-green crystals in acidic pH (<2.5) by the addition of aqueous HCl to the reaction solution. The complex was soluble only in alkaline solution or a large volume of water.

Figure 1 illustrates the model of the molecule. Selected bond distances and angles are summarized in Table 2. Technetium is hexacoordinated. The octahedral geometry is distorted with the Tc atom displaced from the SSNN coordination plane by 0.48Å toward the oxo oxygen atom O1. Tc(V) chemistry is dominated by the oxo group. In most of its complexes it imposes a square-pyramidal coordination geometry with the oxo ligand occupying the axial position. There are several complexes in which a suitable ligand (O,Cl) can occupy the sixth position trans to the oxo group. In such cases the strong trans-effect of the oxo group causes the sixth bond to be longer than usual (2.3Å vs 2.0Å for typical single Tc-O bond in cis position to the

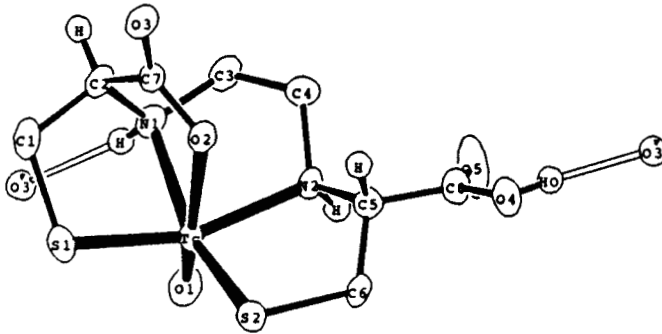


Fig.1. ORTEP drawing of $[TcO(EC)]$ complex showing the atom numbering.

oxo group (20) and 2.5Å vs 2.4Å for a typical Tc-Cl bond (21)). This is also observed in the present complex. There is the short Tc=O1 bond, 1.657(3)Å, and a longer than usual Tc-O2 bond trans to O1 at 2.287(3)Å. The coordination in the present complex is very similar to that of the D-penicillaminato complex (22) with two large differences in the N1-Tc-N2 and S1-Tc-S2 angles.

In the present complex N1-Tc-N2 is small (83.3(1) vs 93.7(1) in the penicillaminato complex) because it is part of the 5-member ring Tc-N1-C3-C4-N2, which allows the angle trans to it to open up 95.5(1) vs 90.55(6). The coordination of O2 is at variance with previous predictions of the structure of the EC complex with technetium (13,19,23) and such variance between prediction and structural determination was also observed for the D-penicillaminato complex (22,24). The most important feature of the packing is that each molecule is involved in four H-bonds and this generates a three-dimensional network. Only two of these H-bonds are independent however, the very strong O4...O3 at 2.590(4)Å and O4-HO4...O3 188(5) and the N1...O3 at 3.060(4)Å and N1-HN1...O3 188(4).

Table 2. Bond distances (Å) and angles (degrees)

| | | | | | | | |
|------|-------|----------|----------|-------|----------|-------|----------|
| Tc | -S(1) | 2.307(1) | O(5) | -C(8) | 1.195(5) | | |
| Tc | -S(2) | 2.286(1) | C(1) | -C(2) | 1.514(6) | | |
| Tc | -O(1) | 1.657(3) | C(2) | -N(1) | 1.477(5) | | |
| Tc | -O(2) | 2.287(3) | C(2) | -C(7) | 1.526(5) | | |
| Tc | -N(1) | 2.131(3) | N(1) | -C(3) | 1.504(5) | | |
| Tc | -N(2) | 2.143(3) | C(3) | -C(4) | 1.506(6) | | |
| S(1) | -C(1) | 1.838(5) | C(4) | -N(2) | 1.510(5) | | |
| S(2) | -C(6) | 1.843(4) | N(2) | -C(5) | 1.489(5) | | |
| O(2) | -C(7) | 1.266(4) | C(5) | -C(6) | 1.512(6) | | |
| O(3) | -C(7) | 1.239(5) | C(5) | -C(8) | 1.538(5) | | |
| O(4) | -C(8) | 1.297(5) | | | | | |
| S(1) | -Tc | -S(2) | 95.5(1) | C(1) | -C(2) | -C(7) | 108.3(3) |
| S(1) | -Tc | -O(1) | 105.2(1) | N(1) | -C(2) | -C(7) | 105.7(3) |
| S(2) | -Tc | -O(1) | 109.2(1) | Tc | -N(1) | -C(2) | 106.9(2) |
| S(1) | -Tc | -O(2) | 80.4(1) | Tc | -N(1) | -C(3) | 108.9(2) |
| S(2) | -Tc | -O(2) | 83.6(1) | C(2) | -N(1) | -C(3) | 117.3(3) |
| O(1) | -Tc | -O(2) | 165.1(1) | N(1) | -C(3) | -C(4) | 114.3(3) |
| S(1) | -Tc | -N(1) | 84.9(1) | C(3) | -C(4) | -N(2) | 110.7(4) |
| S(2) | -Tc | -N(1) | 154.1(1) | Tc | -N(2) | -C(4) | 109.5(2) |
| O(1) | -Tc | -N(1) | 95.6(1) | Tc | -N(2) | -C(5) | 114.3(2) |
| O(2) | -Tc | -N(1) | 70.8(1) | C(4) | -N(2) | -C(5) | 113.3(3) |
| S(1) | -Tc | -N(2) | 154.5(1) | N(2) | -C(5) | -C(6) | 110.4(3) |
| S(2) | -Tc | -N(2) | 85.6(1) | N(2) | -C(5) | -C(8) | 110.6(3) |
| O(1) | -Tc | -N(2) | 98.3(1) | C(6) | -C(5) | -C(8) | 110.3(3) |
| O(2) | -Tc | -N(2) | 74.4(1) | S(2) | -C(6) | -C(5) | 111.4(3) |
| N(1) | -Tc | -N(2) | 83.3(1) | O(2) | -C(7) | -O(3) | 125.2(3) |
| Tc | -S(1) | -C(1) | 98.3(1) | O(2) | -C(7) | -C(2) | 114.4(3) |
| Tc | -S(2) | -C(6) | 99.4(1) | O(3) | -C(7) | -C(2) | 120.4(3) |
| Tc | -O(2) | -C(7) | 114.3(2) | O(4) | -C(8) | -O(5) | 125.8(4) |
| S(1) | -C(1) | -C(2) | 111.5(3) | O(4) | -C(8) | -C(5) | 111.2(3) |
| C(1) | -C(2) | -N(1) | 108.2(3) | O(5) | -C(8) | -C(5) | 123.0(4) |

The IR spectrum of the complex is given at Fig.2. The Tc=O stretching vibration gives rise to an intense single band at 952 cm^{-1} . The absorption at 3171 cm^{-1} is assigned to the N-H stretching vibration while a broad band observed at 1568 cm^{-1} results from the N-H deformation. Although two types of C=O stretches are expected for the complex, only one band at 1708 cm^{-1} is observed which is assigned to the free acid carbonyl group. Crystallography data have shown that the carbonyl bond C(7)-O(3) of the coordinated carboxylate group is longer than the carbonyl bond C(8)-O(5) of the free acid group (1.239 vs 1.195Å). Therefore the C(7)-O(3) carbonyl stretching vibration is expected to occur at a lower frequency. This vibration is likely to overlap with N-H deformation giving rise to the

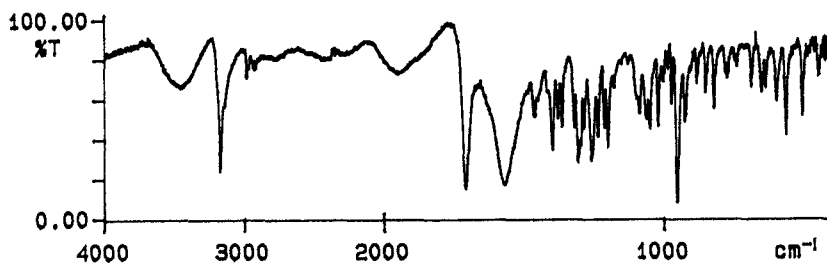


Fig. 2. FT-IR spectra of $[TcO(EC)]$ obtained in KBr pellet.

very broad band observed at 1568 cm^{-1} . Elemental analysis was performed for C.H.N.S and was in agreement with the calculated values.

Although synthesis is performed in alkaline pH, $[TcO(EC)]$ complex precipitates from acid solutions with pH values lower than 2.5. Crystallographic analysis demonstrated that in this pH range, the complex is neutral with amine nitrogens, sulfurs and one deprotonated carboxylate coordinated around the TcO^{3+} core. The second carboxylate group does not participate in the chelation and remains as a free acid.

The water solubility of the complex increases significantly at higher pH values, due to deprotonation of the free acid group. Anion-exchange and cation-exchange HPLC studies performed for the very similar $[TcO(pen)_2]$ complex (pen: D-penicillaminato) have shown that this complex is uncharged at pH 1.5 and below, and anionic at pH 3.0 and above (25).

The UV-Vis spectrum of the complex in phosphate buffer pH 2.5 exhibits absorption maxima at 216, 251(sh), 320 and 407 nm. The spectrum is pH dependent, due to deprotonation of the complex occurring at certain pH values. A two-step deprotonation process was proposed for the complex (28). The first step of deprotonation is assigned to the free acid group (occurring at pH 4-5) and the second one to one of the coordinated nitrogens (occurring at pH 8-9). It is possible that the amine nitrogen

deprotonation is accompanied by breaking of the carboxylate-metal bond trans to the oxo group.

Reverse phase HPLC was employed in order to relate the $[^{99}\text{TcO}(\text{EC})]$ complex with the $^{99\text{m}}\text{Tc}$ -species obtained by either exchange or direct labelling of EC. When a pure sample of $[^{99}\text{TcO}(\text{EC})]$ and a $^{99\text{m}}\text{Tc}$ -preparation coinjected into the HPLC both spectrophotometric detector (that monitors ^{99}Tc -complex) and radiometric detector (that monitors $^{99\text{m}}\text{Tc}$ -complex) produce the same chromatographic profile. This suggests that the technetium complexes formed in all cases have the same chemical structure.

In conclusion $[\text{TcO}(\text{EC})]$ complex has been recently proposed as an alternative derivative in renal tubular secretion studies. The structure of this newly developed complex was not identified and it was proposed that TcO^{3+} is coordinated to the NNS donor set. In our study $[\text{TcO}(\text{EC})]$ complex has been synthesized at carrier level by exchange labelling reaction with Tc(V) -gluconate. Crystals were grown after acidification of an aqueous solution of the complex at pH 2.5. Crystallography demonstrated that technetium in EC complex is hexacoordinated, being bonded to oxygen ($\text{Tc}=\text{O}$), two nitrogens, two deprotonated sulfur atoms, and one deprotonated carboxylate group at the sixth position trans to the oxo group.

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Supporting Data Available for $[^{99}\text{TcO}(\text{EC})]$: Tables of positional and equivalent thermal parameters and anisotropic thermal parameters of the non-hydrogen atoms, table of positional and isotropic thermal parameters for the hydrogen atoms (3 pages), and UV-Vis spectrum in phosphate buffer pH 2.5.

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