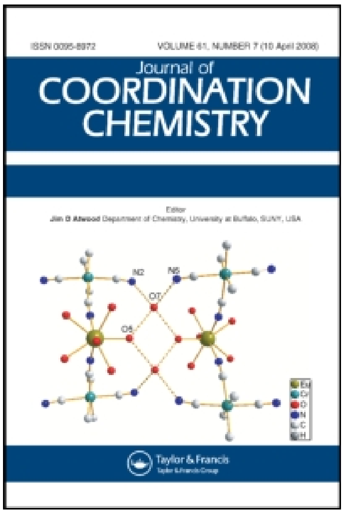

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Synthesis of Neutral and Cationic Technetium(V) Complexes of Heterocyclic-*N,O* Ligands

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NOTE

SYNTHESIS OF NEUTRAL AND CATIONIC TECHNETIUM(V) COMPLEXES OF HETEROCYCLIC-*N,O* LIGANDS

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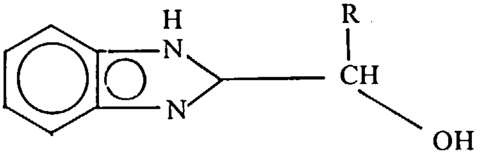
INTRODUCTION

The basic coordination chemistry of technetium has developed rapidly during the past three decades due to the widespread use of complexes of the metastable nuclide ^{99m}Tc in diagnostic nuclear medicine.[1-4] The development of new technetium radiopharmaceuticals is strongly dependent on the further exploration of the basic inorganic chemistry of this element.

The oxidation state of technetium seems to play, together with the ligands coordinated round it and the total charge of the resulting complex, a deciding role in determining the biological pathway of the compound when injected into the blood pool.[3,5] Of particular importance are coordination compounds of technetium of which the lipophilic and polar properties can easily be varied by simple substitutions in the molecular framework of the ligands to optimize the biodistribution of the potential radiopharmaceutical preparations. It was found that cationic technetium complexes apparently accumulate in the myocardial tissue,[6,7] while neutral complexes have found application as brain imaging agents.[8]

As part of our investigations of complexes of technetium with potential application as diagnostic imaging agents, we now report the preparation and characterization of stable monocationic and neutral complexes of this metal with two benzimidazolylalcoholate(I) ligands.



R = H: Hbgo
R = CH_3: Hblo

These ligands coordinate as bidentates, with single deprotonation of the −OH group, *via* O and N donors.[9]

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EXPERIMENTAL

Ammonium pertechnetate ($NH_4{}^{99}TcO_4$) was obtained from the Oakridge National Laboratories, Tennessee, and (n-Bu_4N)[$TcOCl_4$] was prepared as reported.[10] The ligands were synthesized according to literature procedures.[11] All the solvents used were purified and dried by standard methods. Scientific instrumentation used in this study is the same as reported elsewhere.[12]

Preparation of Complexes

[TcO(blo)$_2$]PF$_6$·2H$_2$O

1 Cm^3 of a 0.34 mol dm^{-3} aqueous NH_4TcO_4 solution was added to a stirred solution of 224 mg (1380 μmol) of the ligand Hblo in 5 cm^3 methanol. The addition of 150 mg $Na_2S_2O_4$ in 5 cm^3 aqueous 0.6 mol dm^{-3} NaOH solution changed the colour of the reaction solution to green. After stirring for 1 h at room temperature, the solution was filtered, and 2 cm^3 of a saturated aqueous NH_4PF_6 solution were added. Partial evaporation of the solution led to the precipitation of a green microcrystalline solid, which was filtered and washed with water, ethanol, and diethyl ether. It was dried *in vacuo* at room temperature. The yield of [TcO(blo)$_2$]PF_6·2H_2O was 137 mg (65% based on Tc). *Anal.* Calcd. for $C_{18}H_{22}F_6N_4O_5PTc$: C, 34.96; H, 3.59; N, 9.06%. Found: C, 34.78; H, 3.69; N, 8.77%. UV-vis (CH_3CN, nm, (ε/dm^3 mol^{-1} cm^{-1})): 618(260), 348(4500), 268(18700). Conductivity (10^{-3} mol dm^{-3}, CH_3CN) = 121 ohm^{-1} cm^2 mol^{-1}.

[TcO(bgo)$_2$]PF$_6$·2H$_2$O

1 Cm^3 of a 0.34 mol dm^{-3} aqueous NH_4TcO_4 solution was added to a stirred solution of 204 mg (1380 μmol) of the ligand Hbgo in 5 cm^3 methanol. The addition of 150 mg $Na_2S_2O_4$ in 5 cm^3 aqueous 0.6 mol dm^{-3} NaOH solution changed the colour of the solution to orange. After stirring for 1 h at room temperature, the solution was filtered, and 2 cm^3 of a saturated aqueous NH_4PF_6 solution were added. After standing overnight a green microcrystalline precipitate formed, and was filtered and washed with methanol (3 x 2 cm^3). The product was dried *in vacuo*, and the yield of [TcO(bgo)$_2$]PF_6·2H_2O was 123 mg (60% based on Tc). *Anal.* Calcd. for $C_{16}H_{18}F_6N_4O_5PTc$: C, 32.55; H, 3.07; N, 9.49%. Found: C, 32.39; H, 3.44; N, 9.69%. UV-vis (CH_3CN, nm, (ε dm^3 mol^{-1} cm^{-1})): 612(170), 344(4300), 274(16400). Conductivity (10^{-3} mol dm^{-3}, CH_3CN) = 128 ohm^{-1} cm^2 mol^{-1}.

TcO(blo)$_2$Cl

65 Mg (400 μmol) of the ligand Hblo in 10 cm^3 acetonitrile were added to 100 mg of (n-Bu_4N) [$TcOCl_4$] in 10 cm^3 acetonitrile, and the mixture was heated under reflux conditions for 1 h. After cooling the reaction mixture to room temperature the volume was reduced *in vacuo* to give a green precipitate. The product was filtered and washed with ethanol and diethyl ether, and dried *in vacuo*. The yield was 72%. *Anal.* Calcd. for $C_{18}H_{18}ClN_4O_3Tc$: C, 45.72; H, 3.84; N, 11.85; Cl, 7.50%. Found: C, 45.71; H, 3.48; N, 11.84; Cl, 7.02%. UV-vis (CH_3CN, nm, (ε dm^3 mol^{-1} cm^{-1})): 551(280), 350(3600), 299(6000), 269(14600). Conductivity (10^{-3} mol dm^{-3}, DMF): 8.1 ohm^{-1} cm^2 mol^{-1}

TcO(bgo)$_2$Cl

A solution of 60 mg (400 μmol) of the ligand Hbgo in 10 cm^3 in acetonitrile was added to 100 mg (200 μmol) of (n-Bu_4N) [$TcOCl_4$] in 10 cm^3 acetonitrile, and the mixture was heated under reflux conditions for 30 min. After cooling and reduction of the volume under vacuum the green product was filtered, washed with ethanol and diethyl ether, and dried *in vacuo*. The yield was 66%. *Anal.* Calcd. for $C_{16}H_{14}ClN_4O_3Tc$: C, 43.21; H, 3.17; N, 12.60; Cl, 7.97%. Found: C, 43.21; H, 3.12; N, 12.80; Cl, 8.20%. UV-vis (CH_3CN, nm, (ε $dm^3 mol^{-1} cm^{-1}$)): 548(180), 355(2300), 295(6200), 276(16800). Conductivity (10^{-3} mol dm^{-3}, DMF): 8.2 $ohm^{-1} cm^2 mol^{-1}$.

RESULTS AND DISCUSSION

Cationic Complexes

Complexes of technetium(V) with formula $[TcOL_2]PF_6{\cdot}2H_2O$ (L = blo, bgo) have been prepared by the reduction of pertechnetate by sodium dithionite in the presence of the ligands L. The complexes are soluble in polar organic solvents, and are 1:1 electrolytes in acetonitrile solution.

The infrared spectral data (Table I) for the complexes indicate the presence of the monooxotechnetium(V) core, with the Tc=O stretches observed around 950 cm^{-1}, which are in the range observed for monooxo square-pyramidal technetium(V) complexes (930–1020 cm^{-1}).[13] The Tc–N frequencies are similar to those observed in other technetium(V) complexes with nitrogen ligands,[14] and absorptions in the region 3100–3300 cm^{-1} are due to ν(N–H). The Tc–O stretching vibrations occur around 360 cm^{-1}.

TABLE I

Selected infrared spectral data for the complexes (cm^{-1})[a]

Complex	ν(Tc=O)	ν(Tc–N)	ν(Tc–O)	ν(Tc–Cl)
$[TcO(blo)_2]PF_6{\cdot}2H_2O$	949 vs	438 m	361 m	
$[TcO(bgo)_2]PF_6{\cdot}2H_2O$	952 vs	442 m	364 m	
$[TcOCl(blo)_2]$	943 vs	432 m	351 m	283 m
$[TcOCl(bgo)_2]$	945 vs	434 m	356 m	281 m

[a] As KBr discs.

The electronic spectra of both these complexes, recorded in acetonitrile, exhibit intense absorbances at *ca* 270 nm, with a shoulder trailing into the visible region (*ca* 345 nm) of the spectrum. The peak at about 270 nm is ascribed to the overlapping of an intraligand $\pi \rightarrow \pi^*$ transition with the oxo oxygen to technetium(V) charge transfer transition. The intensity of the peak around 345 nm suggests it to be due to a metal-to-ligand charge transfer, with the peak around 615 nm due to a d–d transition.

Spectroscopic data and elemental analysis confirm the $[TcOL_2]PF_6{\cdot}2H_2O$ formulation. The more probable configuration around the TcO^{3+} core provides the four coordinating sites on the plane perpendicular to Tc=O being occupied by trans-*N*,*O* arrangements of the two bidentate ligands. The sixth site *trans* to the Tc=O group may be occupied by a water molecule. A thermogravimetric analysis of the dihydrate $[TcO(blo)_2]PF_6{\cdot}2H_2O$ in a dynamic nitrogen atmosphere indicated a water loss of 5.99% from 80°C to 168°C (5.83% theoretically).

Neutral Complexes

The neutral complexes with the formulation $TcOClL_2$ (L = blo, bgo) have been prepared by the simple substitution of chloride in the $TcOCl_4^-$ anion by the ligands HL in refluxing acetonitrile. They are non-electrolytes in DMF solution, and are slightly soluble in acetone, chloroform and acetonitrile. They are indefinitely stable in the solid state.

The infrared spectra of the complexes indicate the presence of the monooxotechnetium(V) core with the Tc=O stretches observed around 944 cm^{-1} (Table I). There are no bands that could be ascribed to O–H vibrations, and peaks at about 3360 cm^{-1} indicate the presence of N–H groups in the ligands. The peaks around 430 cm^{-1} and 350 cm^{-1} are ascribed to the existence of the Tc–N and Tc–O stretches, respectively. The presence of the Tc=O group, coupled with the infrared data, indicates coordination of the ligands through the imidazole nitrogen and the alcoholate oxygen. Microanalytical data and the non-conductivity of these complexes infer a distorted octahedral geometry of the complex around technetium.

The electronic spectra of the $TcOClL_2$ complexes are of a complex nature, and quite a number of absorption bands appear in the 260–550 nm range. The peak around 295 nm is ascribed to an intraligand $\pi \rightarrow \pi^*$ transition, with the high energy peak around 270 nm due to oxo oxygen to technetium(V) charge transfer. The intensity of the peak around 350 nm suggests it to be due to a metal-to-ligand charge transfer, with the peak at longer wavelength around 550 nm due to a d–d transition with possible borrowing from the adjacent MLCT band.

The Tc=O stretching vibrations in the $TcOClL_2$ complexes are about 7 cm^{-1} lower than that of the $[TcOL_2]PF_6 \cdot 2H_2O$ compounds. The weaker Tc=O bonds in the neutral complexes can be explained by the presence of a coordinating atom in the site *trans* to the oxo oxygen, and the presence of a positive charge on the complexes $[TcOL_2^+]PF_6^-$. The nature of the coordinating atom *trans* to the oxo group in the complexes $TcOClL_2$ is not clear from our results. It has previously been found that phenolic oxygen coordinates in positions *trans* to the oxo oxygen in the complex $TcOCl(hbt)_2$ [hbt = 2-(2-hydroxyphenyl)benzothiazole].[16] However, due to the existence of only an alcoholate oxygen in the ligands, and due to the weak Tc–Cl bonding [v(Tc–Cl) at around 280 cm^{-1}], we assign the configuration of these six-coordinate complexes containing the chlorine atom *trans* to the Tc=O linkage and the four coordinating atoms (N_2O_2) of the two bidentate *N,O*-ligands bonded on the equatorial plane.

Efforts to prepare complexes of the type $TcOCl_2L$ from (n-Bu_4N) $[TcOCl_4]$ and the ligands HL in an equimolar stoicheiometric ratio in alcohol or acetonitrile proved unsuccessful, and no pure products with sensible analyses could be isolated.

The two *N,O*-ligands used in this study are examples of a series of benzimidazolylalcoholates that may contain different substituents on the ligand backbone. Substituents in the molecular structure of the ligands are possible on the protonated imidazole nitrogen, on the benzene ring, in the R group, and in the –OH group. A large number of stepwise varied ligands can thus be prepared, of which ^{99m}Tc complexes of the type $TcOL_2^+$ and $TcOClL_2$ should show a stepwise variation in their radiopharmaceutical properties.

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