Inorganica Chimica Acta, 179 (1991) 53–57

The synthesis and characterization of $[M(C_8H_5N_2N{=}NH)_3](BPh_4)$, where M = Tc or Re. Tris-diazene chelate complexes of technetium(I) and rhenium(I)

Terrence Nicholson, Ashfaq Mahmood, Gillian Morgan, Alun G. Jones
Department of Radiology, Harvard Medical School and Brigham and Women's Hospital, Boston, MA 02215 (U.S.A.)

and **Alan Davison**
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139 (U.S.A.)

(Received August 1, 1990)

Abstract

The reaction of ammonium pertechnetate or tetrabutylammonium perrhenate with the chelating organohydrazine hydralazine hydrochloride gives the Tc(I) (or Re(I)) cationic tris-chelate complex $[M(C_8H_5N_2N{=}NH)_3]^+$, which is isolated as the tetraphenylborate salt. These dark green complexes are freely soluble in ethanol but decompose in solution in the absence of excess ligand. The infrared spectra of these complexes show no peaks associated with $\nu(M{=}O)$, nor associated with $\nu(C{=}N)$ or $\nu(N{=}N)$, indicative of exclusively chelated organodiazene ligation. A weak absorption near 3250 cm^{-1} is associated with $\nu(N{-}H)$ from the organodiazene ligands. The FAB(+) mass spectra of the complexes show the free parent ions for both metals. For the technetium complex $M^+ = 573$ m/z and for the rhenium complex $M^+ = 661$ m/z. The technetium complex's mass spectrum also shows a peak of 417 m/z associated with a fragment from the loss of one of the three chelated diazene ligands. The ^{99}Tc NMR spectroscopy shows the technetium complexes resonance occurring in the established Tc(V) region, at ~1620 ppm. This downfield shift is attributed to a paramagnetic shielding effect. These complexes are electrochemically active, with each complex exhibiting a pair of reversible oxidations. One of the two observed processes is likely ligand based, since it occurs at very similar $E_{1/2}$ values for both the rhenium and technetium complexes.

Introduction

The coordination chemistry of technetium has received considerable attention in recent years; a result of its increased availability and widespread use in diagnostic nuclear medicine. The favorable nuclear properties of the metastable isotope ^{99m}Tc ($\gamma = 140$ keV, $t_{1/2} = 6$ h) allow images of high resolution to be obtained with low radiation dose to the patient. The chemistry of rhenium is also under increased scrutiny by virtue of its expanding role in therapeutic nuclear medicine.

The organohydrazine ligands are obvious candidates for examination of chemical and biological properties in technetium complexes as potential radiopharmaceutical agents in that they are easily functionalized. They can form a variety of derivatives of the same coordination complex with differing peripheral substituents, allowing the chemical properties and biodistributions to be manipulated by simply altering the ligand precursor employed. In addition, they frequently serve as reducing agents which are subsequently incorporated into the metal complex in an oxidized form. This property might facilitate radiopharmaceutical kit formulation by making the incorporation of a reducing agent unnecessary.

Background

Molybdenum chemistry, which has been shown to frequently mimic that of rhenium, shows extensive chemistry with the organohydrazine ligands. Sodium molybdate (Na_2MoO_4) was shown to react with thiobenzoylhydrazine ($PhC{=}SNHNH_2$) in dilute HCl to give the neutral, tris(thiobenzoyldiazene) molybdenum complex $[Mo(C_6H_5C(S)N{=}NH)_3]$ [1]. The complex displays three, five-membered chelate rings, formed through the coordination of the sulfur and α-nitrogen atoms of the bidentate diazene ligands. The X-ray crystallography showed a facial arrange-

0020-1693/91/$3.50

ment of N—H moieties, with overall distorted trigonal prismatic coordination geometry. The hydrazine ligands are each oxidized by two electrons, coordinating with localized nitrogen–nitrogen double bonds. The other bonds within the five-membered chelate rings of this complex remain nearly identical to those in the free ligand. The molybdenum has been reduced from Mo(VI) in the sodium molybdate precursor by six electrons to give the formally d^6 electronic configuration in the neutral tris-organodiazene complex.

We have now extended this chemistry to the Group VII transition metals rhenium and technetium. The reaction of ammonium pertechnetate or tetrabutylammonium perrhenate with the chelating organohydrazine hydralazine hydrochloride ($C_8H_5N_2NH-NH_2\cdot HCl$ (Aldrich Chemical Co., Milwaukee, WI) and sodium tetraphenylborate gives the cationic trisdiazene complexes $[M(C_8H_5N_2N{=}NH)_3](BPh_4)$.

Experimental

Caution: technetium-99 is a weak β-emitter ($E = 0.292$ MeV, $t_{1/2} = 2.12 \times 10^5$ years). All work has been done in laboratories approved for the use of low levels of radioactive materials. Precautions have been detailed elsewhere [2]. Ammonium pertechnetate was supplied as a gift by DuPont-Biomedical Products. Reagents and solvents were used as received unless otherwise stated.

Routine infrared spectra were obtained on a Mattson Cygnus 100 FTIR. ^{99}Tc NMR spectra were recorded on a Varian XL-300 FTNMR spectrometer and referenced to $[TcO_4]^-$. Fast atom bombardment spectra of samples dissolved in *p*-nitrobenzylalcohol matrix were recorded with a MAT 731 mass spectrometer equipped with a Ion Tech B11N FAB gun and operating at an accelerating voltage of 8 kV. The FAB gun produced a beam of 6–8 keV xenon neutrals. Electrochemical measurements were performed on N_2-purged dichloromethane solutions of the metal complexes with 0.1 M tetrabutylammonium perchlorate as supporting electrolyte. Experiments were conducted using a silver–silver chloride reference electrode, with platinum auxiliary and working electrodes. $E_{1/2}$ values were calculated from the average of the anodic and cathodic peak potentials. The potentiostat employed was a PAR model 174 polarographic analyzer and the cyclic voltamograms were plotted with a Hewlett Packard 7044A XY recorder.

Synthesis of complexes

$[Tc(C_8H_5N_2N{=}NH)_3](BPh_4)$ (1)

A 1 ml aqueous solution of $(NH_4)(TcO_4)$, 0.4 mmol, was evaporated to dryness on a rotary evaporator. To this was added 0.39 g hydralazine hydrochloride (2.0 mmol) and 0.14 g sodium tetraphenylborate (0.4 mmol) dissolved in a minimum amount of methanol. Additional methanol was added to bring the final volume to ~100 ml. The resulting light yellow solution was refluxed under air for 45 min, with the color changing gradually to a dark green–blue. The resulting solution was reduced in volume to ~30 ml, after which 150 ml of distilled water was added causing the dark green material to precipitate out of solution. The dark green product was isolated on a fritted funnel leaving behind a clear filtrate. The air stable product was dried under vacuum overnight. Yield: 55–65%*. FAB-MS(+): $m/z = 573$, $[M]^+$; 417, $[Tc(C_8H_5N_2NNH)_2]\cdot 2H^+$. ^{99}Tc NMR ($CDCl_3$, 22 °C): δ 1620 ppm.

$[Re(C_8H_5N_2N{=}NH)_3](BPh_4)$ (2)

A 0.11 g sample of $(n\text{-}Bu_4N)[ReO_4]$ was combined with 0.37 g of hydralazine hydrochloride and 0.14 g sodium tetraphenylborate, and refluxed in 100 ml of methanol for 1 h. The resulting blue–green solution was reduced in volume to ~30 ml under reduced pressure, and a large excess of distilled water was added causing the green material to precipitate quantitatively. The green material was isolated on a fritted funnel and dried under vacuum overnight. Yield: 60–70%*. FAB-MS(+): $m/z = 661$, $[M]^+$.

Results and discussion

The reaction of $(NH_4)(TcO_4)$ with the chelating organohydrazine hydralazine hydrochloride in dry ethanol gives the formally Tc(I) cationic tris-diazene complex $[Tc(C_8H_5N_2N{=}NH)_3]^+$, which is isolated as the tetraphenylborate salt. (See Fig. 1 for a representation of the proposed structure of this complex.) The complex is freely soluble in ethanol and can be precipitated with the addition of excess water. The reaction with ammonium pertechnetate proceeds in dry ethanol, with the deep green color associated with the complex developing rapidly with warming after addition of the hydralazine hydrochloride and sodium tetraphenylborate. The solubility of the complex and its stability are influenced by the choice of anion. The syntheses are very sensitive to the presence of water, so the aqueous ammonium

---

*Actual yields are estimated, based on the amount of impure product isolated as described in the preparations. The thin layer chromatographic traces which monitor for radioactivity using spiked preparations of the isotopes ^{99}Tc and ^{99m}Tc (pertechnetate) showed that as much as 75% of the $[TcO_4]^-$ is converted to $[Tc(C_8H_5N_2N{=}NH)_3(BPh_4)$ with extended reflux times in ethanol.

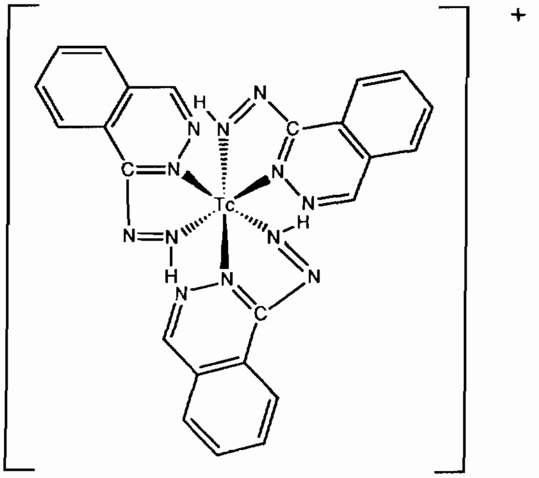

Fig. 1. Proposed structure of the tris-diazene complex $[Tc(C_8H_5N_2N{=}NH)_3]^+$ showing a facial arrangement of N—H moieties. (Actual coordination geometry is likely a distorted trigonal prism rather than octahedral as depicted here.)

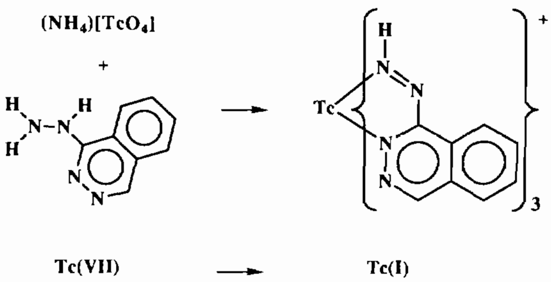

Fig. 2. Reaction scheme for the reduction of pertechnetate to the Tc(I) complex $[Tc(C_8H_5N_2N{=}NH)_3]^+$. Organodiazene ligands in their chelated form are formally neutral bidentate ligands, which coordinate through the available lone pair of electrons on the sp^2 hybridized α-nitrogen of the organodiazene moiety and, in the case of complexes 1 and 2, N_1 of the phthalazine substituent.

pertechnetate is evaporated to dryness with a rotary evaporator and then dissolved in dry ethanol.

The analogous reaction with sodium perrhenate is inhibited in ethanol by the precursor's limited solubility. However, the reaction with tetrabutylammonium perrhenate gives the deep green–blue Re(I) complex in refluxing methanol. The reaction with perrhenate requires a longer reflux time than the reaction with pertechnetate. This is to be expected since pertechnetate, a second row transition metal, is more easily reduced than the third row metal perrhenate. These reactions involve a six electron reduction of the Tc(VII) pertechnetate (or Re(VII) perrhenate) to the Tc(I) or Re(I) cations. This is accomplished by concurrently oxidizing each of the three organohydrazines by two electrons, which coordinate as diazene ligands with nitrogen–nitrogen double bonds (see Fig. 2). The complexes are stable in solution for extended periods of time in the presence of excess ligand; however, they decompose on silica or alumina as the free ligand is removed. This property has prevented recrystallization of the products for X-ray structural determinations and analytical determinations for the two complexes. Thin layer chromatographic traces which monitor for radioactivity in spiked preparations of the gamma emitting isotope ^{99m}Tc and ^{99}Tc reveal the presence of only one technetium species formed during the course of the reaction. This method of synthesis further confirmed that the characteristic green color of these reactions is associated with the technetium complex. Electronic spectroscopy revealed that the high wavelength absorbance maxima for the technetium species occur at 540 and 370 nm.

The fast atom bombardment mass spectrometry (positive mode) of the technetium cation in nitrobenzylalcohol shows the parent ion of 573 *m/z*. Also, a fragment corresponding to the loss of one of the diazene chelates occurs at 417 *m/z* as a doubly-protonated species. The FAB-MS(+) of the rhenium complex shows only the parent ion of 661 *m/z* with the characteristic isotope pattern expected for rhenium containing species.

The infrared spectra of these complexes are characteristic of complexes with the chelated form of this ligand in that the spectra do *not* show absorptions associated with ν(C=N) or ν(N=N). These absorptions would normally occur in the 1750 and 1600 cm^{-1} regions, respectively. This phenomenon has been previously reported for the structurally characterized rhenium hydralazine chelate complex $[ReCl_2(PPh_3)_2(C_8H_5N_4)]$ [3]. Similar to the molybdenum tris-thiobenzoyldiazene complex, the complexes with the hydralazine chelates show a weak absorption in the 3250–3260 cm^{-1} region associated with ν(N—H). The absence of absorptions in the 900–1000 cm^{-1} region confirms the displacement of all of the oxo groups from the pertechnetate and perrhenate precursors.

Nuclear magnetic resonance spectroscopy employing the ^{99}Tc nucleus has recently received considerable attention as a method of characterizing technetium complexes based on an established correlation between oxidation state and chemical shift [4]. The resonance observed for $[Tc(C_8H_5N_2N{=}NH)_3]^+$ occurs at 1620 ppm (linewidth = 2000 Hz) relative to $[TcO_4]^-$, which is well within the established Tc(V) region (see Fig. 3). This downfield shift of the technetium nuclear magnetic resonances for this species can be attributed to a paramagnetic shielding effect. The paramagnetic shielding term, represented by σ_p, is proportional to $-(\Delta E^{-1})$ so

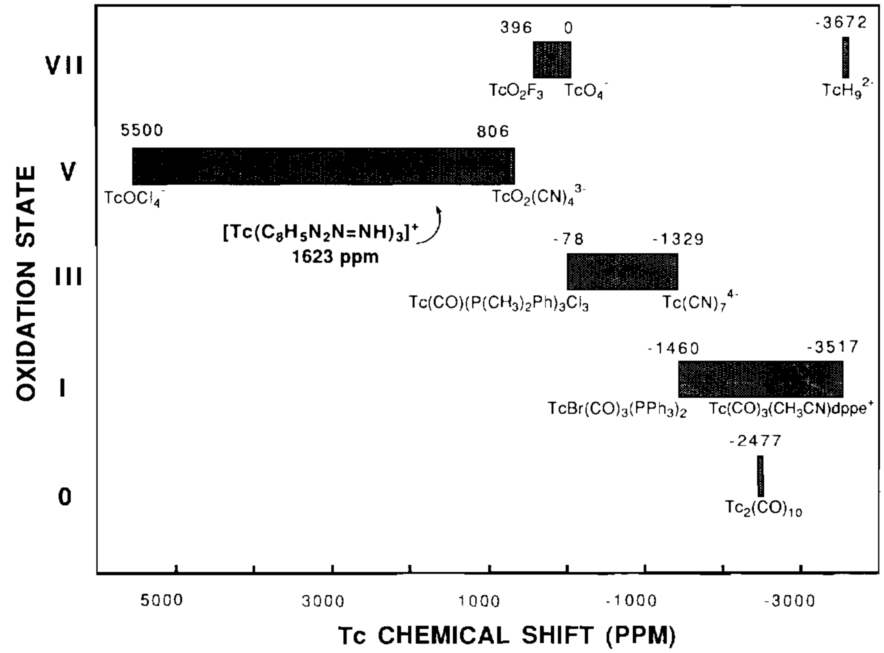

Fig. 3. Plot showing the correlation between formal oxidation state and ^{99}Tc NMR chemical shift. The resonance for the formally Tc(I) cationic complex $[Tc(C_8H_5N_2N{=}NH)_3]^+$ falls in the established Tc(V) region.

that weak field ligands such as nitrogen donors, will result in a deshielding of the technetium nucleus [5]. The formally technetium(I) aryldiazenido complexes $[TcCl_2(PPh_3)_2(NNHAr)(NNAr)]$ and $[TcCl_2(PPh_3)_2(NHNHAr)(NNAr)]Cl$ were shown to resonate in the established Tc(V) region. This observation was however attributed to the technetium having a higher effective oxidation state than the formal oxidation state would suggest [6].

The high lipophilicity of these complexes as the tetraphenylborate salts inhibited their migration in electrophoresis experiments. The cation shows only marginal stability in aqueous solutions as the more hydrophilic salts. The hexafluorophosphate and tetrafluoroborate salts were synthesized, but the characteristic dark green color of the tris-diazene complexes turned to brown–green during their isolation.

These complexes, like the molybdenum tris-diazene complexes, are electrochemically active. The room temperature cyclic voltammogram of the rhenium complex shows a pair of reversible one-electron processes with $E^1_{1/2} = -0.48$ V and $E^2_{1/2} = +0.02$ V versus Ag/AgCl. The technetium complex at room temperature displays only quasi-reversible processes which become nearly reversible when the temperature is lowered to −80 °C. The cyclic voltammetry at this temperature shows processes with $E^1_{1/2} = -0.24$ V and $E^2_{1/2} = +0.004$ V. The ΔE values are roughly 100 mV for each. Ferrocene was shown to behave similarly, so we attribute the deviation from the 59 mV separation expected for a reversible one-electron change at room temperature to *iR* drop. This is normal behavior for a solvent as non-polar as methylene chloride. The E^2 values are very similar for the two complexes, +0.02 and +0.004 V, which suggests that these are likely ligand centered processes. This could not be confirmed by the voltammetry of the free ligand because the hydralazine is oxidized by two electrons upon its coordination as the organodiazene species (see Fig. 2). The 16 mV difference in the E^2 values could be attributed to the metal center's influence on the ligand redox potential. The higher value of E^1 for the rhenium complex as compared to its technetium analogue is to be expected, since the third row transition metal is more difficult to reduce than the technetium.

The neutral Tc(V) bis-diazene complex $[Tc(HNNCSC_6H_5)_2(S_2CC_6H_5)]$ was recently reported [7]. The method of assigning oxidation states for complexes containing organodiazene ligands is inherently ambiguous. The authors of ref. 7 use a different method to assign oxidation states for their complex than we have employed for $[Tc(C_8H_5N_2N{=}NH)_3]^+$. Consequently, what follows is a brief discussion of the technetium thiobenzoyldiazene chemistry in terms of how we present our oxidation state assignments for the hydralazine complexes *vide supra*.

An oxidation state of Tc(V) was reported for the bis-thiobenzoyldiazene complex $[Tc(HNNCSC_6H_5)_2$-

$(S_2CC_6H_5)]$. Structurally, the chelated thiobenzoyldiazene ligands of the 'Tc(V) complex' closely resemble the neutral bidentate ligands reported in the tris-thiobenzoyldiazene molybdenum(0) complex $[Mo(HNNCSC_6H_5)_3]$ [1]. The technetium complex $[Tc(HNNCSC_6H_5)_2(S_2CC_6H_5)]$ was synthesized from the reaction of the Tc(V) complex $(n\text{-}Bu_4N)[TcOCl_4]$ with thiobenzoylhydrazine. By our rational, the reaction involved a four-electron reduction of the Tc(V) precursor by two of the thiobenzoylhydrazine molecules. The two organohydrazines are each concurrently oxidized by two electrons to coordinate as neutral thiobenzoyldiazene ligands in the formally Tc(I) product. A comparison of the bond lengths of the coordinated organodiazene ligands and the structural analogue of the free thiobenzoylhydrazine ligand, thiosemicarbazide $(H_2NC{=}SNHNH_2)$ [8], shows that the only significant bond length contraction upon coordination occurs in the N−N bonds, which are 1.399 Å in the free ligand as compared to 1.27 Å in the coordinated organodiazene ligands. This represents the difference between a single nitrogen–nitrogen bond and a double nitrogen–nitrogen bond, and accounts for the two-electron oxidation of the ligand upon coordination. The neutral charge on the formally Tc(I) bis-thiobenzoyldiazene complex can be attributed to the incorporation of the monoanionic bidentate dithiobenzoate $(C_6H_5CS_2^-)$ which is present as a contaminant from the synthesis of the organohydrazine.

The aromatic amine chelate in the diazene ligands formed in the reaction with hydralazine present fewer structural ambiguities than the thiobenzoyldiazene ligands and makes their oxidation state assignments more straightforward. The two-electron oxidation of the hydralazine upon coordination results in a localized nitrogen–nitrogen double bond within the five-membered chelate ring which is conjugated with the aromatic amine. Any other structural representation would require the disruption of the phthalazine aromaticity, which seems unlikely.

Conclusions

The chemistry presented within further extends our examination of the reactions of the organohydrazines with technetium [6, 9] and serves to emphasize the coordinative versatility of this class of ligands. The title complex has been synthesized at the tracer level with ^{99m}Tc and the biodistribution results will be presented elsewhere.

Acknowledgements

We thank Dr Lynne O'Connell and John Thomas of MIT who performed the ^{99}Tc NMR spectroscopy experiments and Dr Catherine E. Costello and Chen-Hui Zeng of the NIH Northeast Regional Mass Spectrometry Laboratory for the FAB mass spectra. This work was supported in part by NIH Grant 5 R01 CA-34970 and DOE Contract DE-FG02-87ER60526.

References

1 J. R. Dilworth, J. Hyde, P. Lyford, P. Vella, K. Venkatasubramaman and J. A. Zubieta, *Inorg. Chem., 18* (1979) 268–274.

2 A. Davison, C. Orvig, H. S. Trop, M. Sohn, B. V. DePamphilis and A. G. Jones *Inorg. Chem., 19* (1980) 1988–1991.

3 T. Nicholson and J. A. Zubieta, *Polyhedron, 7* (1988) 171–185.

4 L. A. O'Connell, R. M. Pearlstein, A. Davison, J. R. Thornback, J. F. Kronauge and A. G. Jones, *Inorg. Chim. Acta, 161* (1989) 39–43.

5 J. Mason (ed.), *Multinuclear NMR*, Plenum, New York, 1987, Ch. 3, pp. 51–83.

6 T. Nicholson, N. de Vries, A. Davison and A. G. Jones, *Inorg. Chem., 28* (1989) 3813–3819.

7 M. A. Abrams, S. N. Shaikh and J. A. Zubieta, *Inorg. Chim. Acta, 171* (1990) 133–134.

8 P. Domiano, G. Fava Gaspari, M. Nardelli and P. Sgarabotto, *Acta Crystallogr., Sect. B, 25* (1969) 343; G. D. Andreetti, P. Domiano, G. Fava Gaspari, M. Nardelli and P. Sgarabotto, *Acta Crystallogr., Sect. B, 26* (1970) 1005.

9 T. Nicholson, A. Davison and A. G. Jones, *Inorg. Chim. Acta, 168* (1990) 227–231.