Technetium Radiopharmaceutical Development. 1. Synthesis, Characterization, and Structure of Dichloro[hydrotris(1-pyrazolyl)borato]oxotechnetium(V)

Rudy W. Thomas, Gregory W. Estes, R. C. Elder, and Edward Deutsch*

Contribution from the Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221. *Received February 2, 1979*

Abstract: The title complex, $Tc(HBPz_3)Cl_2O$, has been prepared by reduction of $^{99}TcO_4^-$ in aqueous 3 M HCl in the presence of the $HBPz_3^-$ ion, and subsequently characterized by infrared, Raman, and ^1H NMR spectroscopy, as well as by a single-crystal X-ray structure determination. This molecular complex crystallizes in the triclinic space group $P\bar{1}$, $Z = 2$, with a = 7.786 (2) Å, b = 9.052 (2) Å, c = 11.328 (2) Å, α = 103.20 (2)°, β = 92.07 (3)°, and γ = 113.83 (3)°. Refinement based on 1941 independent reflections led to residual indices $R_1 = 0.025$ and $R_2 = 0.024$. The technetium center is in a distorted octahedral coordination environment, the six ligating atoms being the oxo oxygen atom, two chlorine atoms, and the three nitrogen atoms of the $HBPz_3^-$ ligand which occupy one face of the coordination octahedron. The oxo ligand induces a significant structural trans effect, the pyrazolyl ring trans to the oxo oxygen atom being ca. 0.2 Å further from the technetium center than the two rings which are trans to the chlorine atoms. Implications of the synthesis and structure of lipophilic $Tc(HBPz_3)Cl_2O$, and of the properties of the spin-paired $Tc^V{=}O$ center, for the development and understanding of ^{99m}Tc radiopharmaceuticals are discussed.

Introduction

In the practice of diagnostic nuclear medicine, some chemical form of a γ ray emitting isotope is administered to a patient (usually by intravenous injection) with the goal of having the isotope localize in a specific organ. Subsequent scanning of the organ with a γ ray camera provides valuable diagnostic and prognostic information.[1,2] The term "radiopharmaceutical" refers to the overall chemical form of which the isotope is a part, this chemical form of course determining the mechanism and site of in vivo organ localization.[3] Very often the exact chemical structure, and even composition, of clinically used radiopharmaceuticals is not known.[1-4] For reasons which have been amply documented elsewhere,[1,5] ^{99m}Tc is the isotope of choice for diagnostic nuclear medicine procedures; many efficacious imaging procedures based on this isotope are currently in wide use in hospitals around the world.[2,4,6]

We have recently reviewed[1] the state of knowledge concerning the synthesis and composition of ^{99m}Tc radiopharmaceuticals. All ^{99m}Tc radiopharmaceuticals, except pertechnetate itself, are prepared via the reduction of $^{99m}TcO_4^-$ in the presence of a potential ligand, the most commonly employed reductant being stannous chloride in aqueous HCl. It is clear that the chemistry involved in this synthetic approach, and the chemistry of the resultant reduced technetium radiopharmaceuticals, is only poorly understood.[1-4] In order to rectify this situation we have undertaken a research program designed to elucidate the inorganic chemistry of technetium, especially as applied in the practice of nuclear medicine. One of our particular concerns has been the introduction of lipophilic character into technetium complexes prepared in aqueous media. Many important biochemicals and drugs are predominantly lipophilic, but most clinically available ^{99m}Tc radiopharmaceuticals are predominantly hydrophilic.[1-4] In this context, our attention has focused on the lipophilic poly-1-pyrazolyl borate ligands, especially the readily available hydrotris(1-pyrazolyl)borato anion ($HBPz_3^-$). Over 20 transition-metal complexes containing these ligands are known,[7-12] and most are insoluble in water but soluble in polar organic solvents (i.e., exhibit lipophilic rather than hydrophilic character). Utilizing the long-lived ($t_{1/2} = 2.1 \times 10^5$ years) isotope ^{99}Tc, and the aqueous pertechnetate reduction procedure generally used for ^{99m}Tc radiopharmaceutical preparations, we have synthesized a lipophilic $HBPz_3^-$ complex of technetium. This paper then describes the preparation, characterization, properties, and structure of this complex.

Experimental Section

General Data. All common laboratory chemicals were of reagent grade. Elemental analyses and molecular weight determination (by osmometry in dichloromethane) were performed by Galbraith Laboratories, Knoxville, Tenn. Visible-UV spectra were recorded on a Varian 634 spectrophotometer at ambient temperature in dichloromethane. The ^1H NMR spectrum was obtained with a Varian T-60 instrument in acetone-d_6 (internal Me_4Si reference). The infrared spectrum was recorded on a Beckman IR-12 in a Nujol mull. The laser Raman spectrum was obtained in the solid state through the courtesy of Dr. J. E. Smith, Union Carbide Corp., Tarrytown, N.Y.

Dichloro[hydrotris(1-pyrazolyl)borato]oxotechnetium(V), $Tc(HBPz_3)Cl_2O$. This material was prepared by mixing 3.0 mL of 0.36 M NH_4TcO_4 (technetium-99 of >99% radiochemical purity, from Oak Ridge National Laboratories, Oak Ridge, Tenn.) with 100 mL of 3.0 M HCl which was also 0.01 M in $KHBPz_3$. To this aqueous solution 0.20 g of KBH_4 (Metal Hydrides Inc.) was added in small increments over a 5-day period, leading to precipitation of the light green product in about 60% yield. Purification can be effected by column chromatography on silica gel and/or recrystallization from dichloromethane or toluene. Single crystals suitable for X-ray analysis were obtained by recrystallization from hot toluene. Anal. Calcd for $Tc(HBPz_3)Cl_2O$: C, 27.10; H, 2.53; B, 2.71; N, 21.07; Cl, 17.78; mol wt, 399. Found: C, 27.21; H, 2.63; B, 2.74; N, 20.57; Cl, 18.48; mol wt, 394.

X-ray Characterization. A light green crystal of $Tc(HBPz_3)Cl_2O$ with approximate dimensions 0.18 × 0.18 × 0.08 mm was mounted on a glass fiber and Cu Kα radiation used to obtain $hk0$ and $0kl$ precession photographs. From these photographs the crystal was assigned as triclinic and the cell constants estimated to be a = 7.81 Å, b = 9.08 Å, c = 11.36 Å, α = 103.2°, β = 92.0°, γ = 113.8°. This same crystal was then optically centered on a Syntex $P\bar{1}$ diffractometer equipped with a molybdenum target tube (λ 0.710 69 Å) and graphite monochromator, and operated at ambient temperature (22 ± 2 °C). Our usual procedures[13] were employed to check crystal quality (three axial rotation photographs and mosaic-scan measurements), determine unit cell constants (22 pairs of $\pm 2\theta$ values), and measure intensities. Least-squares refined constants for the reduced primitive cell[14] are a = 7.786 (3) Å, b = 9.052 (2) Å, c = 11.328 (2) Å, α = 103.20 (2)°, β = 92.07 (3)°, γ = 113.83 (3)°. With $Z = 2$, d_{calcd} = 1.88 and d_{measd} = 1.89 (3) g cm^{-3}. The rate for the $\theta/2\theta$ scan varied between 1.2 and 4.0°/min depending on the intensity of the reflection being measured. The scan ranged from 0.9° in 2θ below the calculated

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Table I. Spectral Parameters for $Tc(HBPz_3)Cl_2O$

A. ^1H NMR[a,b]

pyrazolyl ring	5 position	4 position	3 position	integration ratio
trans to O	7.2 d	5.9 t	7.5 d	1
trans to Cl	8.3 d	6.8 t	8.5 d	2

B. IR[c,d]

3138 M, 2520 M, 1500 M, 1410 M, 1313 S, 1215 S, 1205 S, 1190 M, 1182 M, 1130 S, 1122 S, 1080 M, 1050 VS, 970 VS, 928 W, 918 VW, 890 W, 863 VW, 820 M, 798 M, 775 VS, 728 M, 712 S, 670 W, 648 M, 615 S, 383 M, 353 VS, 320 M, 309 M, 292 W.

C. Raman[c,e]

3140 VW, 3130 VW, 1440 VW, 1400 VW, 1382 M, 1315 M, 1220 M, 1200 W, 1180 M, 1105 VW, 1070 VW, 1045 VW, 970 VS, 928 M, 852 VW, 790 W, 765 VW, 710 M, 647 W, 612 W, 382 W, 353 VS, 305 M, 275 W, 240 M, 213 M, 190 VS, 123 VS

[a] Spectrum determined in acetone-d_6. Chemical shifts (δ, ppm) are given relative to internal Me_4Si. [b] t = triplet, d = doublet. [c] ν values in cm^{-1}; V = very, S = strong, M = medium, W = weak. [d] Spectrum obtained in Nujol mull. [e] Spectrum obtained in the solid state.

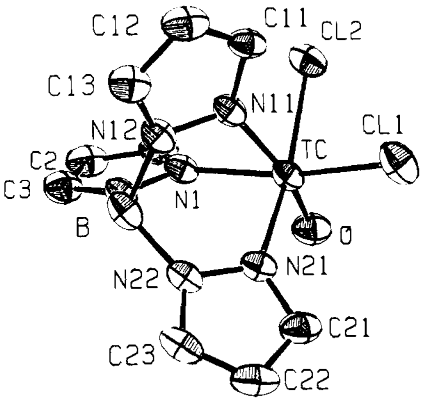

Figure 1. Perspective view of $Tc(HBPz_3)Cl_2O$. The ellipsoids represent 50% probability, and hydrogen atoms have been omitted for clarity.

$K\alpha_1$ peak position to 1.0° above that calculated for $K\alpha_2$. Four standard reflections were monitored to check crystal stability and to account for long-term drift; the drift correction varied from 0.988 to 1.029 in a random manner. Absorption corrections (linear absorption coefficient $\mu = 13.9\ cm^{-1}$) were applied with the resulting transmission coefficients ranging from 0.82 to 0.95. A series of ψ scans[15] was conducted for each of the standard reflections to ensure the validity of the calculated corrections. Within the sphere $2\theta < 46°$, 2498 reflections were measured in the forms $h \pm k \pm l$; from these, 1941 unique reflections were obtained by averaging. The average percent discrepancy for multiply measured reflections was 1.25%. Of the unique reflections, 1788 had $I > 2\sigma(I)$, where p, the ignorance factor used to calculate[13] $\sigma(I)$, was set equal to 0.02.

Structure Solution and Refinement. This structure[16] was solved using normal Patterson techniques and refinement proceeded without difficulty. The pyrazolyl hydrogen atoms were initially placed at their calculated positions and the initial position of the hydrogen atom bonded to boron was determined from a difference map. After refinement of the hydrogen atom positions, a Hamilton significance test[17a] indicated that the new model was significantly improved at the 0.005 confidence level. All hydrogen atoms were arbitrarily assigned an isotropic temperature parameter,[18] B, of 4.0 $Å^2$. In the final cycles of least-squares refinement, 211 parameters were varied including the overall scale factor, positional parameters for all atoms, and anisotropic thermal parameters for all nonhydrogen atoms. Convergence was achieved with $R_1 = 0.025$ and $R_2 = 0.024$.[19] In the final cycle of refinement the maximum shift/error was 0.088 and the average shift/error was 0.013. The largest peak on a final difference electron density map, 0.96 e $Å^{-3}$, was within 0.9 Å of the technetium atom and corresponded to ca. 0.15 the height of a carbon atom peak on the same scale; there were no other maxima or minima with a magnitude greater than 0.33 e $Å^{-3}$. Scattering curves were taken from Cromer;[20] those for H were from Stewart.[21] Anomalous dispersion corrections[17b] were included. Table A[22] lists $|F_o|$ and F_c.

Table II. Fractional Atomic Positional Parameters for Nonhydrogen Atoms in $Tc(HBPz_3)Cl_2O$[a,b]

atom	x	y	z
Tc	0.190 61 (5)	0.257 75 (4)	0.199 08 (3)
Cl (1)	0.3636 (2)	0.2906 (1)	0.383 09 (8)
Cl (2)	0.4439 (2)	0.4891 (1)	0.170 25 (9)
O	0.2161 (4)	0.1013 (3)	0.1044 (2)
B	−0.2321 (7)	0.2554 (6)	0.1985 (4)
N (1)	0.0207 (5)	0.2789 (3)	0.0631 (2)
N (2)	−0.1610 (4)	0.2567 (4)	0.0738 (2)
C (1)	0.0519 (7)	0.3011 (5)	−0.0487 (3)
C (2)	−0.1092 (7)	0.2917 (5)	−0.1092 (3)
C (3)	−0.2394 (7)	0.2665 (5)	−0.0296 (4)
N (11)	0.0943 (4)	0.4453 (3)	0.3078 (2)
N (12)	−0.0917 (4)	0.4174 (4)	0.2899 (2)
C (11)	0.1862 (6)	0.5929 (4)	0.3908 (3)
C (12)	0.0583 (7)	0.6590 (5)	0.4259 (3)
C (13)	−0.1138 (6)	0.5473 (5)	0.3624 (3)
N (21)	−0.0507 (5)	0.1024 (4)	0.2590 (3)
N (22)	−0.2210 (5)	0.1093 (4)	0.2410 (3)
C (21)	−0.0792 (7)	−0.0199 (5)	0.3152 (4)
C (22)	−0.2633 (7)	−0.0904 (5)	0.3348 (4)
C (23)	−0.3469 (7)	−0.0070 (5)	0.2871 (4)

[a] The estimated error in the last digit is given in parentheses. This form is used throughout. [b] The numbering scheme is shown in Figure 1.

Results

Characterization. $Tc(HBPz_3)Cl_2O$ is insoluble in water and soluble in most polar organic solvents. The visible–UV spectrum exhibits maxima at 784 and 311 nm (ϵ 80 and 5600 $M^{-1}\ cm^{-1}$, respectively). The IR spectrum (Table I) exhibits absorptions at 2520 and 353 cm^{-1} which are assigned to be the B-H and Tc-Cl stretches, respectively; absorptions at 928 and 970 cm^{-1} are both in the region predicted for the Tc=O stretch.[23-25] The Raman spectrum exhibits analogous absorptions at 353, 928, and 970 cm^{-1}. $Tc(HBPz_3)Cl_2O$ exhibits a normal diamagnetic ^1H NMR spectrum; peak assignments, made in accordance with those of King[26,27] and Trofimenko,[7] are reported in Table I.

Crystal Structure. Final fractional atomic coordinates, and their estimated standard deviations, for nonhydrogen atoms are listed in Table II, while those for the hydrogen atoms are given in Table B.[22] Anisotropic thermal parameters are collected in Table C,[22] the root mean square displacements calculated therefrom are presented in Table III, and the associated thermal ellipsoids are illustrated in Figure 1. Bond lengths and angles involving the nonhydrogen atoms are listed in Table

Table III. Root Mean Square Displacements (Å) for $Tc(HBPz_3)Cl_2O$

atom	min	med	max	atom	min	med	max
Tc	0.159	0.168	0.203	N (11)	0.151	0.174	0.204
O	0.175	0.227	0.224	N (12)	0.165	0.173	0.212
Cl (1)	0.184	0.214	0.276	C (11)	0.147	0.175	0.224
Cl (2)	0.174	0.235	0.249	C (12)	0.146	0.194	0.272
B	0.161	0.178	0.240	C (13)	0.165	0.200	0.231
N (1)	0.151	0.170	0.214	N (21)	0.162	0.185	0.210
N (2)	0.151	0.179	0.210	N (22)	0.154	0.182	0.217
C (1)	0.157	0.183	0.246	C (21)	0.164	0.207	0.249
C (2)	0.154	0.198	0.280	C (22)	0.162	0.232	0.271
C (3)	0.169	0.208	0.244	C (23)	0.156	0.212	0.263

IV, while those involving the hydrogen atoms are collected in Table D.[22]

The crystal structure consists of discrete $Tc(HBPz_3)Cl_2O$ molecular units. The technetium center of each unit is in a distorted octahedral coordination environment, the six ligating atoms being one oxygen, two chlorines, and the three nitrogens of the $HBPz_3^-$ ligand which occupy one face of the coordination octahedron. Table V compares the Tc-Cl, Tc-N, and Tc-O bond lengths observed in this structure to bond lengths observed in other technetium complexes. From Table V it is seen that the observed Tc-O distance of 1.656 (3) Å is diagnostic for doubly bonded oxo oxygen, singly bonded oxygen ligands giving rise to much longer Tc-O bond lengths (ca. 2.0 Å). Also from Table V it is seen that the Tc-Cl bond lengths, and two of the three Tc-N bond lengths, are quite normal. However, the Tc-N bond trans to the oxo functionality is ca. 0.2 Å longer than are the two "normal" Tc-N bonds which are trans to the chlorine ligands. The magnitude of this structural trans effect (STE) induced by the oxo ligand is consistent with other oxo-induced STEs;[28] Table VI compares relevant data for selected second- and third-row transition metal oxo complexes. Bond lengths and bond angles within the tridentate $HBPz_3^-$ ligand are similar to those observed within the related $C_6H_5BPz_3^-$ ligand in complexes such as $Mo(C_6H_5BPz_3)(C_7H_7)(CO)_2$ and $Mo(C_6H_5BPz_3)(C_3H_3)(CO)_2$.[11]

Table IV. Bond Lengths and Angles between Nonhydrogen Atoms in $Tc(HBPz_3)Cl_2O$

	Bond Lengths (Å)		
Tc-Cl (1)	2.332 (1)	N (11)-N (12)	1.365 (5)
Tc-Cl (2)	2.324 (1)	N (11)-C (11)	1.336 (4)
Tc-O	1.656 (3)	C (11)-C (12)	1.381 (8)
Tc-N (1)	2.086 (4)	C (12)-C (13)	1.356 (5)
Tc-N (11)	2.259 (4)	C (13)-N (12)	1.348 (6)
Tc-N (21)	2.088 (3)	N (12)-B	1.532 (4)
N (1)-N (2)	1.360 (5)	N (21)-N (22)	1.362 (6)
N (1)-C (1)	1.343 (5)	N (21)-C (21)	1.347 (6)
C (1)-C (2)	1.369 (7)	C (21)-C (22)	1.364 (7)
C (2)-C (3)	1.366 (7)	C (22)-C (23)	1.358 (8)
C (3)-N (2)	1.340 (6)	C (23)-N (22)	1.340 (5)
N (2)-B	1.536 (5)	N (22)-B	1.539 (7)
	Bond Angles (deg)		
Cl (1)-Tc-Cl (2)	88.80 (4)	B-N (12)-N (11)	118.7 (3)
Cl (1)-Tc-O	102.8 (1)	B-N (12)-C (13)	132.3 (4)
Cl (2)-Tc-O	101.6 (1)	B-N (22)-N (21)	120.0 (3)
Cl (1)-Tc-N (1)	164.8 (1)	B-N (22)-C (23)	131.3 (4)
Cl (1)-Tc-N (11)	85.39 (8)	N (2)-B-N (12)	106.5 (3)
Cl (1)-Tc-N (21)	87.8 (1)	N (2)-B-N (22)	109.4 (4)
Cl (2)-Tc-N (1)	88.74 (8)	N (12)-B-N (22)	106.9 (3)
Cl (2)-Tc-N (11)	85.66 (8)	N (1)-N (2)-C (3)	108.9 (3)
Cl (2)-Tc-N (21)	163.8 (1)	N (2)-C (3)-C (2)	108.4 (4)
O-Tc-N (1)	92.4 (1)	C (3)-C (2)-C (1)	106.2 (4)
O-Tc-N (11)	168.2 (2)	C (2)-C (1)-N (1)	109.4 (4)
O-Tc-N (21)	94.6 (1)	C (1)-N (1)-N (2)	107.0 (4)
N (1)-Tc-N (11)	78.4 (1)	N (11)-N (12)-C (13)	109.0 (3)
N (1)-Tc-N (21)	90.4 (1)	N (12)-C (13)-C (12)	108.0 (5)
N (11)-Tc-N (21)	78.3 (1)	C (13)-C (12)-C (11)	108.8 (4)
Tc-N (1)-N (2)	121.9 (2)	C (12)-C (11)-N (11)	109.0 (4)
Tc-N (1)-C (1)	131.0 (3)	C (11)-N (11)-N (12)	107.2 (4)
Tc-N (11)-N (12)	119.8 (2)	N (21)-N (22)-C (23)	107.6 (4)
Tc-N (11)-C (11)	133.0 (3)	N (22)-C (23)-C (22)	110.7 (5)
Tc-N (21)-N (22)	121.9 (3)	C (23)-C (22)-C (21)	104.4 (4)
Tc-N (21)-C (21)	131.5 (4)	C (22)-C (21)-N (21)	110.8 (5)
B-N (2)-N (1)	120.0 (3)	C (21)-N (21)-N (22)	106.6 (3)
B-N (2)-C (3)	130.1 (4)		

Discussion

Characterization. The comparative Tc—O and Tc═O bond lengths listed in Table V show conclusively that the coordinated oxygen ligand in $Tc(HBPz_3)Cl_2O$ is a doubly bonded oxo ligand rather than a singly bonded hydroxo or aquo ligand. This result is further substantiated by the absence of an observable O-H stretch in the IR spectrum (Table I) and the absence of an observable O-H resonance in the ^1H NMR spectrum (Table I). The ligand stoichiometry of $Tc(HBPz_3)Cl_2O$ thus demands assignment of a technetium(V) oxidation state and to our knowledge this represents the first known example of a $RBPz_3^-$ complex containing a metal in the +5 oxidation state. Observation of a normal ^1H NMR spectrum for $Tc(HBPz_3)Cl_2O$ implies that this compound is diamagnetic and therefore the technetium(V) center can be described as a spin-paired d^2 system. Nyholm[3,29] has noted that the d^2 configuration in second- and third-row transition metal elements is often spin paired, especially in the presence of strong, asymmetric ligand fields.

In the visible-UV spectrum of $Tc(HBPz_3)Cl_2O$, the low-intensity peak at 784 nm presumably arises from a d-d transition and the high-intensity peak at 311 nm presumably arises from a chloride to technetium(V) charge transfer transition. In the IR and Raman spectra (Table I), assignment of the B-H and Tc-Cl stretching frequencies at 2520 and 353 cm^{-1} is direct, but assignment of the Tc═O stretch is not definite. Since Tc═O stretching frequencies are expected in the 900-1020-cm^{-1} region, either of the observed peaks at 928 and 970 cm^{-1} could correspond to the Tc═O stretch. Because of the greater intensity of the 970-cm^{-1} peak in both the IR and Raman spectra, we tentatively prefer this assignment. Definitive interpretation of both the visible-UV and IR spectra will have to await development of more extensive series of related complexes. The ^1H NMR spectrum clearly shows that in acetone solution one pyrazolyl ring of $Tc(HBPz_3)Cl_2O$ is in a unique chemical environment, whereas the other two rings are in equivalent environments. This observation is consistent with the solid-state crystal structure of $Tc(HBPz_3)Cl_2O$, which shows that one pyrazolyl ring is trans to the oxo ligand whereas the other two rings are trans to chloride ligands. In the solid state the unique pyrazolyl ring is ca. 0.2 Å further from the technetium center than are the two equivalent rings (vide infra) and this oxo-induced trans effect may even be more pro-

Table V. Comparisons of Tc—Cl, Tc—O, Tc═O, and Tc—N Bond Lengths[a]

	compd	ref
	Tc—Cl Bond Lengths	
2.33, 2.32	$Tc(HBPz_3)Cl_2O$	this work
2.35	$TcCl_6^{2-}$	33
2.34, 2.35, 2.37, 2.37	$Tc_2Cl_8^{3-}$	34
2.33, 2.33, 2.46	$TcCl_3(Me_2PPh)_3$	35
2.41, 2.42	$TcCl_2((EtO)_2PPh)_4$	36
2.42	$TcCl(acac)_2(PPh_3)$	37
2.41	$Tc_2(OOCCMe_3)_4Cl_2$	38
2.47, 2.48, 2.49	$TcCl_3(CO)(Me_3PPh)_3{\cdot}EtOH$	39
	Tc—O Bond Lengths	
2.03	$Tc(dmg)_3(SnCl_3)(OH){\cdot}3H_2O$	31
2.03	$Tc_2(OOCCMe_3)_4Cl_2$	38
2.00, 2.01, 2.02, 2.03	$TcCl(acac)_2(PPh_3)$	37
	Tc═O Bond Lengths	
1.66	$Tc(HBPz_3)Cl_2O$	this work
1.66	$(TcOF_4)_3$	40
1.64	$TcO(SCH_2CH_2S)_2^-$	25
1.67	$TcO(SCH_2C(O)S)_2^-$	24
1.65, 1.67, 1.70	Tc_2O_7	41
	Tc—N Bond Lengths	
2.09, 2.09	$Tc(HBPz_3)Cl_2O$, trans to Cl	this work
2.26	$Tc(HBPz_3)Cl_2O$, trans to O	this work
2.07, 2.08, 2.08, 2.09, 2.10, 2.10	$Tc(dmg)_3(SnCl_3)(OH){\cdot}3H_2O$	31
2.16	*trans*-$Tc(NH_3)_4(NO)(OH_2)^{2+}$, $Tc{-}NH_3$	*b*

[a] Bond lengths in Å; acac = acetylacetonate anion; dmg = dimethylglyoxime in unknown protonation state; Me = CH_3; Et = C_2H_5; Ph = C_6H_5. [b] J. L. Hoard, Cornell University, private communication.

Table VI. Oxo Induced Structural Trans Effects in Selected Second- and Third-Row Monooxo Transition Metal Complexes[a]

complex	no. d electrons	M-O distance, Å	STE, Å
$Tc(HBPz_3)Cl_2O$	2	1.66	0.17
$K_2[ReOCl_5]$	2	1.66	0.08
$(ReOF_4)_\infty$	1	1.64	0.30
$(TcOF_4)_3$	1	1.66	0.37
$K_2[MoOF_5]{\cdot}H_2O$	1	1.66	0.17
$(MoOF_4)_\infty$	0	1.64	0.34
$K_2[NbOF_5]$	0	1.68	0.22

[a] All data, except that for $Tc(HBPz_3)Cl_2O$, taken from ref 28.

nounced in solution. Solution models wherein the unique pyrazolyl ring is loosely bonded to technetium, not bonded to technetium at all, or in rapid equilibrium between free and bonded forms are all compatible with the ^1H NMR spectrum.

Crystal Structure. The overall structure of $Tc(HBPz_3)Cl_2O$ is as expected, given the presence of the Tc═O moiety which could not be unambiguously established by IR and Raman spectroscopy. The oxo ligand dominates the structural description of $Tc(HBPz_3)Cl_2O$ in that it not only induces a large structural trans effect (see Tables V and VI), but also the large steric requirements of this group[28] cause the cis ligands to bend away from the Tc═O linkage and toward the trans pyrazolyl ring. The effect of this bending of the equatorial ligands away from the oxo group is readily observed in the inter-ring angles of the $HBPz_3^-$ ligand. Table VII compares inter-ring angles for a variety of $RBPz_3^-$ ligands wherein it is seen that these ligands are very flexible, angles ranging from 94 to 139°. The largest inter-ring angle, 139°, occurs in $Tc(HBPz_3)Cl_2O$ as a result of the cis pyrazolyl rings bending away from the oxo ligand.

Radiopharmaceutical Development. The results of this work have, in themselves, ramifications for the development of ^{99m}Tc radiopharmaceuticals. First, the synthesis of $Tc(HBPz_3)Cl_2O$

Table VII. Comparison of Inter-Ring Angles (deg) in Tris(1-pyrazolyl)borato Complexes[a]

complex	angle 1-2	angle 1-3	angle 2-3	ref
$Tc(HBPz_3)Cl_2O$	110.8	139.0	110.2	this work
$Fe(HBPz_3)(CO)_2(COCH_3)$	115.9	129.7	114.3	42
$Co(HBPz_3)_2$ L1	115.1	128.9	116.5	
L2	120.4	129.8	109.8	43
$Pt(HBPz_3)(CH_3)(CF_3C{\equiv}CCF_3)$	119.9	119.9	120.2	44
$Rh(HBPz_3)(C_5Me_5)^+$	132.2	106.9	120.8	45
$Ru(BPz_4)(C_6H_6)^+$	120.5	120.5	119.0	45
$Mo(HB(pzMe_2Cl)_3)(NO)(Cl)(OCH(CH_3)_2)$	125.5	112.6	121.1	46
$Mo(HBPz_3)(CO)_2(N_2C_6H_5)$	120.3	121.1	118.4	47
$Mo(HBPz_3)(CO)_2(NO)$	120[b]	120[b]	120[b]	48
$Cu(HBPz_3)(CO)$	112.0[c]	133.2[c]	114.7[c]	49
$Mo(C_6H_5BPz_3)(CO)_2(C_7H_7)$	127.6	94.0	138.4	11
$Mo(C_6H_5BPz_3)(CO)_2(C_3H_5)$	97.0	123.3	138.0	11

[a] Unless otherwise noted, angles are calculated from data given in the referenced articles. Me = CH_3. [b] Determined by symmetry. [c] Calculated by authors of ref 49.

demonstrates that lipophilic technetium complexes can be prepared in aqueous solution via the standard pertechnetate reduction route currently utilized to prepare ^{99m}Tc radiopharmaceuticals.[1] By modification of the R group of $RBPz_3^-$, and variation of the other ligands bound to technetium, this system could become the basis for a series of lipophilic technetium radiopharmaceuticals. Second, the kinetic stability of the monodentate chloride ligands of $Tc(HBPz_3)Cl_2O$ implies that the equatorial sites in spin-paired $Tc^V{=}O$ centers are at least moderately substitution inert, and therefore these centers will provide suitable templates about which to construct radiopharmaceuticals that will retain their integrity in vivo.

Moreover, when viewed in the context of recent developments in technetium chemistry, additional ramifications are perceived. Besides $Tc(HBPz_3)Cl_2O$, three technetium complexes have recently been prepared under aqueous, aerobic conditions and then structurally characterized: $Tc(dmg)_3(SnCl_3)(OH)\cdot 3H_2O$,[31,32] $[TcO(SCH_2CH_2S)_2]^-$,[25] and $[TcO(SCH_2C(O)S)_2]^-$.[24] All four complexes contain technetium in the +5 oxidation state,[32] indicating that this is a very likely oxidation state to be assumed by technetium radiopharmaceuticals prepared under similar conditions. Three of the four complexes contain an oxo ligand, and the fourth, $Tc(dmg)_3(SnCl_3)(OH)\cdot 3H_2O$, contains a bridging oxygen atom which might reasonably be assumed to be derived from a Tc=O linkage. It is thus likely that technetium radiopharmaceuticals prepared in aqueous media (especially by the reduction of pertechnetate) will contain oxo groups and therefore the diminished trans ligand affinities and enhanced trans ligand labilities associated with the oxo group should be anticipated in the chemistry of technetium radiopharmaceuticals.

In two of the three complexes based about the $Tc^V{=}O$ center, i.e., $[TcO(SCH_2CH_2S)_2]^-$ and $[TcO(SCH_2C(O)S)_2]^-$, the influence of the oxo group leads to a vacant trans coordination site, although in solution this site presumably contains a loosely bonded solvent molecule. In $Tc(HBPz_3)Cl_2O$ the tridentate $HBPz_3^-$ ligand suppresses five coordination but the influence of the oxo group leads to a weak trans ligand-metal bond as reflected in the observed 0.17-Å structural trans effect. The spin-paired $Tc^V{=}O$ centers therefore provide equatorial and axial ligation sites markedly different in bonding and lability. The different character of these sites must be taken into consideration in the design and synthesis of radiopharmaceuticals based on the $Tc^V{=}O$ center.

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Supplementary Material Available: Tables A–D giving $|F_o|$ and F_c, hydrogen atom positional parameters, anisotropic thermal parameters, and bond lengths and angles involving hydrogen atoms (9 pages). Ordering information is given on any current masthead page.

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