Synthesis and Characterization of Oxotechnetium(V) Complexes with Aza-Substituted 2,6-Dimethyl-4-azaheptane-2,6-dithiol Ligands and Benzyl Mercaptan as Coligand

D. M. Spyriounis,[†] M. Pelecanou,[‡] C. I. Stassinopoulou,[‡] C. P. Raptopoulou,[§] A. Terzis,[§] and E. Chiotellis*,[†]

Institutes of Radioisotopes-Radiodiagnostic Products, Biology, and Materials Science, NCSR "Democritos", PO Box 60228, 153 10 Aghia Paraskevi, Athens, Greece

Received August 10, 1994[⊗]

The design and synthesis of mixed oxotechnetium(V)-99 complexes with a novel series of aza-substituted 2,6-dimethyl-4-azaheptane-2,6-dithiol ligands of the general type NS_2 and benzyl mercaptan as coligand are reported. Ligands (general formula $R-CH_2CH_2N[CH_2C(CH_3)_2SH]_2$ with R = $N(C_2H_5)_2$, piperidin-1-yl, pyrrolidin-1-yl, and morpholin-4-yl) were synthesized through the reduction of aza-substituted heterocyclic aza disulfides which result from the reductive cyclization of 2.2′-dithiobis(2-methylpropanal) with the appropriate primary amine. The ^{99}Tc complexes **5** (general formula $TcO\{[SC(CH_3)_2CH_2]_2NCH_2CH_2R\}X$, where X = benzyl mercaptan) were prepared in high yield by the reaction of ^{99}Tc(V) gluconate with a 1:1 mixture of the appropriate tris-chelating ligand and the monodentate benzyl mercaptan. The resulting complexes were purified through flash column chromatography. Crystals were formed by dissolving complexes in a mixture of MeOH/water and slowly evaporating the solvents. Complexes were characterized by elemental analyses and spectroscopic methods. Complete assignments of ^{1}H and ^{13}C NMR resonances were made for all complexes. X-ray crystallographic analysis of **5d** ($C_{21}H_{35}N_2S_3O_2Tc$, R = morpholin-4-yl) showed that the complex crystallizes in the monoclinic space group $P2_1/c$ with a = 17.166(2) Å, b = 8.9282(7) Å, c = 17.738(2) Å, β = 116.031(3)°, V = 2442.7(4) Å^3, and Z = 4. Complex **5d** has trigonally distorted square pyramidal coordination geometry around technetium with the side chain on nitrogen directed toward the oxygen of the Tc=O core (*syn* configuration). The nOe data confirm that in all cases the major isolated product of the synthesis has the *syn* configuration of the side chain.

Introduction

The design of ^{99m}Tc based lipid soluble complexes as brain perfusion imaging agents continues as an area of nuclear medicine research which is receiving much attention. Ongoing efforts are focused on the design of new ^{99m}Tc radiopharmaceuticals which combine high uptake in the brain with prolonged retention. Compounds which fulfil these requirements should combine high lipophilicity with a low molecular weight.[1]

The hitherto known ^{99m}Tc radiopharmaceuticals which cross the intact blood brain barrier and which accumulate in the brain such as ^{99m}Tc−HMPAO,[2] ^{99m}Tc−ECD,[3] and various representatives of amino-substituted ^{99m}Tc−S_2N_2 complexes[4] are derived from tetradentate ligands. In these complexes the central oxotechnetium(V) core is stabilized by either NNOO or NNSS donor atoms.

An alternative concept for designing small-sized, oxotechnetium(V) complexes involves simultaneous action of a tridentate ligand and a monodentate thiol as coligand on a suitable Tc(V) precursor.[5,6] The tridentate ligand wraps around the TcO^{3+} core to form complexes of the type $TcOL^+$ leaving one open coordination site to bind the monodentate coligand. Tridentate ligands employed so far include dithiol ligands ($HSCH_2CH_2XCH_2CH_2SH$, X = O, S[5]) or Schiff-bases (salicylaldehyde 2-hydroxyanil, salicylaldehyde 2-mercaptoanil, and acetylacetone 2-mercaptoanil[6]). However, animal studies on these series of complexes demonstrated negligible uptake into brain tissue.[5]

In our laboratory, reaction of the ligands *N,N*-bis(2-mercaptoethyl)-*N′N′*-diethylethylenediamine and *N,N*-bis(2-mercaptoethyl)((2-ethylthio)ethyl)amine and various monodentate thiols as coligands with a Tc(V) gluconate precursor resulted in isolation in high yield of mixed ligand oxotechnetium(V) complexes. Biodistribution of these complexes in mice demonstrated high initial brain uptake and significant retention in this tissue displaying high brain to blood ratio in all the time intervals studied.[7]

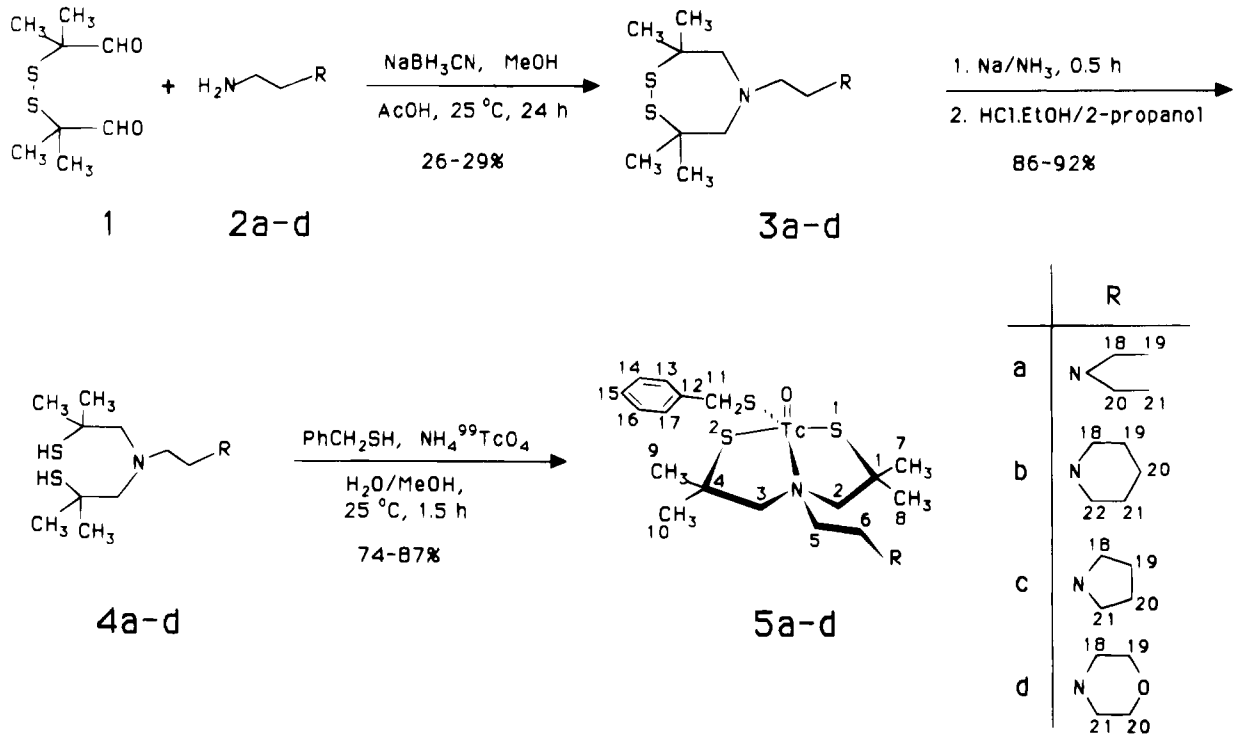
In the present study, we investigated a new series of tris-chelating ligands, **4a−d**, containing tertiary thiol donors, for their ability to form oxotechnetium(V) complexes in the presence of a monodentate thiol. A concise synthetic scheme was developed for the preparation of these ligands. Complexes **5a−d**, with benzyl mercaptan as the monodentate thiol, were prepared and characterized by elemental analysis and spectroscopic methods. The crystal structure of complex **5d** was

* Author to whom correspondence should be addressed.
[†] Institute of Radioisotopes-Radiodiagnostic Products.
[‡] Institute of Biology.
[§] Institute of Materials Science.
[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1995.

(1) Nowotnik, D. P. In *Radiopharmaceuticals Chemistry and Pharmacology*; Nunn, A. D., Ed.; M. Dekker: New York, 1992; p 37.
(2) Neirinckx, R. D.; Canning, L. R.; Piper, I. M.; Nowotnik, D. P.; Pikett, R. D.; Holmes, R. A.; Volkert, W. A.; Forster, A. M.; Weisner, P. S.; Marriott, J. A.; Chaplin, S. B. *J. Nucl. Med.* **1987**, *28*, 191.
(3) Walovitch, R. C.; Hill, T. C.; Garrity, S. T.; Cheesman, E. H.; Burgess, B. A.; O'Leary, D. A.; Watson, A. D.; Ganey, M. V.; Morgan, R. A.; Williams, S. J. *J. Nucl. Med.* **1989**, *30*, 1892.
(4) (a) Lever, S. Z.; Burns, H. D.; Kervitsky, H. N.; Goldfarb, H. W.; Woo, D. V.; Epps, L. A.; Kramer, A. V.; Wagner, H. N. Jr. *J. Nucl. Med.* **1985**, *26*, 1287. (b) Efange, S. M. N.; Kung, H. F.; Billings, J.; Guo Y.-Z.; Blau, M. *J. Nucl. Med.* **1987**, *28*, 1012. (c) Papadopoulos, M.; Stathaki, M.; Mastrostamatis, S.; Varvarigou, A.; Chiotellis, E. *Nucl. Med. Biol.* **1993**, *20*, 105.
(5) Spies, H.; Pietzch, H.-J.; Syhre, R.; Hoffmann, S. *Isotopenpraxis* **1990**, *26*, 159.
(6) Pietzch, H.-J.; Spies, H.; Hoffmann, S.; Scheller, D. *Appl. Radiat. Isot.* **1990**, *41*, 185.
(7) Mastrostamatis, S. M.; Pirmettis, I.; Papadopoulos, M.; Paschali, E.; Varvarigou, A.; Stassinopoulou, C. I.; Raptopoulou, C. P.; Terzis, A.; Chiotellis, E. *J. Med. Chem.* **1994**, *37*, 3212.

0020-1669/95/1334-1077$09.00/0

Scheme 1



determined by X-ray crystallography. Complete assignments of ^1H and ^{13}C NMR resonances were made for complexes **5a−d** extending the NMR information on oxotechnetium(V) complexes with aminothiol ligands,[8] for which few data exist in the literature.[9]

Results and Discussion

Synthesis. The synthesis of complexes **5a−d** is shown in Scheme 1. 2.2′-Dithiobis(2-methylpropanal) (**1**) was synthesized according to the literature[10,11] with minor modifications. Thus, instead of bubbling N_2[10] or CO_2[11] for 15 h for the elimination of HCl, a 5 N NaOH aqueous solution was used for the same purpose.

Heterocyclic aza disulfides **3a−d**, were synthesized by successful bis-alkylation of the primary nitrogen of amines **2a−d** by the use of equimolar quantities of **1** and **2** at pH 6 in the presence of cyanohydroborate anion as the reducing agent.[12] The resulting mixtures were easily purified through column chromatography on neutral aluminum oxide since compounds **3a−d** elute first by employing a nonpolar solvent system (ether/petroleum ether, 1:10). In the ^1H-NMR spectra of **3a−d** the geminal protons of the $N(CH_2CS)_2$ portion of the heterocyclic ring appear as a nonequivalent quartet (J = 14 Hz).

Thiols **4a−d** were synthesized through Na/NH_3 reduction of the corresponding aza disulfides **3a−d**. It was found that substitution of the usual aqueous HCl in the work-up procedure[13] with a mixture of ethanol/2-propanol (2:1) saturated with gaseous HCl resulted in pure products, since oxidation of thiols **4a−d** in the aqueous environment was avoided. Thiols **4a−d** were effectively purified through flash column chromatography[14] by elution with ether and isolated as partially hygroscopic hydrochloride salts. These salts were of sufficient purity to be used directly in the synthesis of complexes **5a−d**.

The mixed complexes **5a−d** were prepared by reacting the tris-chelating ligands **4a−d** and benzyl mercaptan with a ^{99}Tc-(V) gluconate precursor[15] in a ratio of ligand to monodentate thiol, 1:1. Purification was effected through flash column chromatography. After removal of the elution solvents the residue was redissolved in a mixture of MeOH/water (85:15) and crystallized by slow evaporation of the solvents. Complexes **5a−d** were green-brown, air stable, crystalline solids, soluble in most organic solvents. Infrared spectra of each of the complexes **5a−d** showed a distinct absorption peak at a region between 928 and 934 cm^{-1} corresponding to the Tc=O stretching vibration.

X-ray Crystallographic Study of 5d. An ORTEP diagram of complex **5d** is shown in Figure 1. Selected bond distances and angles are given in Table 1. The coordination geometry around technetium can be described as trigonally distorted square pyramidal with the sulfur and nitrogen atoms in the basal plane and the doubly-bonded oxygen atom occupying the apical position. Analysis of the shape-determining angles using the approach of Addison et al.[16] yields a value for trigonality index, τ, of 0.42 for the metal (τ = 0 for perfect square pyramidal geometry and τ = 1 for perfect trigonal bipyramidal geometry). Thus, the geometry about Tc is significantly distorted. The metal−oxygen bond length, 1.664(3) Å, is within the range of several well characterized monoxo complexes of technetium.[17]

(8) (a) Stassinopoulou, C. I.; Pelecanou, M.; Mastrostamatis, S.; Chiotellis, E. *Magn. Reson. Chem.* **1994,** *32,* 532. (b) Stassinopoulou, C. I.; Mastrostamatis, S.; Papadopoulos, M.; Vavouraki, H.; Terzis, A.; Hountas, A.; Chiotellis, E. *Inorg. Chim. Acta* **1991,** *189,* 219.
(9) (a) John, C. S.; Francesconi, L. C.; Kung, H. F.; Wehrli, S.; Graczyk, G.; Carroll, P. *Polyhedron* **1992,** 11, 1145. (b) Lever, S. Z.; Baidoo, K. E.; Mahmood, A. *Inorg. Chim. Acta* **1990,** *176,* 183.
(10) Kung, H. F.; Molnar, M.; Billings, J.; Wicks, R.; Blau, M. *J. Nucl. Med.* **1984,** *25,* 326.
(11) Merz, K. W.; Specker, M. *Arch. Pharm.* **1963,** *296,* 427.
(12) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971,** *93,* 2897.
(13) Corbin, J. L.; Miller, K. F.; Pariyadath, N.; Wherland, S.; Bruce, A. E. *Inorg. Chim. Acta* **1984,** *90,* 41.
(14) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978,** *43,* 2923.
(15) Johansen, B.; Spies, H. in *Chemie und Radiopharmacologie von Technetiumcomplexen,* Akademie der Wiss. d. DDR: Dresden, Germany 1981.
(16) Addison, A. W.; Rao, T. N.; Reedijk, J.; Rijn, J.; Verschoor, G. C. *J. Chem. Soc. Dalton Trans.* **1984,** 1349.

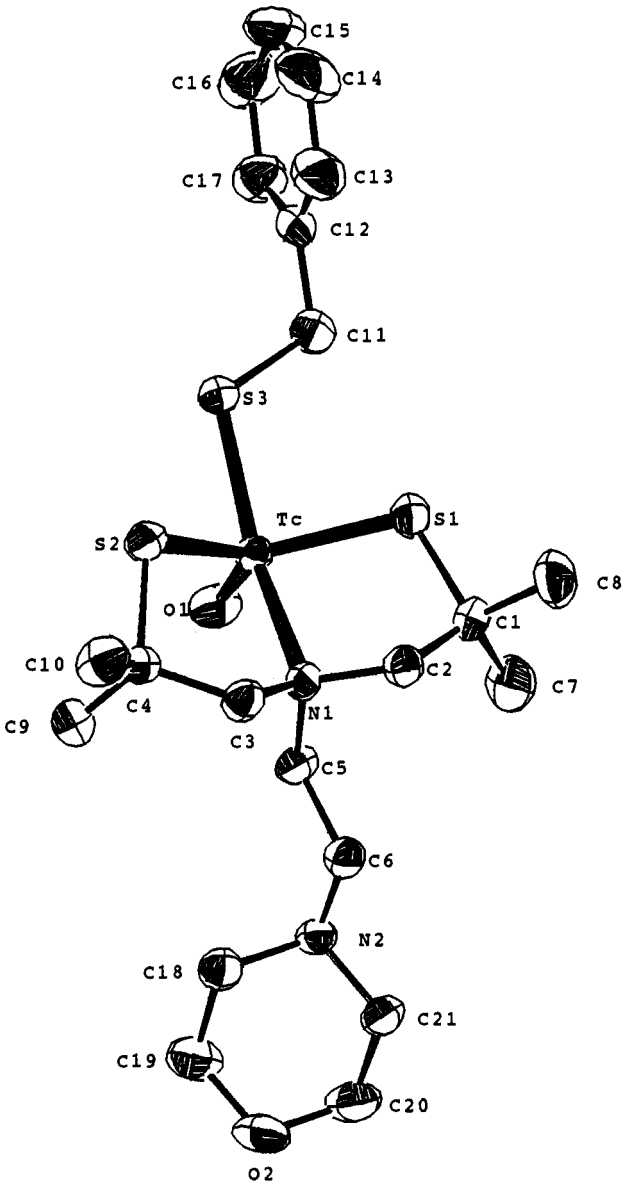


Figure 1. ORTEP diagram of complex **5d**, showing 50% probability of thermal elipsoids.

Table 1. Selected Bond Distances (Å) and Angles (deg) with Esd's

Tc–O1	1.664(3)	Tc–S2	2.284(1)
Tc–N1	2.256(3)	Tc–S3	2.288(1)
Tc–S1	2.271(1)		
O1–Tc–N1	101.1(1)	S1–Tc–S2	128.42(5)
O1–Tc–S1	115.5 (1)	O1–Tc–S3	105.2(1)
N1–Tc–S1	83.07(9)	N1–Tc–S3	153.37(9)
O1–Tc–S2	115.8(1)	S(1)–Tc–S3	88.97(4)
N1–Tc–S2	83.0(1)	S2–Tc–S3	82.20(4)

The metal–sulfur bond lengths are in the range 2.2708(13)–2.2877(12) Å and are also consistent with those for other Tc–thiolate complexes.[17] The Tc–N bond length (2.256(3) Å) was found to be slightly longer than usual (2.0–2.21 Å).[17] Of the two torsion angles that are of interest S1–C1–C2–N1 is equal to 46.4(1)° and S2–C4–C3–N1 is −46.6(1)°. The two five-membered rings formed by the atoms Tc, S1, C1, C2, N1 and by Tc, S2, C4, C3, N1 exist in the envelope form. The atom C2 is 0.504(1) Å off the mean plane defined by the atoms Tc, S1, C2, and N1 while the atom C4 is 0.689(1) Å off the plane defined by Tc, S2, C3, and N1. The atoms O1 and C5 lie 2.588(1) and 1.134(1) Å, respectively, above the plane defined by the atoms S1, S2, and N1; both are on the same side of the plane as expected for the syn isomer. The morpholine ring exists in the most stable chair form with the atom N2 lying 0.640(1) Å below the plane defined by the carbon atoms (C18–C21) and the atom O2 lying 0.672(1) Å above the plane.

(17) (a) Davison, A.; Jones, A. G.; Orving, C.; Sohn, M. *Inorg. Chem.* **1981**, *20*, 1629. (b) Bandoli, G.; Mazzi, U.; Roncari, E.; Deutch, E. *Coord. Chem. Rev.* **1982**, *44*, 191. (c) Melnik, M.; Van Lier, J. E. *Coord. Chem. Rev.* **1987**, *77*, 275. (d) Rao, T. N.; Adhikesavalu, D.; Camerman, A.; Fritzberg, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 5798. (e) Ohmoro, Y.; Francesconi, L.; Kung, M.-P.; Kung, H. F. *J. Med. Chem.* **1992**, *35*, 157.

Table 2. Summary of Crystal, Intensity Collection, and Refinement Data

empirical formula	$TcC_{21}H_{35}N_2O_2S_3$
fw	541.69
temp (K)	293
wavelength (Å)	0.710 70 (Mo Kα)
space group	$P2_1/c$
a (Å)	17.166(2)
b (Å)	8.9282(7)
c (Å)	17.738(2)
β (deg)	116.031(3)
V (Å^3)	2442.7(4)
Z	4
D_{calcd}/D_{measd} (Mg m^{-3})	1.473/1.44
abs coeff, μ (mm^{-1})	0.865
max. abs. cor mode	1.10
octants collcd	$\pm h,k,-l$
goodness-of-fit on F^2	1.046
R indices[a]	R1 = 0.0341, wR2 = 0.0707[b]

[a] $I > 2\sigma(I)$; 2769 reflections; R1 based on F, wR2 based on F^2. [b] $R1 = \sum|F_o - F_c|/\sum|F_o|$, $wR2 = (\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2])^{1/2}$.

Table 3. ^{13}C Chemical Shifts δ_C (ppm) for Complexes **5a–d**

	5a	**5b**	**5c**	**5d**
C-1 (C-4)	56.64	56.66	56.65	56.63
C-2 (C-3)	75.22	75.15	75.24	75.10
C-5	60.91	60.04	61.46	59.75
C-6	47.98	53.97	50.66	53.39
C-7 (C-9)	31.11	31.11	31.13	31.16
C-8 (C-10)	31.53	31.55	31.54	31.54
C-11	44.31	44.30	44.43	44.51
C-12	141.63	141.65	141.63	141.51
C-13 (C-17)	129.22	129.22	129.23	129.22
C-14 (C-16)	128.29	128.29	128.30	128.31
C-15	126.43	126.42	126.44	126.47
C-18	47.12	55.08	54.60	54.13
C-19	11.96	26.06	23.54	66.85
C-20	47.12	24.07	23.54	66.85
C-21	11.96	26.06	54.60	54.13
C-22		55.08		

Table 4. ^1H Chemical Shifts δ_H (ppm) for Complexes **5a–d**

	5a	**5b**	**5c**	**5d**
H-2 (H-3) *exo*	2.24	2.24	2.26	2.27
H-2 (H-3) *endo*	3.85	3.90	3.80	3.79
H-5	4.15	4.17	4.20	4.19
H-6	2.97	2.85	3.04	2.90
H-7 (H-9)	1.90	1.89	1.90	1.89
H-8 (H-10)	1.53	1.52	1.52	1.53
H-11	4.94	4.94	4.94	4.95
H-13 (H-17)	7.43	7.42	7.42	7.42
H-14 (H-16)	7.28	7.28	7.28	7.28
H-15	7.18	7.18	7.18	7.19
H-18	2.58	2.49	2.60	2.55
H-19	1.08	1.60	1.81	3.73
H-20	2.58	1.60	1.81	3.73
H-21	1.08	1.60	2.60	2.55
H-22		2.49		

NMR Studies of Complexes 5a–d. ^{13}C and ^1H chemical shifts for complexes **5a–d** are presented in Tables 3 and 4. At room temperature the two chelated S1–C1–C2–N and S2–C4–C3–N moieties gave identical carbon and proton spectra

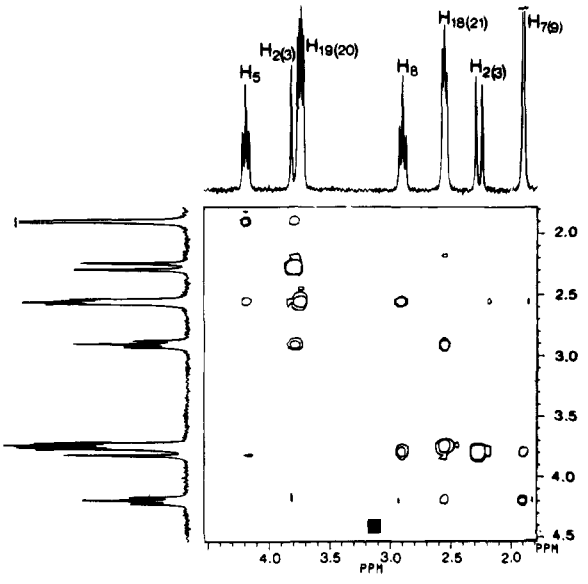


Figure 2. Phase-sensitive NOESY spectrum of complex **5d** (range δ_H 4.5−2.2). Only positive levels are plotted.

due to motional averaging of the different conformations on the NMR time scale.[8]

Assignment of carbon resonances was based on $^{13}C-^{1}H$ correlation (HETCOR[18]) experiments. Assignment of proton resonances was based on chemical reasoning and was confirmed by $^{1}H-^{1}H$ correlation (COSY[19]) and nOe spectra. For example, of the two triplet patterns assigned to H-5 and H-6 (appearing at ca. δ_H 4.2 and 2.9 in all four complexes), the downfield one at δ_H 4.2 was assigned to H-5 protons due to their proximity to the coordinated nitrogen; NOESY[20] spectra (see Figure 2 for the NOESY spectrum of complex **5d**) confirmed the assignment since protons H-18(H-21) have a relatively strong cross peak with the triplet pattern at δ_H 2.90 which reasonably belongs to the spatially close H-6.

HETCOR spectra of all complexes showed that C-2 correlates with two doublets with substantial chemical shift difference (see Figure 3 for the HETCOR spectrum of complex **5c**). These doublets were assigned to geminal H-2(H-3) protons which are magnetically differentiated according to their orientation with respect to the Tc=O core. The assignment of *endo* (close to oxygen) and *exo* (remote from oxygen) protons was based on NOESY experiments in combination with the crystallographic structure available for **5d**: the NOESY spectrum of complex **5d** (Figure 2) showed cross peaks between protons H-5 and H-6 of the free chain and only one of the doublets assigned to protons H-2(H-3), specifically the one appearing at δ_H 3.79. Since in the crystalline state complex **5d** has the *syn* configuration with the side chain directed toward the oxygen of the Tc=O core (Figure 1) the doublet at δ_H 3.79 was assigned to the *endo* H-2(H-3) protons. The chemical shift difference between *endo* and *exo* protons is ca. 1.6 ppm and is attributed to the anisotropic environment created by the Tc=O core.[8,9] Recently, similar anisotropic effects have been reported to arise from the Re=O core in monoamine−monoamide bis(thiol) complexes of oxorhenium.[21] The absolute value of the coupling constant of these geminal protons is 13.0 Hz in complexes **5a**, **5b**, and **5d** and 13.3 Hz in complex **5c**.

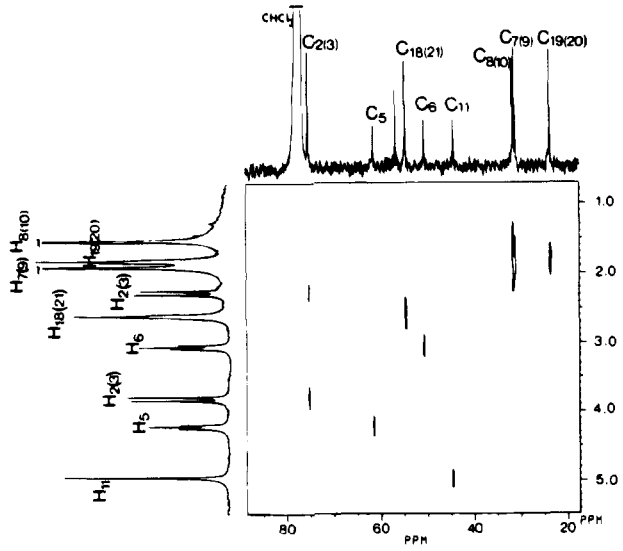


Figure 3. $^{13}C-^{1}H$ correlation spectrum of complex **5c**.

A NOESY cross peak was also observed between the H-5 protons of the side chain and one of the methyl group peaks of compound **5d** (Figure 2) allowing thus the assignment of *endo* and *exo* methyl groups. In accordance to what was observed for the geminal H-2(H-3) protons, *endo* methyl group protons (H-7(H-9)) appear downfield compared to *exo* methyl group protons (H-8(H-10)) with a $\Delta\delta_H(endo-exo) = 0.4$.

The presence of analogous cross-peaks between protons H-5, H-6 and the *endo* H-2(H-3), H-7(H-9) in the NOESY spectra of complexes **5a**, **5b**, and **5c** allowed the assumption that all complexes have the *syn* configuration. To further extend, nOe data in combination with the fact that in this type of complexes *endo* protons appear downfield compared to *exo*[8] could be used alone as a criterion for the recognition of the configuration of the side chain.

To sum up, in the present study a consice synthetic scheme for the preparation of a novel series of aza-substituted 2,6-dimethyl-4-aza-heptane-2,6-dithiol ligands (**4a−d**) was developed. These ligands form air stable, lipid soluble, neutral $^{99}TcO(V)$ complexes (**5a−d**) which were fully characterized. The X-ray crystal structure of one of the complexes (**5d**) showed trigonally distorted square pyramidal coordination geometry. X-ray and NMR data show that the configuration of the side chain is preserved in solution. The study will hopefully prove useful in the preparation and characterization of clinically useful molecules labeled with ^{99m}Tc.

Experimental Section

Caution! Technetium-99 is a low energy (0.292 MeV) β-emitter with a half-life of 2.12×10^5 years. All manipulations of solutions and solids were performed in a laboratory approved for the handling of low-level radioisotopes. Normal safety procedures were followed at all times to prevent contamination.

Synthesis. Melting points were determined using an Electrothermal 9100 capillary melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets in the range 4000−400 cm^{-1} on a Perkin-Elmer 1600 FTIR spectrophotometer and were referenced to polystyrene. NMR spectra were recorded on a Bruker FT-NMR/250 AF spectrometer and referenced to internal TMS. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer. Flash Chromatography was carried out using Merck 9385 silica gel and thin layer chromatography on Merck 5554 silica gel on aluminum sheets or on Fluka 06408 aluminum oxide on aluminum sheets. Petroleum ether refers to the fraction of bp 40−60 °C.

Preparation of 2,2′-Dithiobis(2-methylpropanal) (1). This compound was synthesized according to reported methods[10,11] with minor

(18) Bax, A.; Morris, G. *J. Magn. Reson.* **1981**, *64*, 501.
(19) Aue, W. P.; Bartholdi, E.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229.
(20) Bodenhausen, G.; Kogler, H.; Ernst, R. R. *J. Magn. Reson.* **1984**, *58*, 370.
(21) O'Neil, J. P.; Wilson, S. R.; Katzenellenbogen, J. A. *Inorg. Chem.* **1994**, *33*, 319.

modifications. Isobutyraldehyde (192.6 g, 2.675 mol) in 307 mL of carbon tetrachloride was heated at 55 °C under nitrogen and S_2Cl_2 (180 g, 1.34 mol) was added at a speed that kept the generation of HCl under control. Upon completion of the addition, aqueous 5 N NaOH was slowly added with cooling until the pH of the medium reached 10. The organic layer was separated, washed with water and brine, dried ($MgSO_4$), and filtered. Volatiles were removed under reduced pressure. The residue was distilled under vacuum (bp 97−103 °C/0.5 Torr) to give 134 g (49%) of colorless oil of **1**.

Preparation of Compounds 3a−d. The typical synthetic procedure is described for **3a**. To a solution of **1** (4 g, 19.41 mmol) in dry ($MgSO_4$) MeOH (112 mL) containing powdered molecular sieves (3 Å) were added freshly distilled (2-(diethylamino)ethyl)amine (**2a**) (2.66 g, 22.93 mmol) and sodium cyanoborohydride (1.4 g, 21 mmol). The pH of the mixture was adjusted to 6 with glacial acetic acid and stirred for 12 h under a nitrogen atmosphere. The reaction mixture was subsequently filtered through Celite. Volatiles were removed under reduced pressure and the residue was dissolved in 3 N HCl, stirred for 0.5 h at room temperature, made strongly alkaline with aqueous 5 N NaOH, and extracted with ether (2 × 50 mL). The combined organic extracts were separated, washed with water and brine, dried (K_2CO_3), filtered, and concentrated under reduced pressure. The crude product was submitted to column chromatography on neutral aluminum oxide (65 g) with ether−petroleum ether (1:10) as the eluent. The heterocyclic aza disulfide **3a** was isolated as an oil possesing the highest R_f (0.6) on TLC (aluminum oxide, ether−petroleum ether, 1:1) and analyzed as the corresponding oxalate salt.

5-(2-(Diethylamino)ethyl)-3,3,7,7-tetramethyl[1,2,5]perhydrodithiazepine (3a). Yield: 1.6 g (28%). Recrystallization from MeOH/ether afforded an analytical sample: mp 200−201 °C. Anal. Calcd for $C_{16}H_{32}N_2O_4S_2$: C, 50.49; H, 8.47; N, 7.36; S, 16.85. Found: C, 50.37; H, 8.35; N, 7.28; S, 17.74. ^{1}H NMR (δ, $CDCl_3$): 0.96 (t, 6H, Ndea$(CCH_3)_2$), 1.14 (s, 6H, $(SCCH_3)_2$), 1.27 (s, 6H, $(SCCH_3)_2$), 2.45 (q, 4H, Ndea$(CH_2)_2$), 2,60 (m, 4H, NdeaCH$_2$CH$_2$N), 2.64 (ABq, J(AB) = 14 Hz, 4H, N$(CH_2CS)_2$).

5-(2-Piperidin-1-ylethyl)-3,3,7,7-tetramethyl[1,2,5]perhydrodithiazepine (3b). Yield: 1.5 g (26%). Recrystallization from MeOH/ether afforded an analytical sample: mp 229−231 °C. Anal. Calcd for $C_{17}H_{32}N_2O_4S_2$: C, 52.01; H, 8.21; N, 7.13; S, 16.33. Found: C, 51.72; H, 8.10; N,7.13; S, 17.18. ^{1}H NMR (δ, $CDCl_3$): 1.18 (s, 6H, $(SCCH_3)_2$), 1.31 (s, 6H, $(SCCH_3)_2$), 1.48 (m, 6H, $(CH_2)_3C_2$Npip), 2.35 (m, 4H, Npip$(CH_2)_2$), 2.55 (m, 4H, NpipCH$_2$CH$_2$N), 2.69 (ABq, J(AB) = 14 Hz, 4H, N$(CH_2CS)_2$).

5-(2-Pyrrolidin-1-ylethyl)-3,3,7,7-tetramethyl[1,2,5]perhydrodithiazepine (3c). Yield: 1.5 g (27%). Recrystallization from MeOH/ether afforded an analytical sample: mp 238−240 °C. Anal. Calcd for $C_{16}H_{30}N_2O_4S_2$: C, 50.76; H, 7.98; N, 7.39; S, 16.91. Found: C, 50.80; H, 7.80; N, 7.40; S, 16.74. ^{1}H NMR (δ, $CDCl_3$): 1.19 (s, 6H, $(SCCH_3)_2$), 1.32 (s, 6H, $(SCCH_3)_2$), 1.69 (m, 4H, $(CH_2)_2C_2$Npyr), 2.42 (m, 4H, Npyr$(CH_2)_2$), 2.60 (m, 4H, NpyrCH$_2$CH$_2$N), 2.65 (ABq, J(AB) = 14Hz, 4H, N$(CH_2CS)_2$).

5-(2-Morpholin-1-yl-ethyl)-3,3,7,7-tetramethyl[1,2,5]perhydrodithiazepine (3d). Yield: 1.7 g (29%). Recrystallization from MeOH/ether afforded an analytical sample: mp 230−232 °C. Anal. Calcd for $C_{16}H_{30}N_2O_5S_2$: C, 48.70; H, 7.66; N, 7.09; S, 16.24. Found: C, 48.58; H, 7.71; N, 7.34; S, 16.65. ^{1}H NMR (δ, $CDCl_3$): 1.18 (s, 6H, $(SCCH_3)_2$), 1.31 (s, 6H, $(SCCH_3)_2$), 2.42 (m, 4H, Nmor$(CH_2)_2$), 2.62 (m, 4H, NmorCH$_2$CH$_2$N), 2.70 (ABq, J(AB) = 14Hz, 4H, N$(CH_2CS)_2$), 3.70 (t, 4H, O$(CH_2)_2$).

Preparation of Compounds 4a−d. The typical synthetic procedure is described for **4a**. Sodium (0.47 g, 0.02 mol) cut in small pieces was placed in a round-bottom flask immersed in a liquid N_2 bath. With stirring under a nitrogen atmosphere, dry (CaO lumps) liquid NH_3 (100 mL) was collected in the flask. Into the resulting deep blue solution was syringed **3a** (2.5 g, 8.62 mmol) dissolved in dry ($MgSO_4$) ether (10 mL). Stirring was continued for 0.5 h. In case of decoloration a small piece of sodium was added to restore the color of the solution. The NH_3 solvent was subsequently swept away under a stream of N_2 and a solution of ethanol/2-propanol (2:1, 90 mL) saturated with HCl was carefully added to the residue. The warm mixture was then immediately filtered to remove salt. The filtrate was condensed under reduced pressure and water (80 mL) and ether (100 mL) was added to the residue. The pH of the medium was adjusted to 8 with aqueous NaOH (2.5 N). The organic phase was separated, washed with water and brine, dried ($MgSO_4$), and filtered. The filtrate was directly absorbed on silica gel and flash chromatographed with ether as the eluent, to afford compound **4a** as an oil which was directly converted to the corresponding partially hygroscopic **4a**·2HCl salt and analyzed as the corresponding oxalate salt.

2,6-Dimethyl-4-(2-(diethylamino)ethyl)-4-aza-2,6-heptanedithiol (4a). Yield: 2.16 g (86%). Recrystallization from MeOH/ether afforded an analytical sample: mp 200−201 °C. Anal. Calcd for $C_{16}H_{34}N_2O_4S_2$: C, 50.23; H, 8.95; N, 7.32; S, 16.73. Found: C, 49.74; H, 8.63; N, 7.21; S, 17.22. ^{1}H NMR (δ, D_2O) of **4a**·2HCl: 1.37 (t, 6H, Ndea$(CCH_3)_2$), 1.62 (s, 12H, $(SC(CH_3)_2)_2$), 3.36 (q, 4H, Ndea$(CH_2)_2$), 3.70 (s, 4H, N$(CH_2CS)_2$), 3.90, 4.13 (AA′BB′m, 4H, NdeaCH$_2$CH$_2$N).

2,6-Dimethyl-4-(2-piperidin-1-ylethyl)-4-aza-2,6-heptanedithiol (4b). Yield: 2.21 g (88%). Recrystallization from MeOH/ether afforded an analytical sample: mp 198−199 °C. Anal. Calcd for $C_{17}H_{34}N_2O_4S_2$: C, 51.74; H, 8.68; N, 7.09; S, 16.23. Found: C, 51.36; H, 8.18; N, 7.12; S, 16.25. ^{1}H NMR (δ, D_2O) of **4b**·2HCl: 1.59 (s, 12H, (SC$(CH_3)_2)_2$), 1.86 (m, 6H, $(CH_2)_3C_2$Npip), 3.66 (s, 4H, N$(CH_2CS)_2$), 3.84, 4.09 (AA′BB′m, 4H, NpipCH$_2$CH$_2$N).

2,6-Dimethyl-4-(2-pyrrolidin-1-ylethyl)-4-aza-2,6-heptanedithiol (4c). Yield: 2.21 g (88%). Recrystallization from MeOH/ether afforded an analytical sample: mp 199−200 °C. Anal. Calcd for $C_{16}H_{32}N_2O_4S_2$: C, 50.49; H, 8.47; N, 7.36; S, 16.84. Found: C, 50.43; H, 8.79; N, 7.68; S, 17.57. ^{1}H NMR (δ, D_2O) of **4c**·2HCl: 1.62 (s, 12H, $(SC(CH_3)_2)_2$), 2.15 (m, 4H, $(CH_2)_2C_2$Npyr), 3.25 (m, 2H, $(CH)_2$Npyr), 3.70 (s, 4H, N$(CH_2CS)_2$), 3.85 (m, 2H, $(CH)_2$Npyr), 4.00, 4.15 (AA′BB′m, 4H, NpyrCH$_2$CH$_2$N).

2,6-Dimethyl-4-(2-morpholin-4-ylethyl)-4-aza-2,6-heptanedithiol (4d). Yield: 2.31 g (92%). Recrystallization from MeOH/ether afforded an analytical sample: mp 206−207 °C. Anal. Calcd for $C_{16}H_{32}N_2O_5S_2$: C, 48.45; H, 8.13; N, 7.06; S, 16.17. Found: C, 48.35; H, 7.62; N, 6.95; S, 16.87. ^{1}H NMR (δ, D_2O) of **4d**·2HCl: 1.60 (s, 12H, $(SC(CH_3)_2)_2$), 3.48, (s, 4H, N$(CH_2CS)_2$), 3.55 (m, 4H, $(CH_2)_2$Nmor), 3.82, 3.92 (AA′BB′m, 4H, NmorCH$_2$CH$_2$N), 4.12 (m, 4H, $(CH_2)_2$Omor).

Preparation of Complexes 5a−d. The typical synthetic procedure is described for **5a**.

Solution A. To a solution of $NH_4{}^{99}TcO_4$ (36.2 mg, 0.2 mmol) and sodium gluconate (200 mg) in H_2O (3.5 mL) containing 0.1 mL of $^{99m}TcO_4^-$ (0.5 mCi) a solution of stannous chloride (45 mg, 0.24 mmol) in aqueous HCl (0.1 N, 2 mL) was added. The pH of the medium was brought up to 8 with aqueous NaOH (2.5 N).

Solution B. **4a**·2HCl (73.09 mg, 0.2 mmol) was dissolved in H_2O (2.0 mL) and the pH of the solution was brought up to 8 with aqueous NaOH (2.5 N). To the resulting solution was added benzyl mercaptan (24.84 mg, 0.2 mmol). Solution A was added dropwise and with stirring to solution B. Immediate formation of an oil was observed and stirring was continued for 1.5 h at room temperature. At the end of this period the mixture was diluted with water (50 mL) and extracted with dichloromethane (2 × 50 mL). The organic phase was separated, washed with water and brine, dried ($MgSO_4$), and filtered. Flash chromatography of the residue, after evaporation of the solvent under reduced pressure at room temperature, with ether and subsequently with acetone as the eluents, afforded **5a** as an oil. Crystals were obtained by addition of a mixture of MeOH/water (85:15) to the residue and slow evaporation of the solvents.

[Benzylthiolato][*N*,*N*-bis(2,2-dimethyl-2-mercaptoethyl)(2-(diethylamino)ethyl)amine]oxotechnetium(V) (5a). Yield: 82 mg (78%). Anal. Calcd for $C_{21}H_{37}N_2S_3OTc{\cdot}^1/_2H_2O$: C, 46.90; H,7.13; N,5.21; S, 17.87. Found: C, 45.82; H, 6.44; N, 5.54; S, 17.04. FTIR (cm^{-1}, KBr): 934 (Tc=O). See Tables 3 and 4 for detailed ^{1}H and ^{13}C NMR data.

[Benzylthiolato][*N*,*N*-bis(2,2-dimethyl-2-mercaptoethyl)(2-piperidin-1-ylethyl)amine]oxotechnetium (V) (5b). Yield: 90 mg (84%). Anal. Calcd for $C_{22}H_{37}N_2S_3OTc$: C, 48.86; H, 6.89; N,5.18; S, 17.78. Found C, 48.48; H, 6.55; N, 5.73; S, 16.75. FTIR (cm^{-1}, KBr): 934 (Tc=O). See Tables 3 and 4 for detailed ^{1}H and ^{13}C NMR data.

[Benzylthiolato][*N,N*-bis(2,2-dimethyl-2-mercaptoethyl)(2-pyrrolidin-1-ylethyl)amine]oxotechnetium(V) (5c). Yield: 78 mg (74%). Anal. Calcd for $C_{21}H_{35}N_2S_3OTc.H_2O$: C, 46.29; H, 6.84; N, 5.14; S, 17.66. Found: C, 46.20; H, 6.85; N, 4.67; S, 17.63. FTIR (cm^{-1}, KBr): 928 (Tc=O). See Tables 3 and 4 for detailed ^1H and ^{13}C NMR data.

[Benzylthiolato][*N,N*-bis(2,2-dimethyl-2-mercaptoethyl)(2-morpholin-4-ylethyl)amine]oxotechnetium(V) (5d). Yield: 93 mg (87%). Anal. Calcd for $C_{21}H_{35}N_2S_3O_2Tc$: C, 46.47; H, 6.50; N, 5.16; S, 17.72. Found: C, 46.23; H, 6.18, N, 5.40; S, 17.32. FTIR (cm^{-1}, KBr): 928 (Tc=O). See Tables 3 and 4 for detailed ^1H and ^{13}C NMR data.

X-ray Crystal Structure Determination of Complex 5d. Slow evaporation from a mixture of MeOH/water (85:15) yielded brown prismatic crystals. A crystal with approximate dimensions 0.18 × 0.25 × 0.30 mm was mounted in air. Diffraction measurements were made on a $P2_1$ Nicolet diffractometer upgraded by Crystal Logic using Zr-filtered Mo radiation. Unit cell dimensions were determined and refined by using the angular settings of 24 automatically centered reflections in the range $11 < 2\theta < 24$, and they appear in Table 1. Intensity data were recorded using a $\theta-2\theta$ scan to $2\theta_{max} = 49°$ with scan speed 1.5 deg/min and scan range 2.4 plus $\alpha_1\alpha_2$ separation. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization, and absorption corrections were applied using Crystal Logic software. Symmetry equivalent data were averaged with $R = 0.0188$ to give 4021 independed reflections from a total 4173 collected. The structure was solved by direct methods using SHELXS-86[22] and refined by full-matrix least-squares techniques on F^2 with SHELXL-93[23] using 4017 reflections and refining 402 parameters. All hydrogen atoms were located by difference maps and their positions were refined isotropically. All non-hydrogen atoms were refined anisotropically. The final values for R1, wR2, and GOF for observed data are in Table 1; for all data they are 0.0749, 0.1837 and 1.080 respectively. The maximum and minimum residual peaks in the final difference map were +0.387 and −0.304 e/Å^3. The largest shift/esd in the final cycle was 0.005. Selected bond distances and angles are given in Table 2. Atomic scattering factors were from ref 24 .

NMR 2D Structural Studies of Complexes 5a−d. The ^1H (250.13 MHz) and ^{13}C (62.90 MHz) NMR spectra were recorded on a Bruker AC 250E spectrometer equipped with an Aspect 3000 computer (using the DISNMR program, version 1991) and a 5 mm $^{13}C/^1H$ dual probe head (^1H 90° pulse width = 10.2 μs; ^{13}C 90° pulse width = 10.4 s). Samples were dissolved in $CDCl_3$ at a concentration of ca. 1−2%. The temperature of the experiments was 25 °C. Chemical shifts δ ppm) are relative to internal TMS.

2D $^1H-^1H$ shift correlated spectra (COSY) were acquired with a spectral window of 2090 Hz, 1024 data points, 256 t_1 increments, and a 1 s relaxation delay between pulse cycles. The data were processed by applying a sine−bell (nonshifted) multiplication in both dimensions and by zero-filling to 512 data points in the F_1 dimension. After inspection the final matrix (digital resolution 4.1 Hz/pt) was symmetrized.

Phase-sensitive NOESY spectra were acquired with the same parameters as for the COSY experiment and a mixing time of 1 s. The data were processed by applying a sine-bell squared ($\pi/2$ shifted) multiplication in both dimensions and by zero-filling to 1024 data points in the F_1 dimension. After inspection the final matrix was symmetrized.

2D $^{13}C-^1H$ shift correlated spectra (HETCOR) were obtained with spectral windows of 2090 Hz in the F_1 dimension and 10200 Hz in the F_2 dimension, 2048 data points, 128 t_1 increments and relaxation delay of 1 s. The experiment was optimized for $J(^{13}C, ^1H) = 130$ Hz. The data were processed by applying a sine−bell ($\pi/2$ shifted) multiplication in both dimensions and by zero-filling to 256 data points in the F_1 dimension. Digital resolution was 16.3 Hz/pt in the F_1 dimension and 10.0 Hz/pt in the F_2 dimension.

Acknowledgment. C.P.R. is grateful to John Boutari and Son Co. for financial support.

Supplementary Material Available: Tables of fractional atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms, fractional atomic coordinates of H-atoms, and full bond lengths and angles (5 pages). Ordering information is given on any current masthead page.

IC9409367

(22) Sheldrick, G. M. *SHELXS-86: Structure Solving Program*; University of Gottingen: Gottingen, Germany, 1993.
(23) Sheldrick, G. M. *SHELXL-93: Program for Crystal Structure Refinement*, University of Gottingen: Gottingen, Germany, 1993.
(24) *International Tables for X-ray Crystallography*, Kynoch Press: Birmingham, 1974; Vol. IV.