

STUDIES OF THE CHEMISTRY OF TECHNETIUM(V)

by

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To my parents, on the occasion
of my father's retirement.

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Submitted to the Department of Chemistry in May, 1981, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

ABSTRACT

Chapter 1

The isolation of the ^{99}Tc compound $(\text{Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$ (1) as the major product in the reduction of TcO_4^- by a large molar excess of 10% thioglycolic acid at pH 7.5 shows that the +5 oxidation state of Tc can be stabilized in aqueous solution by the appropriate choice of ligands. Further, the avidity of Tc for an impurity in this preparation suggests caution be exercised in assuming that a particular $^{99\text{m}}\text{Tc}$ -radiopharmaceutical is simply a complex of technetium with the intended ligand. The cis form of 1 was characterized by a single crystal X-ray structural determination. The anion is pentacoordinate and has a very nearly square pyramidal arrangement of the donor atoms. The oxygen occupies the apex of the pyramid with the sulfur atoms in the base. The average Tc-S distance is 2.325(3) Å, with the Tc-O distance being 1.672(8) Å. The technetium atom lies 0.791 Å above the basal plane of the sulfur atoms. The trans form of the anion was observed in the ^1H NMR of the crude product of the reaction of TcOCl_4^- with an authentic sample of HSCH_2COSH , but the geometric isomers were not separable by fractional crystallization. The structurally similar $(\text{Bu}_4\text{N})[\text{TcO}(\text{S}_2\text{C}_6\text{H}_3(\text{CH}_3))_2]$ was prepared by the dithionite reduction of TcO_4^- in aqueous alkaline medium in the presence of 3,4-toluenedithiol. It is the first anionic transition metal complex to be identified by cation field desorption mass spectrometry.

Chapter 2

The compound $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ was prepared by the dithionite reduction of TcO_4^- in aqueous alkaline medium in the presence of β -mercaptoethanol. The X-ray crystal structure of this compound shows that the anion is square-pyramidal, with an apical oxo-oxygen and the β -mercaptoethanolate ligands arranged in cis fashion, defining the basal plane. The average Tc-S distance (2.290 Å) and the Tc-O (apical) distance (1.662 Å) compare favorably with the corresponding distances in $(\text{Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$. The average Tc-O (ligand) distance is 1.950 Å. These structural results support the literature report of the isolation of bis(2-mercaptopropionate)oxotechnetate(V).

Chapter 3

The complexes $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$ (1) and $(\text{Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$ (2) have been prepared by reacting TcOCl_4^- with the respective diols in methanol. The compound 1 was identified by its elemental analysis and field desorption mass spectrum. Compound 2 was positively identified by its X-ray crystal structure. The anion of 2 is square pyramidal, as seen for the structurally characterized TcOS_4 and TcOS_2O_2 complexes discussed in the previous chapters. Compound 1 is hydrolytically unstable in pure water, but can be stabilized by the addition of a several-fold molar excess of ethylene glycol. Compound 2 decomposes minimally in pure water after $99\frac{3}{4}$ hours. These complexes are shown to be good structural models for $^{99\text{m}}\text{Tc}$ -radiopharmaceuticals containing purely oxygen-donor ligands.

Comparison of the physical properties of the structurally characterized members of the series of complexes with core structures $\text{TcOS}_x\text{O}_{(4-x)}$ ($x = 0, 2, 4$) shows a shift to low energy in the frequency of the terminal oxygen-technetium band in the IR correlated with increasing softness of the basal plane donor atom set.

Chapter 4

The ligand exchange reactions of various oxotechnetium(V) complexes with 1,2-dithiols have been investigated. The complexes $\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2$ (1), $\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2^-$ (2), and $\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2^-$ (3) all react with 2 equivalents of 1,2-ethanedithiol to ultimately form $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ (4). Different mechanisms and/or intermediates are observed in each case, however. The reaction of 1 proceeds without evidence for the formation of intermediates; an intermediate is detected in the reaction of 2, and is probably a mixed ligand oxotechnetium monomer; and the spectrum of the intermediate formed in the reaction of 3 with 1,2-ethanedithiol is similar to that of the dimer species $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{S})_3$ (5). The relation of these results to ligand exchange reactions of 1,2-dithiols with citrate complexes of technetium is discussed. Reaction of 1,3-propanedithiol with TcOCl_4^- gives a compound formulated as $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_3$, which does not react with further amounts of ligand to form the bis(1,3-dithiolato) monomer, as is anticipated from the sequential formation of 4 from 5 in the reaction of TcOCl_4^- with 1,2-ethanedithiol. The complex $\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2^-$ reacts with 1,2-ethanedithiol to form 4, and the reaction is acid-catalyzed. A simple kinetic study of the catalyzed reaction suggests the formation of a monomeric intermediate.

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Foreword

Nuclear medicine¹ is relying increasingly upon radiopharmaceuticals containing the metastable isomer of technetium (^{99m}Tc) as agents of choice for imaging organ systems in the diagnosis of disease². This widespread use³ is due to the favorable nuclear properties of ^{99m}Tc, which decays by emission of a 140 keV gamma ray and has a half-life of only 6 hours. The energy of the gamma ray is optimal for detection by current instrumentation, and the combination of gamma energy and short half-life allows a relatively large amount to be administered for better image quality^{4a,b}, with very low radiation dose^{5a,b,c} to the patient. Chemically, the element has been combined with a variety of ligands to produce highly specific radiopharmaceuticals for imaging bones, kidney, liver, gall bladder, blood pool, etc.

Ironically, although it lies in the very center of the d-block of the periodic table, little was known about the chemistry^{6a-d} of technetium, especially in the aqueous media universally used in radiopharmaceutical preparation, as late as 1976. The concentration of technetium in a typical preparation is 10^{-8} - 10^{-9} M, (i.e., less than 2 ng of ^{99m}Tc per 10 mCi patient dose), which precludes characterization by most of the traditional methods of inorganic chemistry.

There has been a generally accepted "conventional wisdom" in nuclear medicine^{7a,b} that technetium is most stable in aqueous solution in the +7 or +4 oxidation state. The former state is represented by pertechnetate (TcO_4^-), which itself is used for brain and thyroid imaging, and the latter state is justified by the ubiquitous formation of insoluble TcO_2 under reducing conditions in aqueous media. The well-known⁸ kinetic stability of octahedral d^3 complexes was assumed to be operative in

radiopharmaceutical preparations where pertechnetate is reduced in the presence of an excess of a potentially chelating ligand. Eckelman and co-workers^{9a,b,c} concluded from several lines of evidence that the most probable oxidation state of ^{99m}Tc in radiopharmaceuticals is +4. However, no water-stable complex of Tc(IV) was isolated.

We have used the long-lived radionuclide ^{99}Tc , a β^- -emitter with a half-life of 212,000 years, to investigate the chemistry of technetium on a scale amenable to the use of commonly available methods of study. By isolating macroscopic amounts of ^{99}Tc -containing complexes, and determining their structures and reactivity, we have tried to add to the fund of chemical knowledge of this element, and hopefully contributed to the design and synthesis of the improved radiopharmaceuticals of the future. The results of this research are described in the following chapters.

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CHAPTER I

Synthesis and Characterization of Some
Bis(1,2-dithiolato)Oxotechnetium(V) Complexes

INTRODUCTION .

In order to learn something about the chemical state of ^{99m}Tc in radiopharmaceuticals, it was deemed desirable to investigate the chemistry of ^{99}Tc complexes, especially water soluble ones where the metal oxidation state is less than +7. Unfortunately, no such complexes were known^{1a-c} at the outset of this work. The hexahalotechnetate(IV) complexes (TcX_6^{2-} ; X=Cl, Br, I) were well-characterized², but their stability in aqueous media is restricted to the concentrated hydrohalic acid solutions in which they are synthesized.

Our approach to this problem was to survey the analytical literature for colorimetric methods for determining technetium. A number of these had been developed because of the growing amounts of ^{99}Tc being produced as a by-product of nuclear reactor operation. These analytical methods include reactions with potassium xanthate³, dimethylglyoxime/stannous chloride³, thiourea³, potassium thiocyanate³, and 1,5-diphenylcarbohydrazide⁴. These reactions take place in 1-2-N acid media, still unacceptably far-removed from physiological pH (7.4).

The reported reaction of technetium with thioglycolic acid⁵ at pH 8 appeared to be worthy of closer investigation. The remarkable isolation⁶ of $\text{TcO}(\text{SCH}_2\text{COS})_2^-$ from this solution, a square pyramidal complex of Tc(V) coordinated by four sulfur atoms in the basal plane, pointed to a totally unexpected new class⁷ of water-stable technetium complexes. With this knowledge, the rational synthesis⁸ of the 3,4-toluenedithiolate analog $\text{TcO}(\text{S}_2\text{C}_6\text{H}_3(\text{CH}_3))_2^-$ was successfully undertaken.

These two complexes, discussed in the present chapter, represent the first well-characterized examples of the Tc(V)OS_4 core.

EXPERIMENTAL

Technetium as $\text{NH}_4^{99}\text{TcO}_4$ in aqueous solution was obtained from New England Nuclear. The concentration was determined⁹ by measuring the absorbance at 244 nm ($\epsilon = 6,220 \text{ L mole}^{-1} \text{ cm}^{-1}$). ^{99}Tc is a weak β^- emitter (0.292 keV; half-life 2.12×10^5 years); therefore, all manipulations were carried out in a licensed radiation laboratory¹⁰ with a monitored fume hood. Personnel wore lab coats and disposable gloves at all times. All wastes were disposed of in accordance with the regulations of the Harvard University Radiation Protection Office or the M.I.T. Radiation Protection Office. Samples sent outside of the laboratories' jurisdiction were wipe-tested prior to shipment, and all regulations¹¹ regarding such transportation were followed. Microanalyses of elements other than Tc were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y., and Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

Thioglycolic acid was obtained from either Fisher or MCB. 3,4-toluene-dithiol was purchased from Aldrich. Sodium dithionite was obtained from Fisher.

Mercaptothioacetic acid (HSCH_2COSH) was obtained by a modification of the procedure¹² of Satsumabayashi. Chlorothioacetic acid was prepared as described¹², by the reaction of chloroacetyl chloride with H_2S . This was converted into mercaptothioacetic acid as follows. A solution of KOH (31.2 g) in 95 mL of $\text{EtOH}/\text{H}_2\text{O}$ (95% v/v) was saturated with H_2S gas at 0°C (ca. 0.75 h). This solution was cooled to -5°C and ClCH_2COSH (10.4 g) was added dropwise over 2.5 h. KCl was removed by filtration, and the filtrate was concentrated to ca. 30 mL. The resulting solution was acidified (pH 3) with ice-cold 3N HCl and extracted with Et_2O . This procedure was repeated; the combined ether extracts were evaporated in

vacuo, and benzene (100 mL) was added. The mixture was fractionated by distillation: mercaptothioacetic acid (8.1 g, 79%), bp 40°C (2 mm Hg); ^1H NMR (CCl_4) δ 1.96 (t, $J = 8.5$ Hz, 1H), 3.38 (d, $J = 8.5$ Hz, 2H), 4.60 (br s, 1H).

Infra-red spectra were recorded on a Perkin-Elmer 180 grating spectrophotometer in the range 4000-200 cm^{-1} as KBr pellets. Optical spectra were obtained with a Cary Model 17 spectrophotometer. NMR spectra were measured on either a Bruker 270-MHz spectrometer or a Perkin-Elmer Hitachi R24B 60-MHz spectrometer. Magnetic susceptibilities were obtained on a home-built Faraday balance with a Varian V-4005 electromagnet with constant-force pole faces and a Cahn RG electrobalance. Diamagnetic corrections were taken from published tables¹³, and the magnetic moment was derived from the expression:

$$\mu_{\text{eff}} = 2.84(\chi_{\text{m}}^{\text{corr}} T)^{\frac{1}{2}}$$

$\text{HgCo}(\text{SCN})_4$ was used as the calibrant.

Field desorption mass spectra were obtained¹⁴ with a Varian MAT 731 double focusing mass spectrometer fitted with a combination EI/FI/FD ion source. Carbon activated tungsten wire emitters were loaded by dipping them into a methylene chloride solution of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{S}_2\text{C}_6\text{H}_3(\text{CH}_3)_2)_2]$. The compound was desorbed at emitter currents of 22-26 mA. Best overall results were obtained with a source temperature of between 160° and 200°C. Spectra were recorded on an oscillographic recorder, and mass assignments were based on the instrument's mass marker which had been calibrated with tris(pentafluoroethyl)-S-triazine and tris(pentadecafluoroheptyl)-S-triazine, obtained from P.C.R., Inc.

Preparation¹⁵ of (n-Bu₄N)[TcOCl₄]

A 50 mL beaker equipped with a Teflon-jacketed stir bar was filled with 32 mL of 12N hydrochloric acid. To the stirred solution 4.0 mL of 0.32 M (1.28 mmol) NH₄TcO₄ in water was added. After 10 minutes, 4.0 mL of a 75% w/v tetrabutylammonium chloride solution (Eastman) were added dropwise to the green solution. The resultant gray-green microcrystalline powder was filtered and collected on a medium porosity fritted filter. The solid was washed with 3.0 mL of 12N hydrochloric acid, followed by five 3.0 mL aliquots of isopropanol. The solid was dried in vacuo for two hours. The yield is 0.63 g (99%, based on ammonium pertechnetate).

Analysis, C₁₆H₃₆Cl₄NO₃Tc, calcd: C, 38.49; H, 7.27; N, 2.81; Cl, 28.40.
found: C, 38.42; H, 7.22; N, 2.67; Cl, 28.04.

Preparation of Tetrabutylammoniumbis(mercaptothioacetato)oxotechnetate (V).

To a solution consisting of 6 mL (86.3 mmol) of thioglycolic acid and 54 mL of water, adjusted to pH 7.5 with 50% w/v and 2.5% w/v aqueous NaOH, was added 2.1 mL of a 0.34 M (0.71 mmol) NH₄TcO₄ solution. After 8 minutes of stirring, a concentrated solution of n-Bu₄NBr in 10 mL of water was added to the dark brown solution. After 4 hours, the mixture was filtered, washed with water, and then air-dried. The solid was extracted with two 4 mL aliquots of methanol and then air-dried again. The remaining solid was recrystallized from acetone/water, filtered, washed with water and methanol, and then dried in vacuo. The yield of orange brown crystals of (n-Bu₄N)[TcO(SCH₂COS)₂] was 0.09 g (22%, based on Tc).

Analysis, C₂₀H₄₀NO₃S₄Tc, calcd: C, 42.18; H, 7.03; N, 2.46; S, 22.50.
found: C, 41.38; H, 7.90; N, 2.80; S, 21.69.

Reaction of TcOCl_4^- with HSCH_2COSH

A solution of 12 μL (1.2×10^{-4} mol) of HSCH_2COSH in 10 mL of MeOH was added dropwise to a solution of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ (0.027 g, 5.37×10^{-5} mol) in 10 mL of MeOH. The yellow-brown reaction mixture began to deposit a fine, dark solid within a few minutes. To this mixture was added 1 mL of NaOH solution (pH 11) followed immediately by 1.5 mL of $n\text{-Bu}_4\text{NCl}$ (50% w/v H_2O). The solvent was removed by rotary evaporation, and the resulting solid was separated and washed with water. The solid was dissolved in acetone and filtered, and water was added to the filtrate to the point of incipient crystallization. After 24 hours at room temperature, two types of crystals were observed: light yellow needles and dark yellow-brown plates. These were separated by filtration; attempts to separate the mixture by fractional crystallization were not successful. A 270-MHz ^1H NMR (in CD_2Cl_2) spectrum of the combined reaction products indicated that there are two components. The methylene protons of the (SCH_2COS) ligand appear as two AB pairs (δ 3.93, $J_{\text{AB}} = 17.3$ Hz; δ 3.87, $J_{\text{AB}} = 14.8$ Hz). The optical spectra and infrared spectra of the various fractions were similar to those of the cis- $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$ obtained in the original preparation described above.

Preparation of Tetrabutylammoniumbis(3,4-toluenedithiolato)oxotechnetate(V)

After 0.2474 g of 3,4-toluenedithiol (1.59 mmol) was dissolved in 50 mL of 0.6 M NaOH solution, 2.25 mL of 0.325 M NH_4TcO_4 solution (0.792 mmol) was added. A freshly prepared solution of 0.555 g $\text{Na}_2\text{S}_2\text{O}_4$ (3.19 mmol) in 10 mL of 0.6 M NaOH was added to the reaction mixture dropwise, followed one minute later by 1.0 mL of 50% w/v $n\text{-Bu}_4\text{NCl}$ in H_2O . After five minutes of stirring the suspension was filtered, and the solids washed with a few milliliters of the hydroxide solution and distilled

water. The crude precipitate was extracted three times with 5 mL aliquots of acetone. The combined filtered extracts were mixed with 5 mL of water and stored for 24 hours at -23°C . The resulting crystals were filtered, washed with water, and dried for 12 hours in vacuo. The yield of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{S}_2\text{C}_6\text{H}_3(\text{CH}_3))_2]$ was 0.184 g (35% based on Tc).

Analysis, $\text{C}_{30}\text{H}_{48}\text{NOS}_4\text{Tc}$, calcd: C, 54.14; H, 7.22; N, 2.11; S, 19.25.
found: C, 54.30; H, 7.23; N, 2.11; S, 20.56.

Attempted Coordination of Pyridine

A sample of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$ was dissolved in methylene chloride and its optical spectrum compared to samples prepared in methylene chloride/pyridine medium ranging from a ratio of 10:1 methylene chloride:pyridine to neat pyridine. In each case, no change in the absorption spectrum of the anion could be discerned.

Attempted Reaction with Me_2SO

A solution composed of 25 mL of ethanol, 4 mL of acetonitrile, and 1.0 mL (14.0 mmol) of dimethylsulfoxide was refluxed with 0.016 g (0.024 mmol) of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{S}_2\text{C}_6\text{H}_3(\text{CH}_3))_2]$ for 24 hours. Only starting material could be recovered.

X-Ray Crystallographic Study of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$

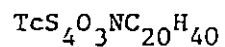
Crystals of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$ suitable for x-ray diffraction studies were obtained by slow evaporation of an acetone/ H_2O solution of the purified compound. Experimental¹⁶ details are summarized in Tables 1 through 3.

Table I

Structure Determination of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$

A. Crystal Data

A. Crystal Data



F.W. 569.80

F(000) = 600

Crystal dimensions: 0.10 x 0.30 x 0.35 mm

Peak width at half-height = 0.20°

Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$)

Temperature = 23 \pm 1°C

Monoclinic (C-centered) space group C_m (confirmed by refinement).

a = 10.451(5) \AA

b = 14.855(8) \AA

c = 9.927(7) \AA

$\alpha = 90^\circ$

$\beta = 114.88(5)^\circ$

$\gamma = 90^\circ$

V = 1398.1 \AA^3

Z = 2

$\rho = 1.356 \text{ g/cm}^3$ (calcd)

$\mu = 8.19 \text{ cm}^{-1}$

Table 2

Structure Determination of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$

B. Intensity Measurements

B. Intensity Measurements

Instrument:	Enraf-Nonius CAD4 diffractometer
Monochromator:	Graphite crystal, incident beam
Take-off angle:	2.8°
Counter aperture width:	2.0 mm
Crystal-to-detector distance:	21 cm
Scan type:	θ-2θ
Scan rate:	4° to 20°/min
Scan range:	From 2θ(MoKα ₁)-0.8° to 2θ(MoKα ₂)+0.8°
Range of data:	0° < 2θ(MoKα) < 60°
No. of reflections measured:	2267 total, 2207 unique
Corrections:	Lorentz and polarization Intensity ^a Absorption ^b

a) Intensities and standard deviations on intensities were calculated using the following formulas:

$$I = S(C-RB)$$
$$\sigma(I) = [S^2(C+R^2B)+(pI)^2]^{\frac{1}{2}}$$

where S is the scan rate, C is the total integrated peak count, R is the ratio of scan time to background counting time (= 2.0 here), B is the total background count, and the parameter p is a factor introduced to downweight intense reflections. Here p was set to 0.05.

b) An absorption correction was made using an empirical ψ scan correction. The structure factor was divided by a correction factor varying from 0.727 to 1.000 with an average correction of 0.829.

Table 3

Structure Determination of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$

C. Structure Solution and Refinement

C. Structure Solution and Refinement

Solution:	Patterson method
Hydrogen atoms:	Not included
Refinement:	Full-matrix least-squares
Minimization function:	$\Sigma w(F_o - F_c)^2$
Least-squares weights:	$4F_o^2/\sigma^2(F_o^2)$
Anomalous dispersion:	All non-hydrogen atoms
Reflections included:	1248 with $F_o^2 > 3.0\sigma(F_o^2)$
Parameters refined:	126
Unweighted agreement factor:	0.082
Weighted agreement factor:	0.091
E.s.d. of observation of unit weight:	2.416
Maximum parameter shift:	0.1 times its e.s.d.
Highest peak in final difference Fourier:	< 0.5 carbon atom

RESULTS AND DISCUSSION

Incubation of TcO_4^- in a 10% solution of thioglycolic acid, adjusted to pH 7.4, yields a yellow-brown precipitate with Bu_4NBr which is easily crystallized⁶ from acetone/water. The elemental analysis of this material suggested the presence of an abundance of sulfur, and along with its infrared (Figure 1) and optical (Figure 2) spectra, did not suffice to identify it. A crystal was therefore submitted¹⁶ for x-ray diffraction analysis. The compound was determined to be $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$ (1), and the structure of the anion is shown in Figure 3.

In the anion the technetium atom is coordinated by an oxygen and four sulfur atoms in very nearly a square pyramid, with the sulfur atoms forming the basal plane and the oxygen atom the apex. Table 4 lists the bond lengths for this compound, and Table 5 gives the bond angles. The technetium atom lies 0.791 \AA above the basal plane, and the Tc-O_1 line is perpendicular to the least squares plane formed by the four sulfur atoms.

The anion was found to lie on a crystallographic mirror plane. The n-butylammonium cation was also found on the mirror plane and determined to be 50-50 disordered in all n-butyl chains. The bond lengths and angles in the cation are otherwise unremarkable. Final positional and thermal parameters for this compound are given in Appendix 1.

The oxidation state of technetium in 1 is easily seen to be +5. It is weakly paramagnetic in the solid state. The effective moment, which is field strength dependent, lies in the range $1.2\text{--}1.5 \mu_B$ (295 K). Similar behavior is found for some oxomolybdenum and oxorhenium complexes, with a d^2 configuration having local C_{4v} symmetry, where the ground state is expected to be 1A_1 . This has been suggested^{17a,b} to be due to temperature-independent paramagnetism.

Figure 1

Infrared Spectrum of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$

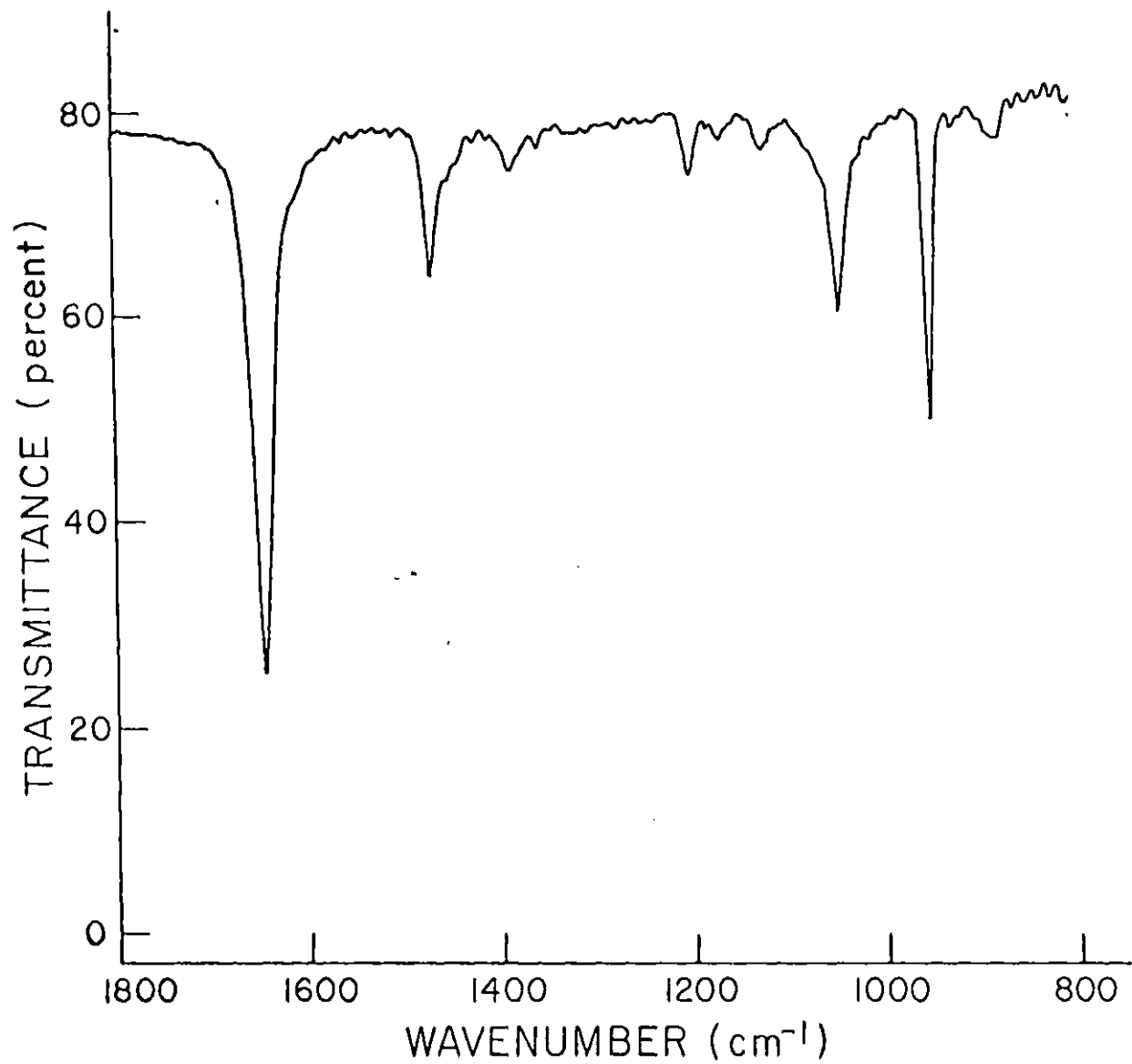


Figure 2

Electronic Spectrum of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$

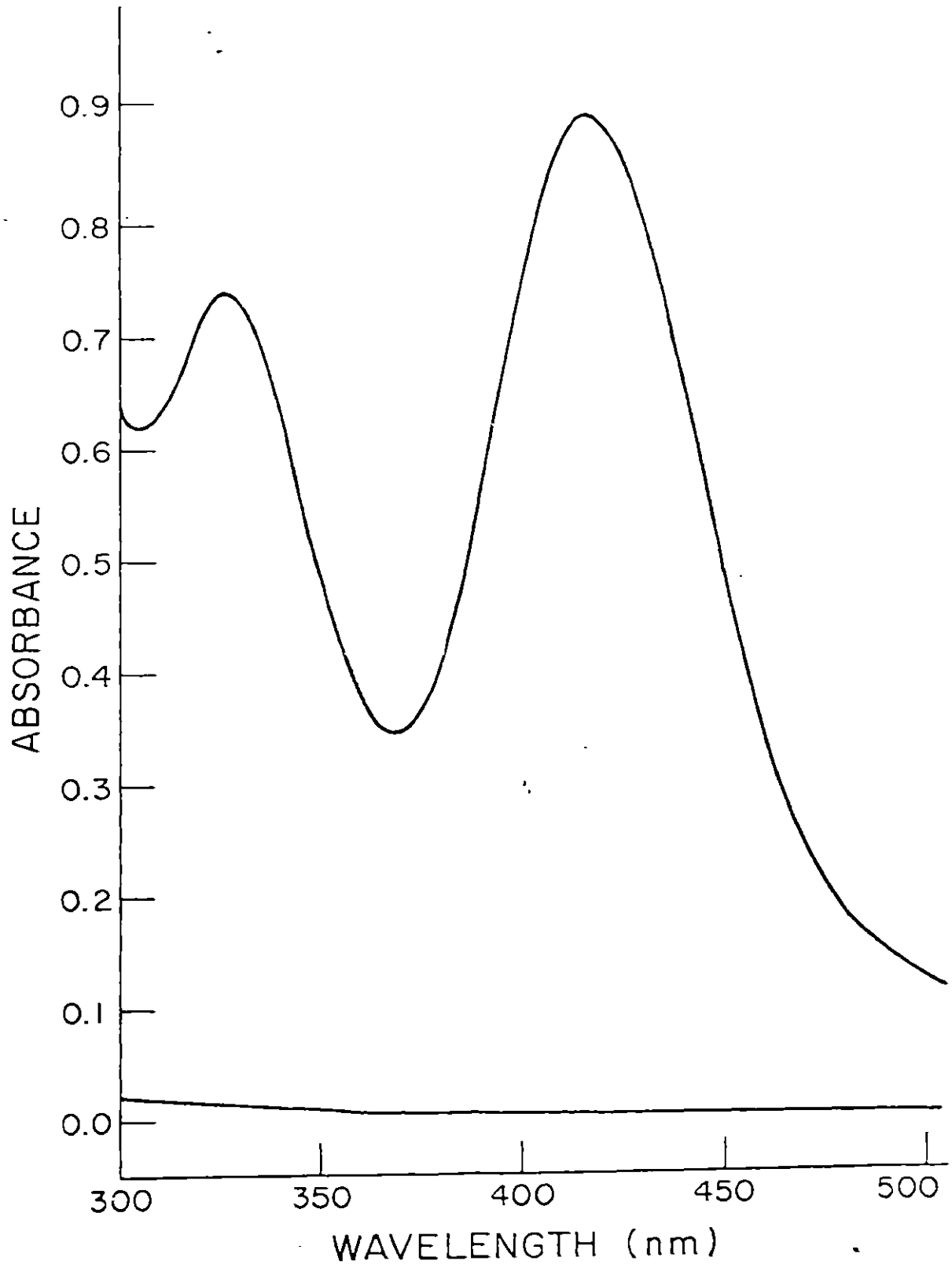
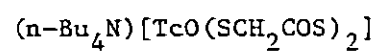


Figure 3

Structure of the Anion of



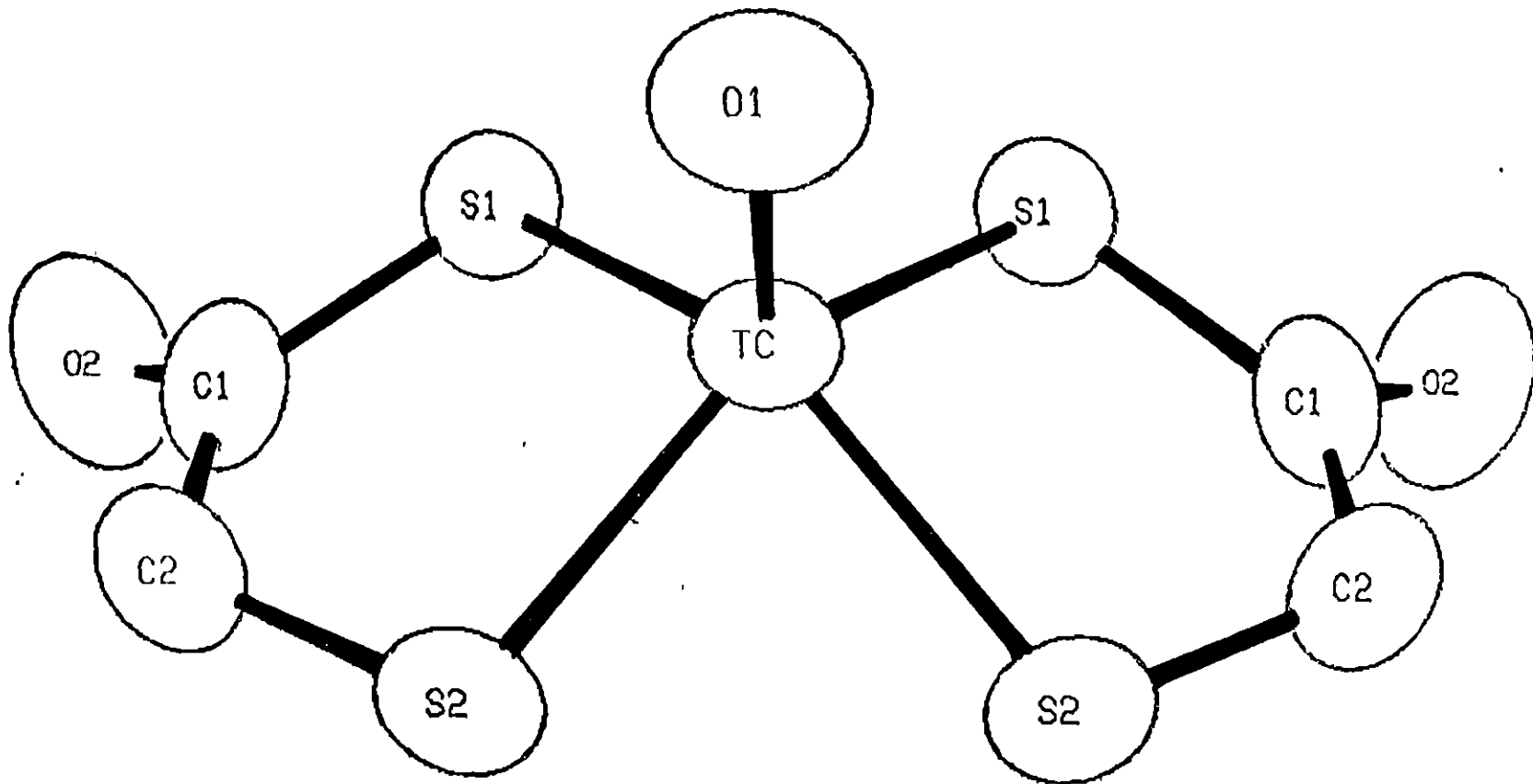


Table 4

Bond Distance (in Å) in Crystalline $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$

For atomic numbering scheme, see Figure 3.

(C₁₁ through C₄₄, and N₁ refer to the
tetrabutylammonium ion.)

TABLE OF BOND DISTANCES IN ANGSTROMS

<u>Atoms</u>	<u>Distance</u>
Tc - S1	2.336(3)
Tc - S2	2.303(3)
Tc - O1	1.672(8)
S1 - S1'	3.041(5)
S2 - S2'	3.016(6)
S1 - S2	3.139(4)
S1 - S2'	4.361(4)
S1 - C1	1.741(12)
S2 - C2	1.762.(13)
O2 - C1	1.26(2)
C1 - C2	1.46(2)
N1 - C11	1.56(2)
N1 - C21	1.52(2)
N1 - C31	1.53(2)
N1 - C41	1.54(2)
C11 - C12	1.55(3)
C12 - C13	1.44(4)
C13 - C14	1.68(5)
C21 - C22	1.55(3)
C22 - C23	1.44(4)
C23 - C24	1.61(6)
C31 - C32	1.36(3)
C32 - C33	1.41(3)
C33 - C34	1.49(3)
C41 - C42	1.32(3)
C42 - C43	1.34(3)
C43 - C44	1.58(3)

NUMBERS IN PARENTHESES ARE ESTIMATED STANDARD DEVIATIONS IN THE LEAST SIGNIFICANT DIGITS.

Table 5

Bond Angles (in degrees) in Crystalline $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$

For atomic numbering scheme, see Figure 3.

(C_{11} through C_{44} , and N_1 refer to the
tetrabutylammonium ion.)

TABLE OF BOND ANGLES IN DEGREES

<u>Atoms</u>	<u>Angle</u>	<u>Atoms</u>	<u>Angle</u>
S1 - Te - S1'	81.2(1)	C21 - N1 - C31	110.(1)
S1 - Te - S2	85.1(1)	C21 - N1 - C41	109.(1)
S1 - Te - S2'	140.1(1)	C31 - N1 - C41	111.(1)
S1 - Te - O1	109.7(3)	N1 - C11 - C12	114.(2)
S2 - Te - S2'	81.8(2)	C11 - C12 - C13	106.(2)
S2 - Te - O1	110.2(3)	C12 - C13 - C14	108.(2)
Te - S1 - C1	106.5(5)	N1 - C21 - C22	117.(2)
Te - S2 - C2	105.9(4)	C21 - C22 - C23	109.(2)
S1 - C1 - O2	117.(1)	C22 - C23 - C24	101.(3)
S1 - C1 - C2	118.9(9)	N1 - C31 - C32	125.(1)
O2 - C1 - C2	124.(1)	C31 - C32 - C33	130.(1)
S2 - C2 - C1	115.6(8)	C32 - C33 - C34	123.(2)
C11 - N1 - C21	114.(1)	N1 - C41 - C42	130.(1)
C11 - N1 - C31	107.(1)	C41 - C42 - C43	134.(1)
C11 - N1 - C41	106.(1)	C42 - C43 - C44	128.(1)

NUMBERS IN PARENTHESES ARE ESTIMATED STANDARD DEVIATIONS IN THE LEAST SIGNIFICANT DIGITS.

The complex 1 has two moderately intense bands in its optical spectrum (Figure 2): λ_{max} (nm) 325, 415 (ϵ (L mol⁻¹ cm⁻¹) 3100, 3700), respectively, in acetonitrile solution. A band at 950 cm⁻¹ in the infrared (Figure 1) and Raman¹⁸ spectra of 1 not corresponding to ligand or cation modes is assigned to the Tc-O stretch.

The novel formation of 1 from commercially available thioglycolic acid (HSCH₂COOH) illustrates the avidity of the oxotechnetium(V) core for dithiolate ligands. We suspected that mercaptothioacetic acid (HSCH₂COSH) was a significant impurity in commercial thioglycolic acid. It was synthesized by a modification of the published procedure¹² and its ¹H NMR spectrum was compared to that of commercial thioglycolic acid. It was seen to be present at a sizeable concentration (ca. 15%) as an impurity.

In this system, with an unsymmetrical bidentate ligand, it is reasonable to expect the occurrence of cis and trans isomers. Employing the ligand exchange reaction of TcOCl₄⁻ with 1,2-dithiols developed by Trop⁷, we have demonstrated that mercaptothioacetic acid gives a mixture of both cis and trans complexes in the preparation of 1 from TcOCl₄⁻ and pure HSCH₂COSH. Although we can obtain the pure cis material by fractional crystallization, we have been unable to obtain the pure trans complex. However, it is clear that we are producing two isomers from an examination of the 270 MHz ¹H NMR spectrum of the various fractions obtained from the mercaptothioacetic acid reaction. The methylene absorptions of the ligand in the ¹H spectrum of the mixture show the presence of two AB pairs. Fractions containing the more soluble trans isomer are contaminated with the less soluble cis isomer.

Smith, et al¹⁹, prepared the compound (Ph₄As)[TcO(SCH₂CH₂S)₂] (2) by reduction of TcO₄⁻ in ethanol by NaBH₄ in the presence of .

1,2-ethanedithiol, and published¹⁹ its structure concurrently with the structure of 1. The anion of 2 is of the square pyramidal type, very similar to 1. Table 6 includes a comparison of the structural parameters and the Tc-O stretching frequencies of these prototypical complexes.

It is interesting to note the similarity of the Tc(V)OS₄ core of these complexes to the isoelectronic Mo(IV)OS₄ core²⁰ of MoO(S₂CN-n-Pr₂)₂. The Mo atom in the latter compound is coordinated in the same square pyramidal fashion as in 1 and 2, and corresponding bond lengths are similar (Table 6). The Mo-O bond order has been determined to be 3, using Cotton and Wing's correlation method²¹, and the infrared stretching frequencies for the Mo-O bond of the dithiocarbamate complexes MoO(Et₂dtc)₂²² and MoO(Me₂dtc)₂²³ (962 and 975 cm⁻¹, respectively), correspond well to a strong band in the infrared spectra of 1 and 2. This stretch occurs at a higher energy in (Bu₄N)[TcOCl₄]²⁴ (1019 cm⁻¹) than in the bis(dithiolato)oxotechnetate(V) complexes.

Armed with the knowledge of this new structural type, we attempted to rationally synthesize a new member of the series from aqueous solution. The reduction of TcO₄⁻ by dithionite in the presence of 3,4-toluenedithiol afforded⁸ (Bu₄N)[TcO(S₂C₆H₃(CH₃)₂)₂] (3). The compound was identified, in part, by its elemental analysis, and the presence of a band in its infrared spectrum at 930 cm⁻¹, diagnostic for the presence of the Tc-O bond. Its optical spectrum in MeCN is dominated by an absorption maximum at 361 nm ($\epsilon = 13,000 \text{ L mol}^{-1} \text{ cm}^{-1}$) and has, in addition, a peak at 313 nm ($\epsilon = 7,400$) and an inflection at 405 nm ($\epsilon = 6,300$).

The identification of 3 was confirmed¹⁴ by field desorption mass spectrometry (FDMS). In this technique, the sample is stripped off the emitter by a powerful electric field. This causes little, if any,

Table 6

Comparison of Bond Lengths (in Å) of the MO_4 Cores of Three d^2 Square-Pyramidal Complexes, and Their M-O Stretching Frequencies.

Bond	$\text{TcO}(\text{SCH}_2\text{COS})_2$ ^{-a}	$\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2$ ^{-b}	$\text{MoO}(\text{S}_2\text{CN}(\text{n-Pr})_2)_2$ ^c
M-O	1.672(8)	1.64(1)	1.664(8)
M-S (av)	2.320(4)	2.300(13)	2.413(4)
M-to-basal plane	0.791	0.761(2)	0.83
$\nu(\text{M-O})$	950 cm^{-1}	940	962 ^d

a) Reference 6

b) Reference 26

c) Reference 20

d) for $\text{MoO}(\text{S}_2\text{CNEt}_2)_2$; see Reference 23

fragmentation, and in the experimental setup used, cations are sorted by their m/e ratio. Ionization can occur by electron extraction from neutral cation-anion pairs giving rise to a molecular ion m^+ , or by cationization by counter ion attachment. The spectrum (Figure 4) of 3 seems to be dominated by the latter mechanism. This spectrum represents the first positive identification of an anionic transition metal complex by FDMS.

The compound $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2]$ was also prepared by dithionite reduction in a manner similar to 3. This preparation, and that of 3, suggest the generality of the aqueous dithionite reduction using either aliphatic or aromatic 1,2-dithiols.

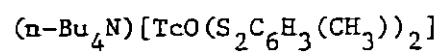
In spite of their structural similarities to bis(dialkyldithiocarbamate)oxomolybdenum(IV) species, the reactivity of these oxotechnetium(V) complexes towards oxygen and oxygen atom transfer reagents differs markedly. While the molybdenum species are easily oxidized²⁵ by atmospheric oxygen or dimethylsulfoxide to cis-dioxomolybdate(VI) complexes, none of the Tc(V) complexes discussed here is in the least bit air-sensitive, and 3 did not react with DMSO, even at reflux temperatures.

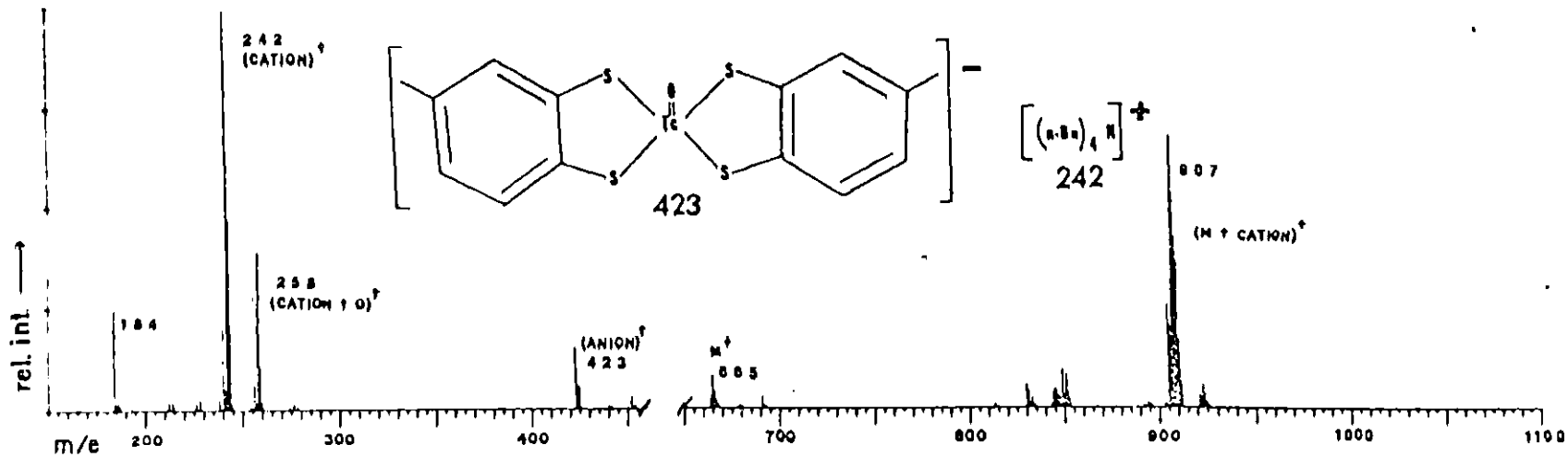
The optical spectrum of 1 in methylene chloride is not perturbed by the addition of pyridine in any quantity. This suggests that there is no tendency in these compounds to accept a ligand in their sixth coordination site.

The formation of these novel compounds demonstrates the possibility of stabilizing the +5 oxidation state of technetium by the appropriate choice of ligand. The ease of synthesis and the stability of these complexes are in marked contrast to the mistaken belief^{1a} that technetium(V) coordination complexes are unstable in aqueous solution. This belief had

Figure 4

Cation Field Desorption Mass Spectrum of





been based on the chemistry of the tetrahalooxotechnetate(V) and hexahalotechnetate(IV) anions. The avidity of technetium for an impurity of manufacture in thioglycolic acid suggests caution be exercised in assuming that a particular ^{99m}Tc -labeled radiopharmaceutical is simply a complex of technetium with the intended ligand, as the ligand-to-metal ratios in these preparations are much greater than the nominally 250:1 ratio of thioglycolic acid to pertechnetate that led to the isolation of 1.

The aqueous chemistry of technetium is probably much more varied than initially believed, and by careful selection of ligand and oxidation state, the rational design of radiopharmaceuticals containing technetium should be possible.

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CHAPTER 2

Preparation and Crystal Structure of
Tetraphenylarsonium Bis(2-mercaptoethanolato)Oxotechnetium(V)

INTRODUCTION

The isolation and characterization of $\text{TcO}(\text{SCH}_2\text{COS})_2^{-1}$, $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^{-1}$, and $\text{TcO}(\text{S}_2\text{C}_6\text{H}_3(\text{CH}_3))_2^{-3}$ conclusively demonstrated the existence of the square pyramidal Tc(V)OS_4 core, its preparation in aqueous solution, and its stability against oxidation or decomposition. The unexpected synthesis¹ of $\text{TcO}(\text{SCH}_2\text{COS})_2^{-}$ from an impurity in thioglycolic acid⁴ showed the avidity of the oxotechnetium moiety for bis-chelating dithiols, and demonstrated the possibility that $^{99\text{m}}\text{Tc}$ radio-pharmaceuticals might sometimes be complexes of unanticipated ligands.

To further our understanding of the oxotechnetium(V) core, we decided to investigate the possibility of its synthesis and stability with ligands other than 1,2-dithiols. We explored the use of 2-mercaptoethanol as ligand because we felt it represented a conservative variation on the use of 1,2-ethanedithiol. Reduction of pertechnetate in the presence of 2-mercaptoethanol by dithionite affords $\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2^{-}$, whose structure⁵ is discussed in this chapter.

EXPERIMENTAL

Aqueous $\text{NH}_4^{99}\text{TcO}_4$ was obtained from New England Nuclear. The concentration was determined by a literature method⁶. Sodium dithionite (Fisher) and β -mercaptoethanol (Eastman) were used without further purification. Water was passed through a Barnstead D8904 cartridge for removal of organics and a Corning 3508-B demineralizer cartridge and then distilled using a Corning Mega-Pure still. All other solvents were used as received.

Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. Solution optical spectra were recorded on a Cary 17 spectrophotometer. Infrared spectra were recorded on a Perkin Elmer 180 grating spectrophotometer as KBr pellets.

The field desorption mass spectrum (FDMS) was obtained⁷ with a Varian MAT 731 double focusing mass spectrometer fitted with a combination EI/FI/FD ion source. Because of technical difficulties in obtaining the positive ion FDMS of a tetraphenylarsonium salt, it became necessary to replace the cation in $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$. This was done by dissolving 0.04147 g of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ in 10 mL of CH_2Cl_2 , and adding 8 mg of NaClO_4 dissolved in 8 mL of H_2O . After thorough mixing and centrifugation, the aqueous phase, containing $\text{Na}[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$, was submitted for FDMS analysis. Carbon activated tungsten wire emitters were loaded by dipping them into this solution. Conditions of the measurement of the spectrum and its calibration are described in Chapter I.

Preparation of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$

In a typical synthesis, 1 mL of a 0.43 M solution of $\text{NH}_4^{99}\text{TcO}_4$ (0.43 mmol) was diluted with 75 mL of H_2O and 0.062 mL of neat β -mercaptoethanol (0.88 mmol) was added. A solution of 0.216 g of $\text{Na}_2\text{S}_2\text{O}_4$ (1.24 mmol) in 10 mL of 2 M NaOH was added dropwise to the stirred reaction mixture. After 20 minutes, several drops of a concentrated solution of Ph_4AsCl in H_2O were added, and a voluminous metallic-pink precipitate appeared in the straw-yellow mother liquor. The crude product was filtered and washed with H_2O (2 x 2.5 mL), then dried for 24 hours in vacuo. The solid was dissolved in 10 mL of absolute EtOH and filtered. The filtrate was taken to dryness on a rotary evaporator. The residue was dissolved in ca. 5 mL of CH_3CN and, after adding an approximately equal volume of Et_2O , the solution was stoppered and stored at -28°C for 24 hours. The crystals were filtered, washed with Et_2O , and air-dried. Overall yield was 0.102 g (0.16 mmol, 53%).

Analysis, $\text{C}_{28}\text{H}_{28}\text{AsO}_3\text{S}_2\text{Tc}$, calcd: C, 51.69; H, 4.34; As, 11.52; S, 9.86.
found: C, 52.33; H, 4.39; As, 12.41; S, 10.56.

X-ray Crystallographic Study of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$

The X-ray structure determination was performed by the crystallographic staff of Molecular Structure Corporation, College Station, Texas, 77840. All calculations were performed on a linked PDP-11/45-11/60 computation system using the Enraf-Nonius Structure Determination Package and private programs of the Molecular Structure Corporation.

The crystal used for the collection of the data set had dimensions 0.20 mm x 0.20 mm x 0.25 mm. It was mounted with its long axis roughly

parallel to the-phi axis of the goniometer. Details of the data collection are given in Tables 7-9.

The structure was solved by direct methods using 3,478 unique reflections; hydrogen atoms were not included in the calculations. Only the 2,555 reflections with $F_0 > 3.0\sigma(F_0)$ were used in the full-matrix least-squares refinement, which resulted in final unweighted and weighted agreement factors of $R_1 = 0.050$ and $R_2 = 0.071$. The highest peak in the final difference Fourier was $0.47(4) \text{ e } \text{Å}^{-3}$. Final positional and thermal parameters are collected in Appendix 2.

Table 7

Structure Determination of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$

A. Crystal Data

Table of Experimental Details

A. Crystal Data

To H28 As C28 03 S2

F.W. 649.58 F(000) = 2624

Crystal dimensions: 0.20 x 0.20 x 0.25 mm

Peak width at half-height = 0.20°

Mo K α radiation ($\lambda = 0.71073$ A)

Temperature = 23 \pm 1°

orthorhombic space group Pbca

a = 15.039 (2) A b = 18.510 (3) A c = 19.196 (3) A

V = 5343.8 A³

Z = 8 $\rho = 1.61$ g/cm³

$\mu = 20.1$ cm⁻¹

Table 8

Structure Determination of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$

B. Intensity Measurements

Table of Experimental Details

B. Intensity Measurements

Instrument:	Enraf-Nonius CAD4 diffractometer
Monochromator:	Graphite crystal, incident beam
Attenuator:	Zr foil, factor 20.7
Take-off angle:	2.8°
Detector aperture:	2.0 to 2.4 mm horizontal 2.0 mm vertical
Crystal-to-detector distance:	21 cm
Scan type:	ω - θ
Scan rate:	2 - 20°/min (in ω)
Scan width, deg:	$0.6 + 0.350 \tan \theta$
Maximum 2θ :	45.0°
No. of reflections measured:	3873 total, 3478 unique
Corrections:	Lorentz-polarization

Table 9

Structure Determination of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$

C. Structure Solution and Refinement

Table of Experimental Details

C. Structure Solution and Refinement

Solution:	Direct methods
Hydrogen atoms:	Not included
Refinement:	Full-matrix least-squares
Minimization function:	$\sum w(F_o - F_c)^2$
Least-squares weights:	$4F_o^2 / \sigma^2(F_o^2)$
"Ignorance" factor:	0.050
Anomalous dispersion:	All non-hydrogen atoms
Reflections included:	2555 with $F_o^2 > 3.0\sigma(F_o^2)$
Parameters refined:	161
Unweighted agreement factor:	0.050
Weighted agreement factor:	0.071
Factor including unobserved reflections:	0.082
Std of observation of unit weight:	2.10
Convergence, largest shift:	0.003
Highest peak in final difference Fourier:	0.47 (4) e/A ³
Computer hardware:	Linked PDP-11/45-11/60
Computer software:	Enraf-Nonius SDP and private programs of Molecular Structure Corporation

RESULTS AND DISCUSSION

In a manner directly analogous to the preparation of $(\text{Bu}_4\text{N})[\text{TcO}(\text{S}_2\text{C}_6\text{H}_3(\text{CH}_3)_2)_2]^{3-}$ and $(\text{Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2]^{2-}$, the dithionite reduction of TcO_4^- in the presence of $\text{HSCH}_2\text{CH}_2\text{OH}$ yields $\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2^-$, isolated⁵ as its tetraphenylarsonium salt (1). In order to obtain the positive-ion FDMS of this complex, the cation had to be exchanged for a Na^+ ion. This was done using phase-transfer methods, and the resulting FDMS⁷ is presented in Figure 5. A list of spectral assignments is given in Table 10.

As discussed in Chapter 1, the spectrum is dominated by species comprising the molecule plus attached cations. Traces of Ph_4As^+ and ClO_4^- left in the sample after its metathetical preparation are seen either as themselves (Ph_4As^+) or in combination with the other ions, as in the peaks at $m/e = 458, 481$ and 603 .

Bond lengths and angles for 1 are given in Tables 11 and 12. The distances and angles for the Ph_4As^+ ion are unexceptional and will not be discussed. The structure of the anion (Figure 6) is approximately square pyramidal. The basal plane is distorted towards a trapezoid because of the difference between the average Tc-O(ligand) and Tc-S distances (1.950(4) vs. 2.291(2) Å, respectively).

The average Tc-S bond length in 1 compares favorably with that of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ (2) (2.30(1) Å),⁸ and $\text{TcO}(\text{SCH}_2\text{COS})_2^-$ (3) (2.320(3) Å).¹ The Tc-O(oxo) distance of 1 is also very similar to that of 2 (1.64(1) Å) and 3 (1.672(8) Å). However, the metal atom-to-basal plane distance of 1 (0.720(1) Å) is considerably shorter than that of 2 (0.761(2) Å) or 3 (0.791(3) Å). It has been proposed⁹ that the steric demands of the oxo-oxygen in dichloro[hydrotris(1-pyrazolyl)borato]oxotechnetium(V) (4)

Figure 5

Field Desorption Mass Spectrum of $\text{Na}[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$
Prepared by Cation Metathesis of
 $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ and NaClO_4

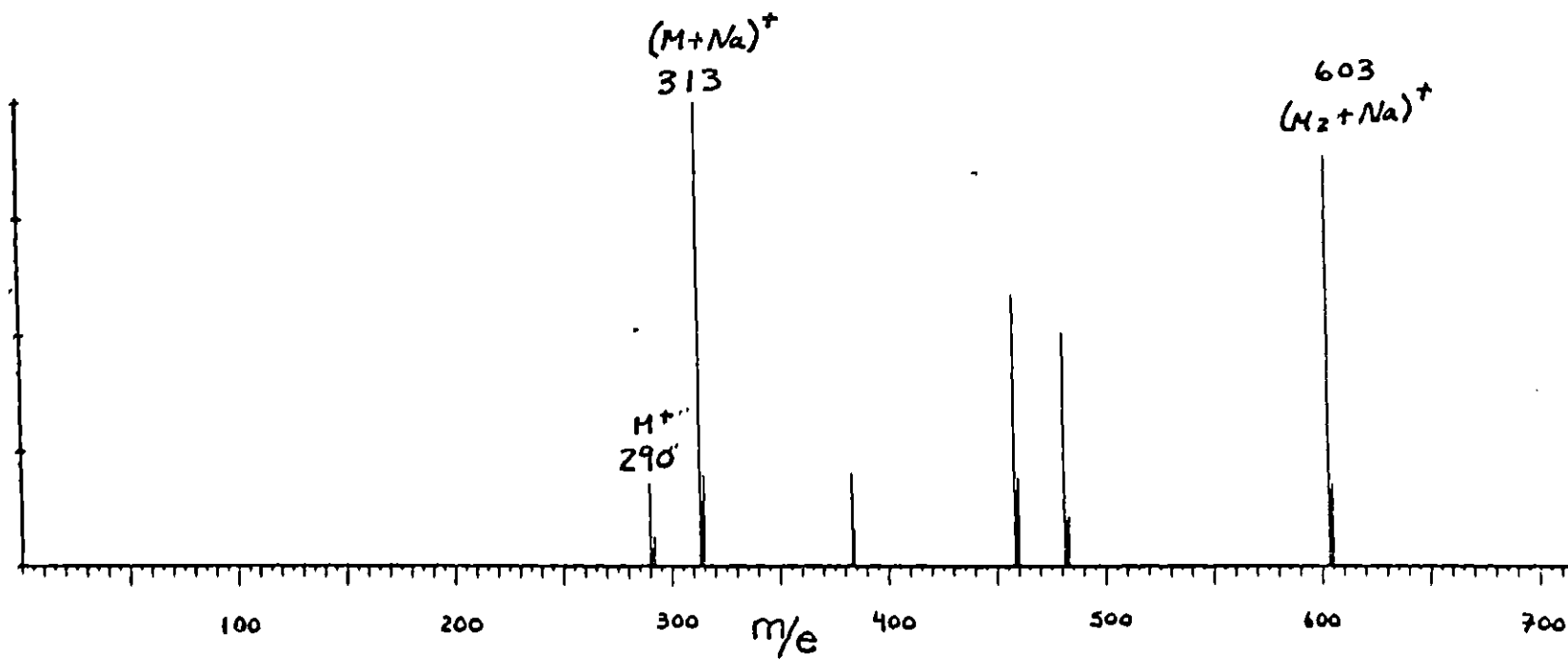


Table 10

Field Desorption Mass Spectral Assignments for
 $\text{Na}[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$, Prepared by Cation Metathesis of
 $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ and NaClO_4

<u>m/e</u>	<u>Assignment</u>
290	$\{\text{Na}[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]\}^+$
313	$\{\text{Na}_2[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]\}^+$
383	Ph_4As^+
458	$\{\text{Na}_4[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]\text{ClO}_4\}^+ \text{ a}$
481	$\{\text{Na}_5[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]\text{ClO}_4\}^+ \text{ a}$
603	$\{\text{Na}_3[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]_2\}^+ \text{ a}$
	or
	$\{\text{Na}_6[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2](\text{ClO}_4)_2\}^+ \text{ a}$

a) tentative assignment

Figure 6

Structure of the Anion of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$

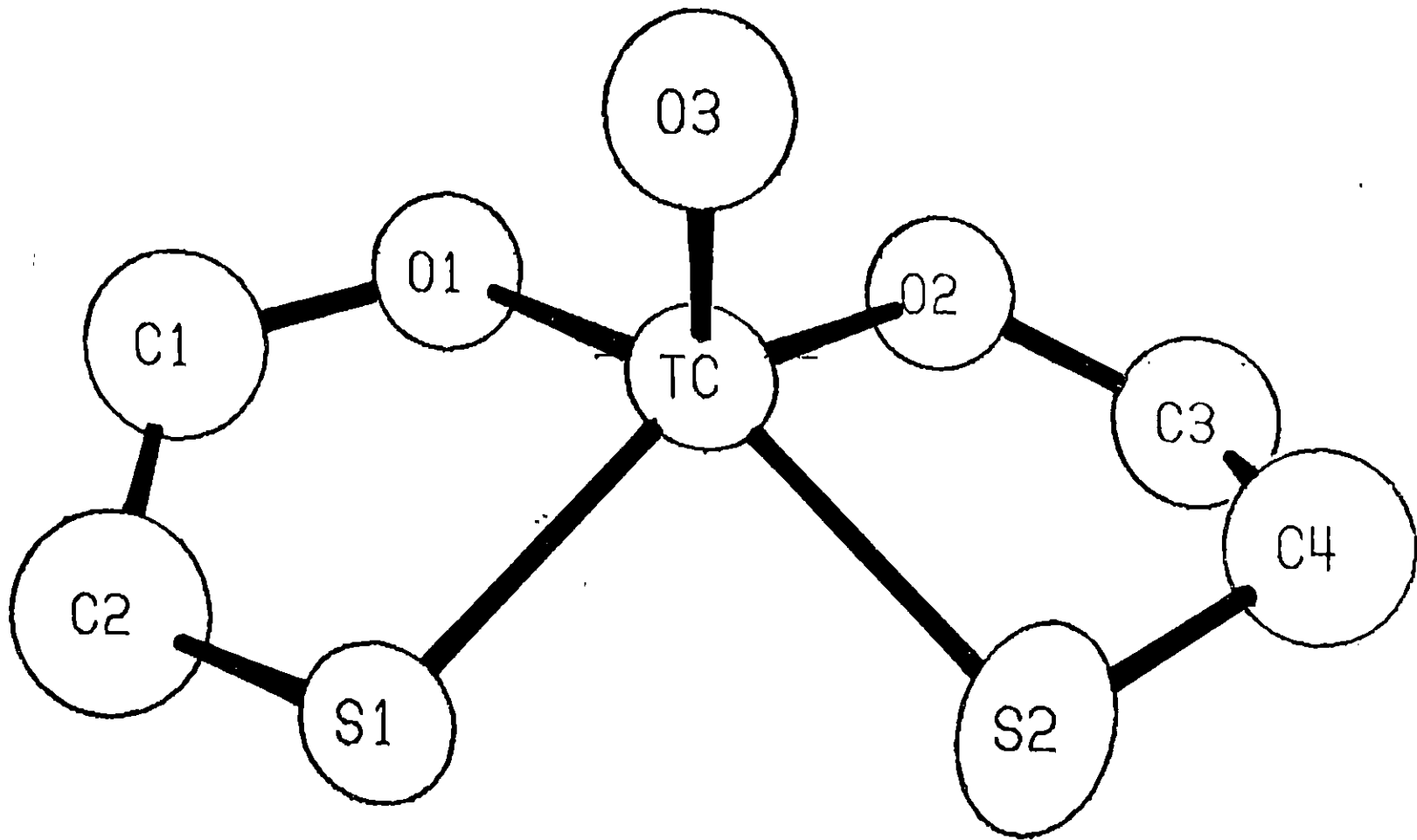


Table II

Bond Distances in Crystalline $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$

For atomic numbering scheme, see Figure 6.

(C_5 through C_{28} , and As, refer to the tetraphenylarsonium ion.)

Table of Bond Distances in Angstroms

<u>Atom 1</u>	<u>Atom 2</u>	<u>Distance</u>	<u>Atom 1</u>	<u>Atom 2</u>	<u>Distance</u>
Tc	S ₁	2.283(2)	C ₉	C ₁₀	1.421(9)
Tc	S ₂	2.297(2)	C ₁₁	C ₁₂	1.416(8)
Tc	O ₁	1.963(4)	C ₁₁	C ₁₆	1.390(8)
Tc	O ₂	1.936(4)	C ₁₂	C ₁₃	1.425(9)
Tc	O ₃	1.662(5)	C ₁₃	C ₁₄	1.393(9)
S ₁	C ₂	1.848(10)	C ₁₄	C ₁₅	1.361(9)
S ₂	C ₄	1.841(9)	C ₁₅	C ₁₆	1.439(9)
O ₁	C ₁	1.429(9)	C ₁₇	C ₁₈	1.382(8)
O ₂	C ₃	1.435(9)	C ₁₇	C ₂₂	1.404(8)
C ₁	C ₂	1.438(11)	C ₁₈	C ₁₉	1.419(9)
C ₃	C ₄	1.478(11)	C ₁₉	C ₂₀	1.392(9)
As	C ₅	1.919(5)	C ₂₀	C ₂₁	1.370(9)
As	C ₁₁	1.908(6)	C ₂₁	C ₂₂	1.410(9)
As	C ₁₇	1.899(6)	C ₂₃	C ₂₄	1.394(8)
As	C ₂₃	1.918(5)	C ₂₃	C ₂₈	1.379(8)
C ₅	C ₆	1.394(8)	C ₂₄	C ₂₅	1.405(8)
C ₅	C ₁₀	1.395(8)	C ₂₅	C ₂₆	1.370(9)
C ₆	C ₇	1.400(9)	C ₂₆	C ₂₇	1.394(9)
C ₇	C ₈	1.404(9)	C ₂₇	C ₂₈	1.397(8)
C ₈	C ₉	1.407(9)			

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 12

Bond Angles in Crystalline $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$

For atomic numbering scheme, see Figure 6.

(C_5 through C_{28} , and As, refer to the tetraphenylarsonium ion.)

Table of Bond Angles in Degrees

<u>Atom 1</u>	<u>Atom 2</u>	<u>Atom 3</u>	<u>Angle</u>	<u>Atom 1</u>	<u>Atom 2</u>	<u>Atom 3</u>	<u>Angle</u>
S ₁	Tc	S ₂	86.09(7)	C ₆	C ₇	C ₈	118.7(6)
S ₁	Tc	O ₁	83.8(1)	C ₇	C ₈	C ₉	121.4(6)
S ₁	Tc	O ₂	138.1(1)	C ₈	C ₉	C ₁₀	119.8(6)
S ₁	Tc	O ₃	109.7(2)	C ₅	C ₁₀	C ₉	117.7(6)
S ₂	Tc	O ₁	141.8(2)	As	C ₁₁	C ₁₂	118.4(4)
S ₂	Tc	O ₂	83.6(1)	As	C ₁₁	C ₁₆	117.8(4)
S ₂	Tc	O ₃	109.4(2)	C ₁₂	C ₁₁	C ₁₆	123.7(6)
O ₁	Tc	O ₂	79.8(2)	C ₁₁	C ₁₂	C ₁₃	116.3(6)
O ₁	Tc	O ₃	108.7(2)	C ₁₂	C ₁₃	C ₁₄	120.5(7)
O ₂	Tc	O ₃	112.0(2)	C ₁₃	C ₁₄	C ₁₅	121.9(7)
Tc	S ₁	C ₂	101.9(3)	C ₁₄	C ₁₅	C ₁₆	120.3(7)
Tc	S ₂	C ₄	96.3(3)	C ₁₁	C ₁₆	C ₁₅	117.2(6)
Tc	O ₁	C ₁	117.9(4)	As	C ₁₇	C ₁₈	119.1(4)
Tc	O ₂	C ₃	123.0(4)	As	C ₁₇	C ₂₂	118.4(4)
O ₁	C ₁	C ₂	118.5(8)	C ₁₈	C ₁₇	C ₂₂	122.4(6)
S ₁	C ₂	C ₁	108.2(7)	C ₁₇	C ₁₈	C ₁₉	118.7(6)
O ₂	C ₃	C ₄	112.0(6)	C ₁₈	C ₁₉	C ₂₀	119.2(6)
S ₂	C ₄	C ₃	108.2(6)	C ₁₉	C ₂₀	C ₂₁	121.3(7)
C ₅	As	C ₁₁	109.5(2)	C ₂₀	C ₂₁	C ₂₂	121.0(6)
C ₅	As	C ₁₇	106.9(2)	C ₁₇	C ₂₂	C ₂₁	117.4(6)
C ₅	As	C ₂₃	105.6(2)	As	C ₂₃	C ₂₄	116.3(4)
C ₁₁	As	C ₁₇	113.2(2)	As	C ₂₃	C ₂₈	121.6(4)
C ₁₁	As	C ₂₃	110.4(2)	C ₂₄	C ₂₃	C ₂₈	122.0(6)
C ₁₇	As	C ₂₃	110.8(2)	C ₂₃	C ₂₄	C ₂₅	118.2(6)
As	C ₅	C ₆	119.7(4)	C ₂₄	C ₂₅	C ₂₆	120.7(6)
As	C ₅	C ₁₀	117.7(4)	C ₂₅	C ₂₆	C ₂₇	120.0(7)
C ₆	C ₅	C ₁₀	122.6(5)	C ₂₆	C ₂₇	C ₂₈	120.6(6)
C ₅	C ₆	C ₇	119.9(6)	C ₂₃	C ₁₈	C ₂₇	118.5(5)

Numbers in parentheses are estimated standard deviations in the least significant digits.

cause the *cis* ligands to bend away from the Tc=O moiety in the compound. If such an explanation were invoked to explain the relatively short metal-to-basal plane distance in 1, it might be expected that the $O_3\text{-Tc-O}_{1,2}$ (av) angle would be significantly smaller than the $O_3\text{-Tc-S}_{1,2}$ (av) angle. This is not so. The average angles are $110.4(2)^\circ$ and $109.6(2)^\circ$, respectively. Indeed, $O_3\text{-Tc-O}_2$ is the largest angle of the set. The average O-Tc-S angle in the TcOS_4 core of 3 is $110.0(3)^\circ$, and in 2 it is $109.3(4)^\circ$. It can be concluded that the short Tc-to-basal plane distance in 1 is entirely due to the relative Tc-S and Tc-O(ligand) bond lengths, and not to sterically-induced bond angle deformation.

Although the *cis* form of 1 was isolated, there is no *a priori* reason to doubt the existence of the *trans* isomer. A similar situation occurred for 3; the *cis* isomer was isolated, but the *trans* isomer could be detected⁴ by NMR in the unfractionated reaction product. The complex 1 has a moderately intense band in its optical spectrum (Figure 7) ($\lambda_{\text{max}} =$ (MeCN) 357 nm; $\epsilon = 2770 \text{ L mol}^{-1} \text{ cm}^{-1}$) and a much weaker one ($\lambda_{\text{max}} = 525 \text{ nm}$, $\epsilon = 180 \text{ L mol}^{-1} \text{ cm}^{-1}$). Any bands at shorter wavelengths are obscured by the absorptions of the tetraphenylarsonium ion. The more intense band has position and extinction coefficient similar to the principal features in the spectra of 2 and 3, and is most likely due to sulfur-to-metal charge transfer absorption. The weaker band by virtue of its position and intensity may be a d-d transition. The infrared spectrum (Figure 8) of 1 (KBr pellet) exhibits a strong band at 948 cm^{-1} , with a weaker, poorly resolved shoulder at 935 cm^{-1} which can be attributed to the technetium-oxo stretching mode (the splitting probably results from a solid state effect).

Figure 7

Electronic Spectrum (in MeCN) of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$

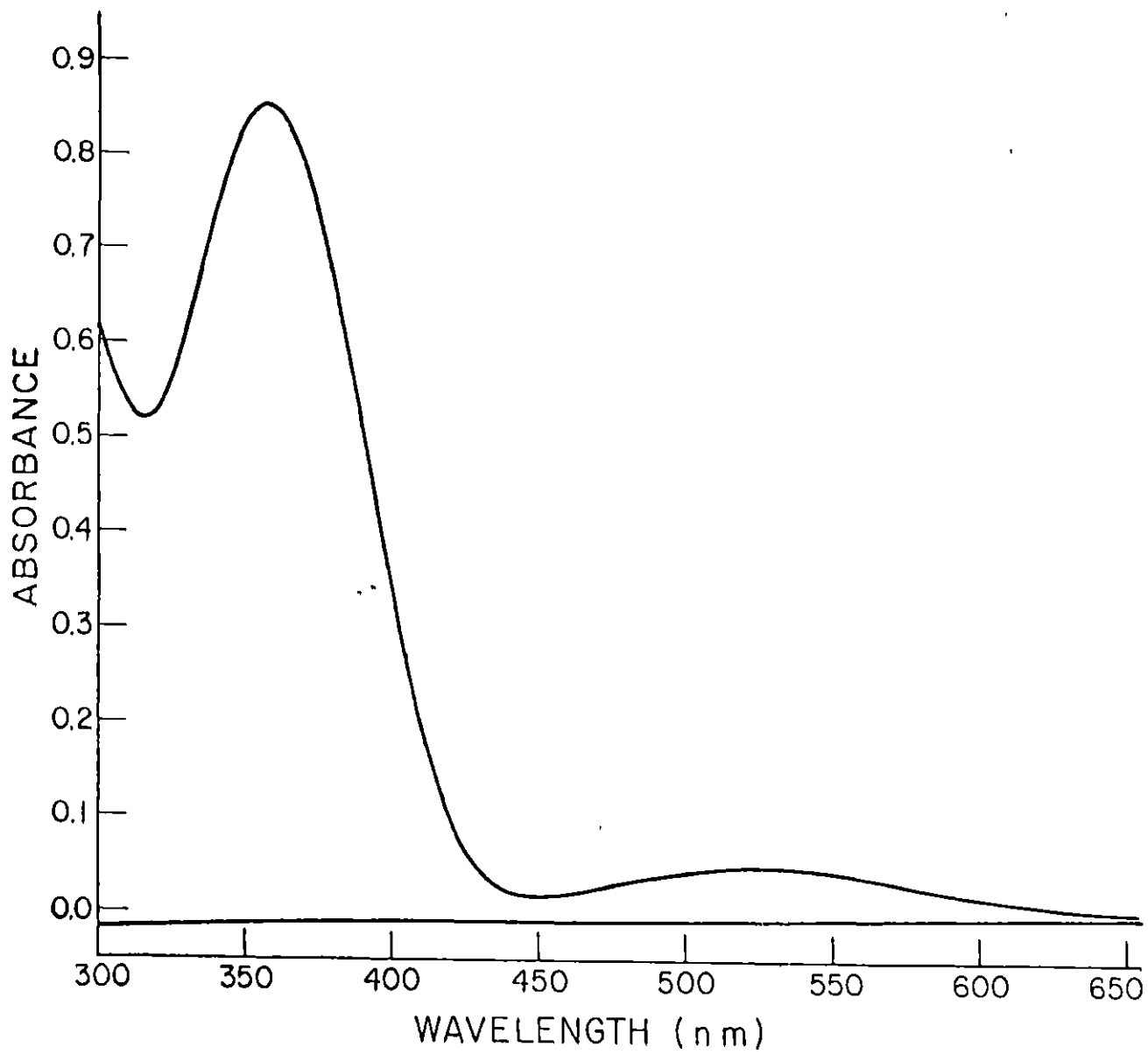
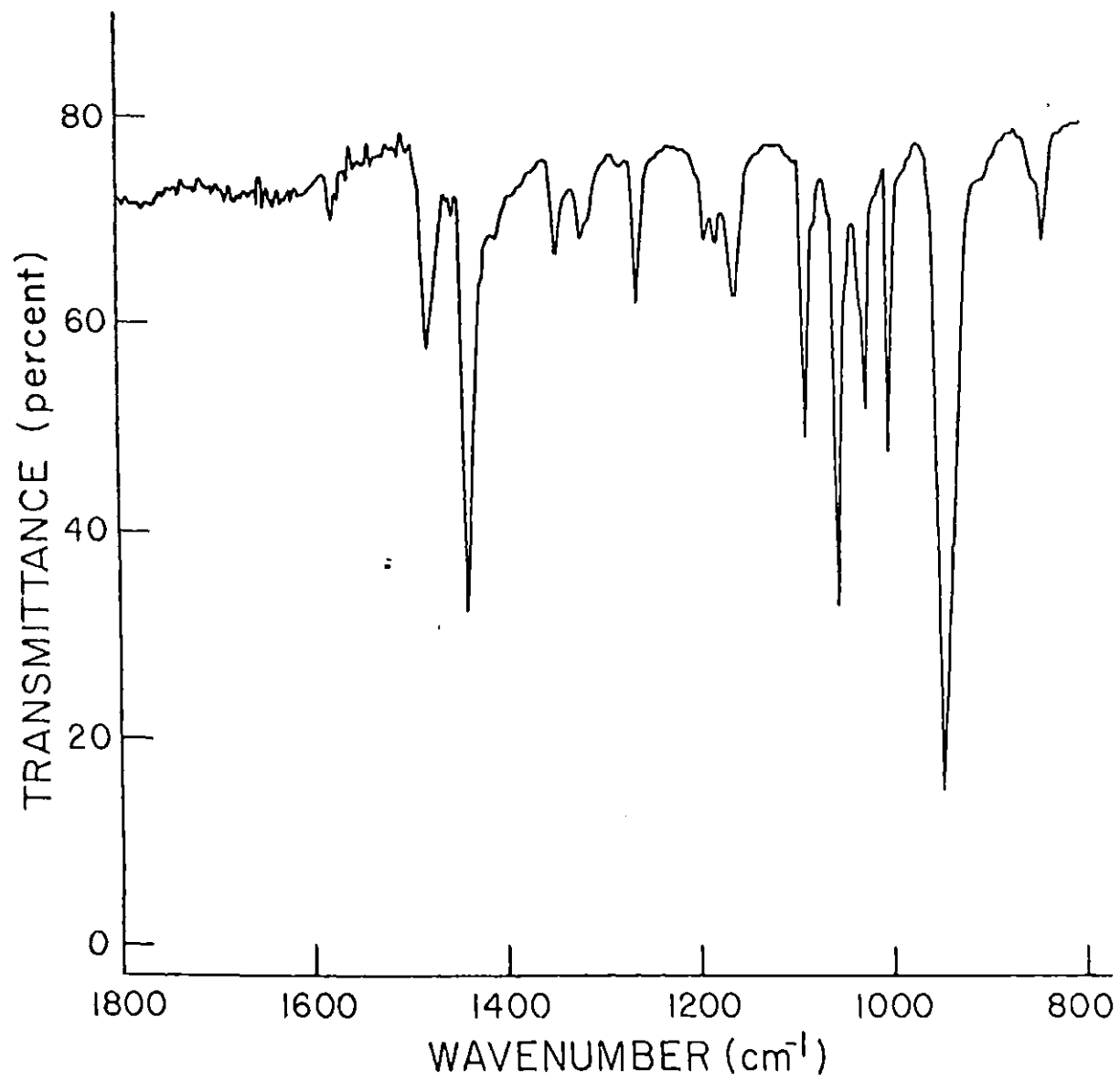


Figure 8

Infrared Spectrum of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$



It is interesting to note that for solutions of 1 in MeOH, λ_{\max} of the weak peak in the optical spectrum blue-shifts to 508 nm. The attack of the sixth position of oxotechnetium(V) complexes of cyanide by water, methanol, and excess cyanide ion has been described by Trop¹⁰. The possibility of substitutional lability of this complex intrigued us, and this investigation is recounted in Chapter 4.

In a recent investigation of the myocardial uptake of long-chain fatty acids complexed to technetium, Livni¹¹ prepared the amorphous tetraphenylarsonium salt of bis(2-mercapto-*propionato*)oxotechnetate(V). This compound was synthesized by reacting TcO_4^- with excess 2-mercapto-*propionic acid* in glacial acetic acid, and was identified by its elemental analysis, infrared spectrum (Tc=O stretch at 980 cm^{-1}), optical spectrum ($\lambda_{\max} = 382$, $\epsilon = 2628\text{ L mol}^{-1}\text{ cm}^{-1}$) and FDMS (m/e 322.89, 383.08, 705.97). In this compound, the ligating oxygens are contributed by carboxylate groups, and this suggests a lack of significant difference in binding ability of alkoxy-oxygen and carboxylate-oxygen in this class of chelate complexes.

The isolation of 1 again demonstrates the ease with which the oxotechnetium(V) core is formed during the aerobic reduction of pertechnetate and that the TcO^{3+} core can be stabilized by donors other than four bis-chelated sulfur atoms. This enlarges the scope of potential ligands for rationally designed radiopharmaceuticals.

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CHAPTER 3

Synthesis and Characterization of Complexes
Containing the Bis(1,2-diolato)Oxotechnetium(V) Core

INTRODUCTION

In the previous investigations of the chemistry of ^{99}Tc pertinent to radiopharmaceuticals containing $^{99\text{m}}\text{Tc}$, the syntheses of bis(1,2-dithiolato)^{1a,b} and bis(2-mercaptoethanolato)² complexes of oxotechnetium(V) were demonstrated. Both classes of complexes can be readily synthesized by the dithionite reduction, in aqueous alkaline medium, of stoichiometric amounts of pertechnetate (TcO_4^-) and the dithiol or β -mercaptoethanol. The X-ray crystallographic studies^{1a,2}, described in Chapters 1 and 2, have established the core structures of these complexes to be square pyramids, with the oxo-oxygen occupying the apical position and either four sulfur atoms or two oxygen atoms and two sulfur atoms constituting the basal plane.

It seemed logical to investigate the possibility of the existence of a Tc(V)OO_4 core structure. There are a number of $^{99\text{m}}\text{Tc}$ -containing radiopharmaceuticals with ligands that are purely oxygen donors. A $^{99\text{m}}\text{Tc}$ -complex of citrate ion was used by Yeh and Kriss³ as a renal agent; $^{99\text{m}}\text{Tc}$ -glucoheptonate is used as a renal⁴ and brain-imaging agent, and $^{99\text{m}}\text{Tc}$ -gluconate^{4a,b,5} has been used for imaging the kidney and myocardial infarctions. Lebowitz, et al, reported⁶ the use of $^{99\text{m}}\text{Tc}$ -mannitol as a renal agent. At the outset of this research there was no structural information available for these agents, and, in fact, the oxidation state of the technetium in the polyol complexes was assumed⁷ to be +4.

By utilizing the lability of TcOCl_4^- towards ligand exchange, first described by Trop et al^{1b} for the case of 1,2-dithiols, we have been able to isolate and characterize oxotechnetium(V) complexes of ethylene glycol and catechol, and have obtained the X-ray crystal structure of the catechol complex. This work is described in the present chapter.

EXPERIMENTAL

Water was passed through a cartridge (Barnstead D8904) for removal of organics, then through an ion-exchanger (Corning 3508-B), and finally distilled. All other reagents were used as received, except as noted. Pertechnetate (as $\text{NH}_4^{99}\text{TcO}_4$) was obtained from New England Nuclear. Catechol was obtained from Aldrich, as was 1,2-cyclohexyldiol. The latter was crystallized from hot ethyl acetate. Ethylene glycol was obtained from Fischer. The starting material for the ligand exchange preparations, $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$, was prepared by the method⁸ described in Chapter 1.

Microanalysis of elements other than Tc was performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. The ^{99}Tc analysis of $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$ was done by a liquid scintillation counting method⁹. A sample of 0.02061 g of the compound was dissolved in 20 mL of H_2O , and then 1.5 mL of 1N NaOH and 1.5 mL of cold 30% H_2O_2 were added. The solution was bleached instantly. After boiling the reaction mixture for 10 minutes, it was cooled to room temperature and neutralized with 1N HCl. The digest was made up to exactly 100 mL with H_2O .

A 50 μL aliquot of this solution was mixed with 10 mL of a commercial scintillation cocktail (Biofluor[®], New England Nuclear) and counted for one minute in a liquid scintillation spectrometer (Packard Tri-Carb Model 3385) previously optimized for $^{99}\text{TcO}_4$ (gain = 11.0%; lower discriminator = 50; upper discriminator = 1000). The observed count rate was 122,959 CPM (0.2% relative standard deviation). A 100 μL aliquot of 1.240×10^{-4} M $\text{NH}_4^{99}\text{TcO}_4$ solution (calibrated by a spectrophotometric method¹⁰) was added to the scintillation vial, and the vial was re-counted.

The new count rate was 161,709 CPM (0.2% r.s.d.). The concentration (C) of the digest was determined from the following⁹ equation:

$$C = 1.240 \times 10^{-4} \text{ M} \times \frac{100 \mu\text{L}}{50 \mu\text{L}} \times \frac{122,959}{161,709 - 122,959}$$
$$= 7.869 \times 10^{-4} \text{ M}$$

Using this figure, the final analysis is 37.80% Tc.

Infrared spectra were recorded on a Perkin-Elmer 180 grating spectrophotometer as KBr pellets. Optical spectra were obtained with a Cary 17 spectrophotometer. The field desorption mass spectrum (FDMS) of $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$ was obtained¹¹ with a Varian MAT 731 double focusing mass spectrometer fitted with a combination EI/FI/FD ion source. Carbon activated tungsten wire emitters were loaded by dipping them into a methanol solution of the compound.

The X-ray crystal structure of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$ was obtained through the courtesy of Professor C.J.L. Lock, McMaster University, Toronto, Canada.

Preparation of Tetrabutylammonium Bis(catecholato)oxotechnetium(V)

A solution of 0.09137 g (0.8301 mmol) catechol in 6.2 mL MeOH was added dropwise to a solution of 0.20674 g (0.4143 mmol) $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ with constant stirring. The deep red-purple reaction mixture was treated with approximately 0.5 mL of 0.63 N NaOH, until it was a stable red-orange in color. The dropwise addition of 1 mL of 50% w/v $\text{Bu}_4\text{NCl}/\text{H}_2\text{O}$ and 25 mL of H_2O resulted in a large mass of small golden crystals. These were filtered from the reaction mixture, washed with water (2 x 5 mL) and then dried in vacuo. The yield of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$ was 0.19244 g, 81% based on Tc.

The product is easily recrystallized from methanol-water or acetone-water. Crystals suitable for X-ray diffraction analysis were grown by slow recrystallization from acetone-isobutanol.

Analysis, $C_{28}H_{44}NO_5Tc$, calcd: C, 58.62; H, 7.73; N, 2.44.

found: C, 58.58; H, 7.27; N, 2.75.

Preparation of Sodium Bis(1,2-ethanediolato)oxotechnetium(V).

A 2.85 mL aliquot of neat ethylene glycol (51.23 mmol) was added in one portion to a solution of 1.02307 g (2.05 mmol) of $(n-Bu_4N)[TcOCl_4]$ in 20 mL of MeOH. A solution of 0.77627 g (9.46 mmol) of sodium acetate in 20 mL MeOH was added dropwise to the reaction mixture. The addition of 300 mL of Et_2O to this solution affords a light purple precipitate, which was separated by filtration, and extracted with three 50 mL portions of boiling EtOH. The combined filtered extracts were reduced in volume on a rotary evaporator until a substantial yield of small blue-purple crystals was produced. The crystals were carefully filtered from the mother liquor, washed with 5 mL of cold EtOH, and dried in vacuo. This synthesis yielded 0.23242 g of $Na[TcO(OCH_2CH_2O)_2]$, 44% based on Tc.

Analysis, $C_4H_8NaO_5Tc$, calcd: C, 18.61; H, 3.12; Na, 8.91; Tc, 38.36.

found: C, 19.18; H, 3.19; Na, 8.64; Tc, 37.80.

RESULTS AND DISCUSSION

The synthetic utility of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ as precursor to the large class of bis(1,2-dithiolato)oxotechnetate complexes was conclusively demonstrated^{1b} by Trop et al. We have now extended its utility by reacting it with catechol and ethylene glycol, and have isolated and characterized the first examples of bis(1,2-diolato) complexes of oxotechnetium(V).

Tetrabutylammonium bis(catecholato)oxotechnetium(V) (1) was positively identified by X-ray crystallography (Figure 9). Pertinent bond lengths and bond angles are given in Tables 13 and 14, respectively. The coordination geometry is square pyramidal, just like the TcOS_4 and TcOS_2O_2 complexes discussed in the previous chapter.

There is a strong band in the infrared spectrum of 1 at 970 cm^{-1} , which can be assigned to the Tc-oxo (apical) stretch (Figure 10). A similar band occurs at 930 cm^{-1} in $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{S}_2\text{C}_6\text{H}_3(\text{CH}_3))_2]^{12}$, 940 cm^{-1} in $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2]^{13}$, and 948 cm^{-1} in $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]^{2}$, which suggests that the π -bonding between the Tc atom and the terminal oxygen atom becomes stronger as the cis donor atoms bonded to the Tc atom in the basal plane become harder in nature.

A structurally analogous low spin d^2 complex is found in the oxoosmium(VI) diester $\text{OsO}(\text{O}_2\text{C}_2\text{H}_4)_2^{14}$. The Os-O (terminal) bond length is $1.66(1)\text{ \AA}$; the Os-O (ester) average bond length is $1.89(1)\text{ \AA}$; and the average O(terminal)-Os-O(ester) bond angle is 110° . There is an Os=O stretch at 992 cm^{-1} in the IR. All of these parameters agree well with those of $\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2^-$.

The optical spectrum of 1 in MeCN (Figure 11) is dominated by a single, intense, unsymmetrical band ($\lambda_{\text{max}} = 278\text{ nm}$; $\epsilon = 14,000\text{ L mol}^{-1}\text{ cm}^{-1}$).

Figure 9

Structure of the Anion of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$

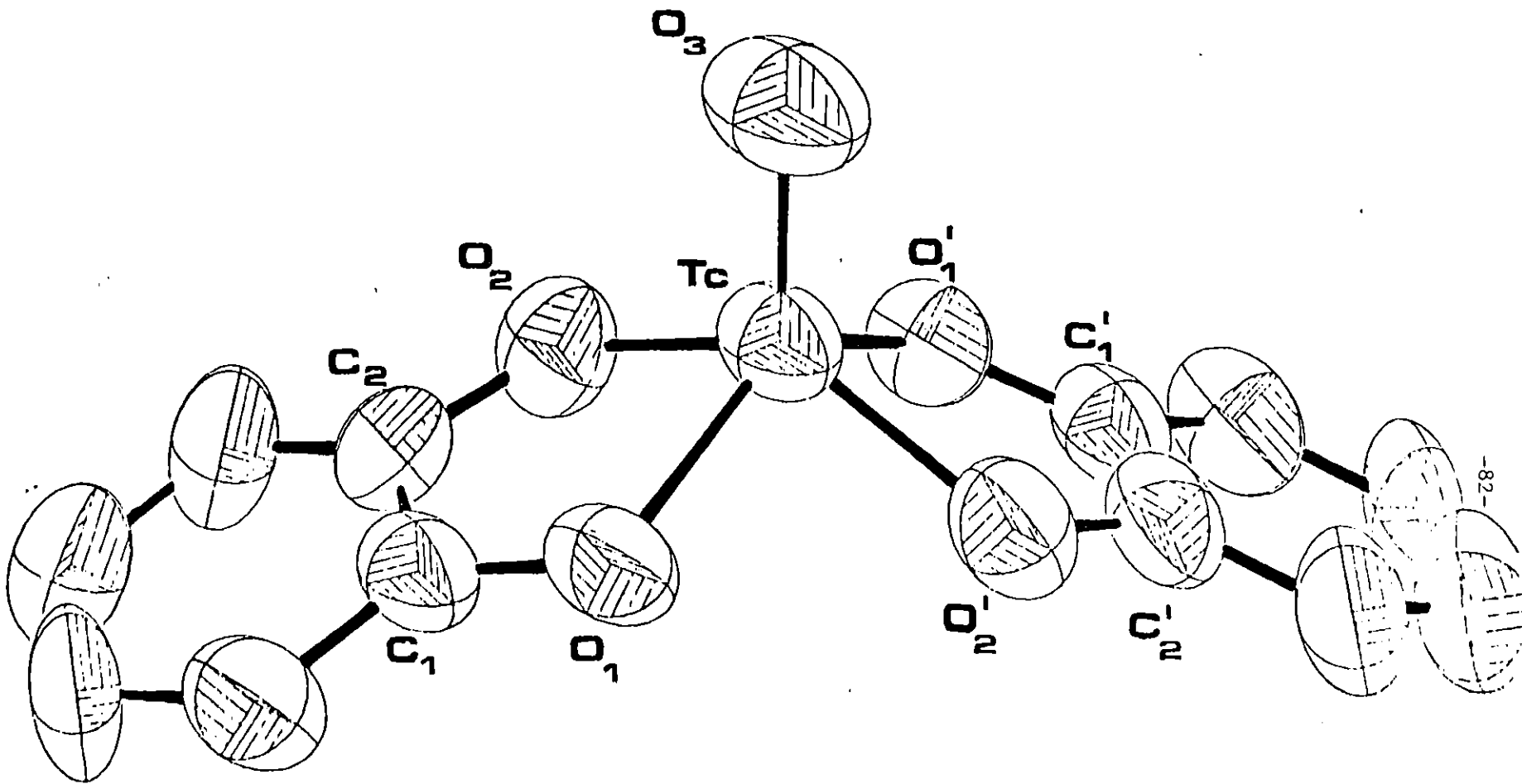
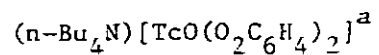


Table 13

Selected Bond Lengths in Crystalline

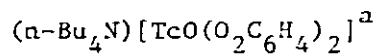


<u>Atom 1</u>	<u>Atom 2</u>	<u>Distance (Å)</u>
Tc	O ₁	1.955(5)
Tc	O ₂	1.953(5)
Tc	O ₃	1.622(7)
C ₁	O ₁	1.366(9)
C ₂	O ₂	1.365(9)
C ₁	C ₂	1.36(1)

a) For atomic numbering scheme, see Figure 9.

Table 14

Selected Bond Angles in Crystalline



<u>Atom 1</u>	<u>Atom 2</u>	<u>Atom 3</u>	<u>Angle (degrees)</u>
O ₁	Tc	O ₂	81.6(2)
O ₁	Tc	O ₂	83.5(2)
O ₁	Tc	O ₁	134.4(2)
O ₂	Tc	O ₂	140.8(2)
O ₁	Tc	O ₃	112.8(1)
O ₂	Tc	O ₃	109.6(2)

a) For atomic numbering scheme, see Figure 9.

Figure 10

Infrared Spectrum of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$

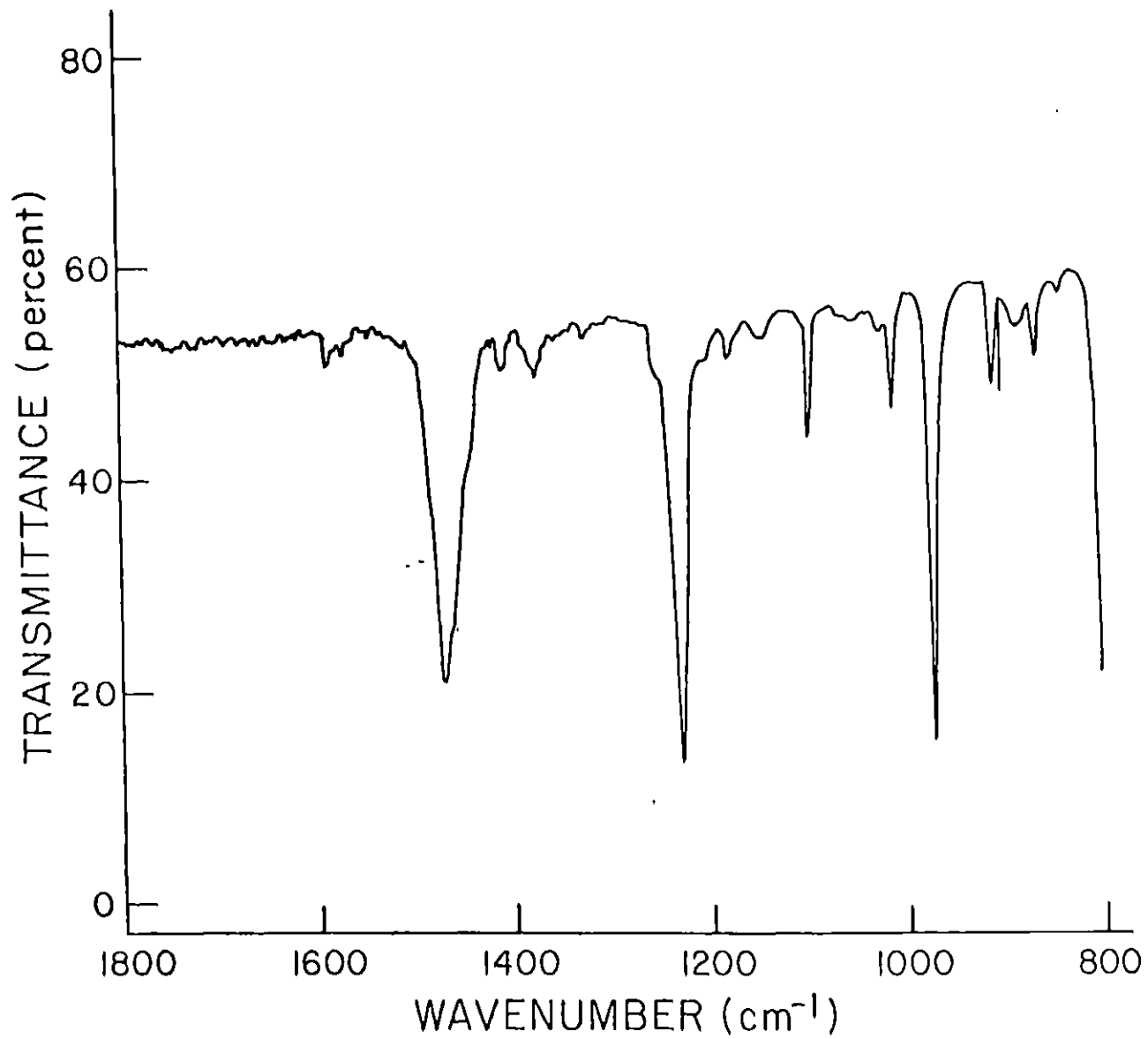
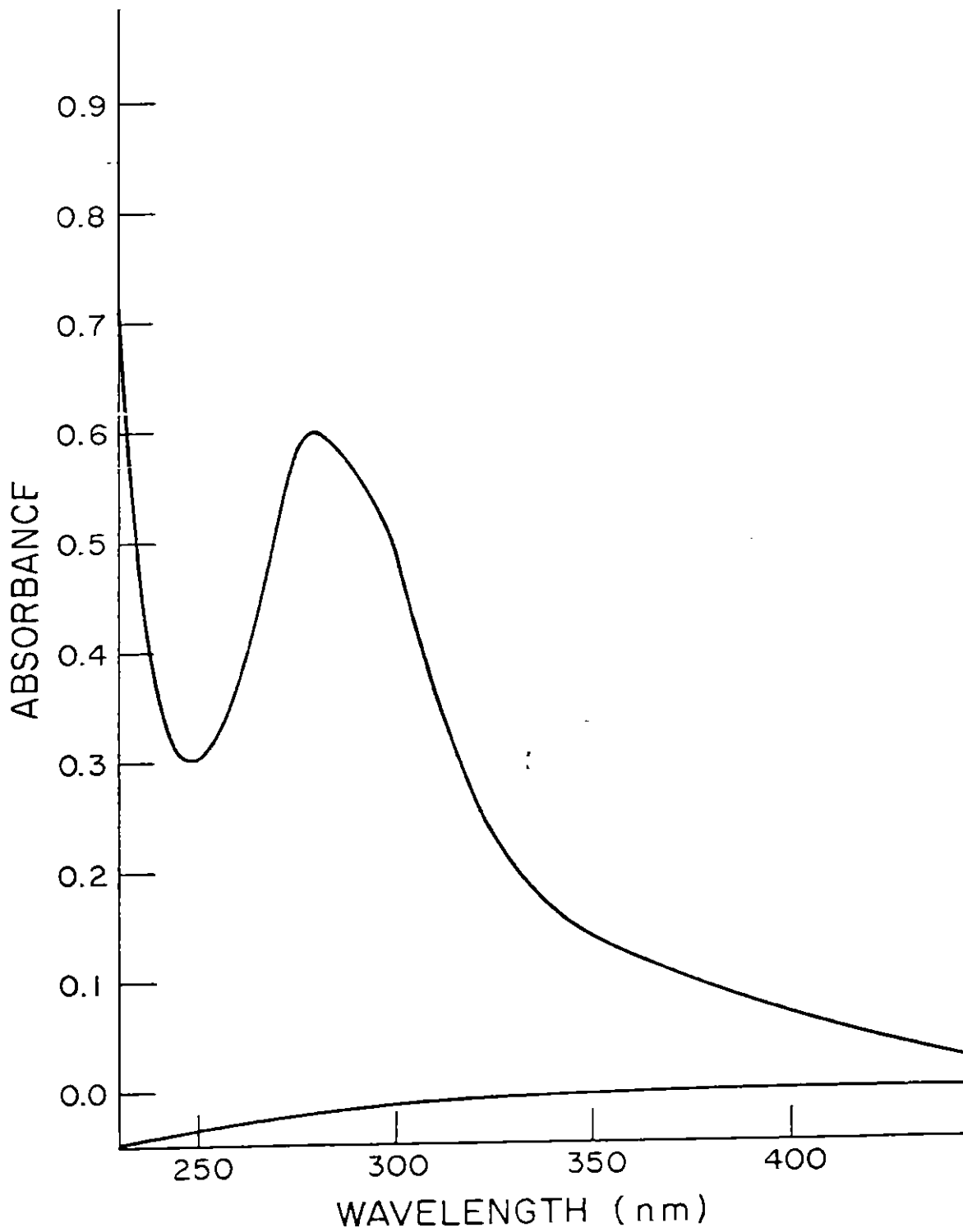


Figure II

Electronic Spectrum of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$



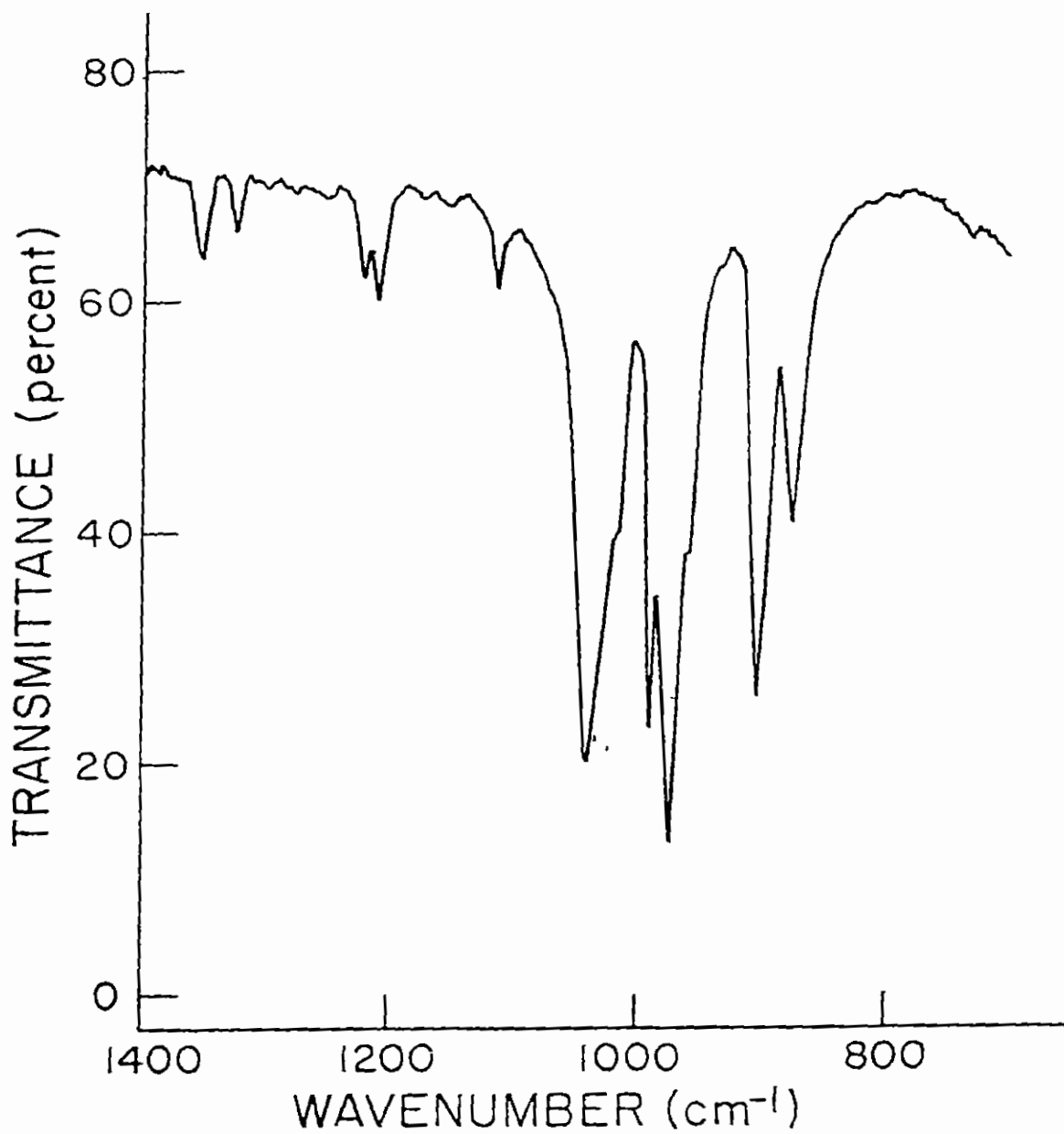
It should be recalled that the major spectral feature of the toluene-dithiolato member of the TcOS_4 series¹² was also intense ($\epsilon = 13,000 \text{ L mol}^{-1} \text{ cm}^{-1}$).

The compound $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$ (2) was prepared by reacting TcOCl_4^- with a 25-fold excess of ethylene glycol and a greater-than 4-fold excess of sodium acetate. Unlike the reaction^{1b} of 1,2-dithiols with TcOCl_4^- , there is no visible change in the color of the reaction mixture when a stoichiometric amount of ethylene glycol is added. Even at large molar excesses of the ligand, when the complex has formed, the addition of water and Bu_4NCl or Ph_4AsCl did not effect precipitation of the product as salts of these cations. In an effort to make the product less water-soluble, 1,2-cyclohexyldiol was used as the ligand in a similar preparation. Treatment of the reaction mixture with four equivalents of sodium acetate in the absence of additional counter-ions caused the precipitation of an amorphous blue powder, which was insoluble in all the common solvents tried, and thus could not be crystallized. It was finally possible to bring 2 out of solution by the addition of a large quantity of Et_2O , and the product was recrystallized easily from hot EtOH .

Identification of 2 depends on its elemental analysis and its field desorption mass spectrum¹¹. Peaks are observed in the cation FDMS of this compound at $m/e = 235$ ($[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]^+$), 258 ($\{\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]\}^+$), and 271 ($\{\text{Na}_2[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]\}^+$). The infrared spectrum of 2 has a number of strong bands in the $900\text{--}1000 \text{ cm}^{-1}$ region (Figure 12). Although the strongest of these is at 972 cm^{-1} and is a very likely candidate for the $\text{Tc}=\text{O}$ stretch, the presence of bands at 955 and 989 cm^{-1} makes this assignment ambiguous.

Figure 12

Infrared Spectrum of $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$



The optical spectrum of 2 in MeOH (Figures 13 and 14) is characterized in the visible region by a weak band at 535 nm ($\epsilon = 60 \text{ L mol}^{-1} \text{ cm}^{-1}$). There is also an inflection at 355 nm ($\epsilon = 50 \text{ L mol}^{-1} \text{ cm}^{-1}$). At higher energy, there is an almost-resolved inflection at 250 nm ($\epsilon = 3500 \text{ L mol}^{-1} \text{ cm}^{-1}$). The extinction coefficient of this band is similar to that of the main spectral features of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2^-$ (3) and $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ (4) and the progression in values of λ_{max} for each of these (250 nm for 2, 357 nm² for 3, and 400 nm^{13b} for 4), suggests a red shift as sulfurs are added to, and oxygen removed from, the $\text{TcOS}_x\text{O}_{(4-x)}$ core. The complex $(\text{n-Bu}_4\text{N})[\text{TcOCl}_4]$ instantly decomposes¹⁵ in water to TcO_4^- and TcO_2 . By contrast, a solution of 2 in water turns brown over several minutes. It can be stabilized indefinitely by the addition of some ethylene glycol to the solution. Furthermore, if a methylene chloride solution of 1 is extracted with aqueous NaBPh_4 , the $\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2^-$ now in the aqueous phase is substantially stable for 24 hours, after which there is only slight decomposition. Surprisingly, when TcO_4^- is reacted with a stoichiometric amount of ethylene glycol and sodium dithionite in alkaline medium, the characteristic purple color of $\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2^-$ develops and persists for several minutes, before decomposition sets in. This attests to the relative affinity of the ligand for the TcO^{3+} core, even under conditions where TcO_4^- would be instantly reduced to $\text{TcO}_2 \cdot x\text{H}_2\text{O}$.

The synthesis and characterization of 1 and 2 are relevant to our understanding of $^{99\text{m}}\text{Tc}$ radiopharmaceuticals already in use. The large ligand-to-Tc ratios in all such preparations suggest that complexes of the TcOO_4^- -type will be readily formed and stable under the reducing conditions used.

Figure 13

Electronic Spectrum of $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$,
Showing Low Energy Features

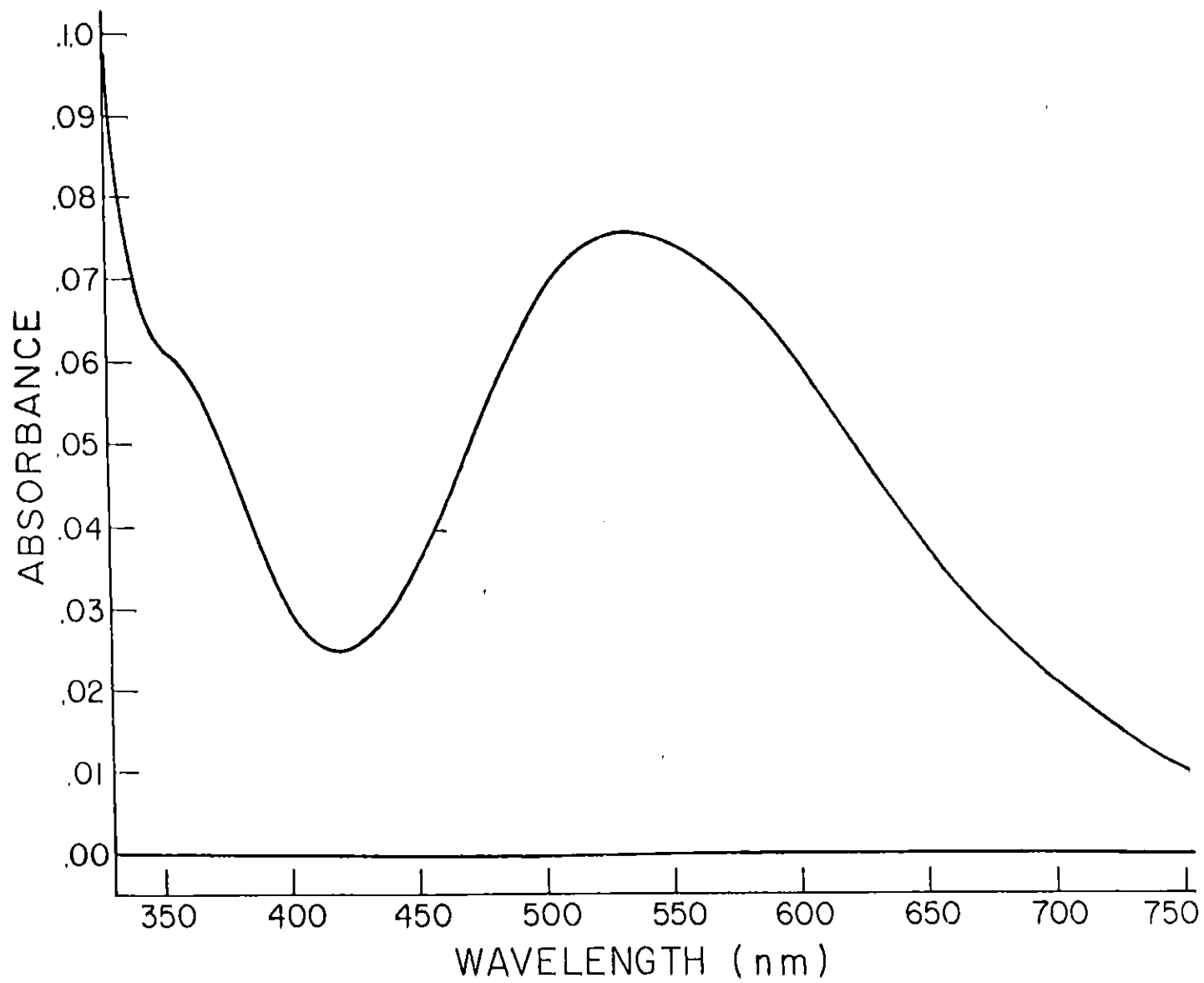
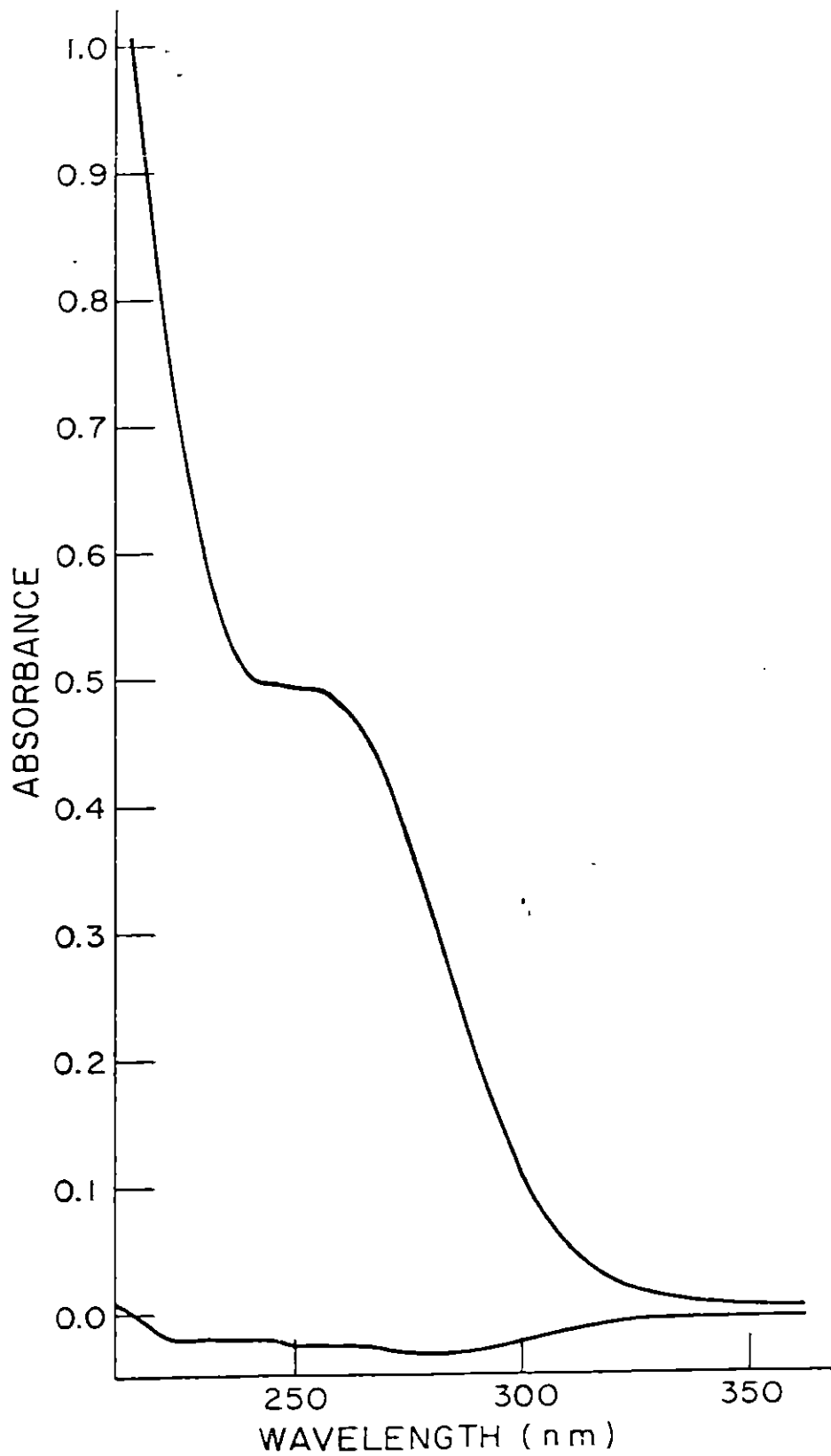


Figure 14

Electronic Spectrum of $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$,

Showing High Energy Features



Recently, de Kieviet investigated¹⁶ the structure of ^{99m}Tc-glucoheptonate (a renal agent) by studying the properties of a ⁹⁹Tc complex formed by Sn(II) reduction of a solution of ⁹⁹TcO₄⁻ and excess glucoheptonate. The product (which was not isolated) had absorbances in its optical spectrum at 502 nm ($\epsilon = 65 \text{ L mol}^{-1} \text{ cm}^{-1}$) and 270-280 nm ($\epsilon \sim 2,800$). Bands in the IR at 930 and 970 cm^{-1} suggested the presence of the Tc=O moiety, and it was deduced from the IR that the carboxylate-oxygen of the ligand was involved in the binding. The final identification¹⁶ of this unisolated species as bis(glucoheptonato)oxotechnetium(V) is consistent with what we now understand about 1 and 2.

It is instructive at this point to summarize and compare the relevant structural parameters and $\nu(\text{Tc}=\text{O})$ of the representative members of the class of complexes with the $\text{TcOS}_x\text{O}_{(4-x)}$ core (Table 15). The average Tc-S bond length seems to be the same in the TcOS_4 and TcOS_2O_2 cores, and the average Tc-O (ligand) distance also seems to be independent of the core type, be it TcOS_2O_2 or TcOO_4 . The Tc-oxo bond length varies but slightly across the series, and the distance from the metal to the basal plane varies a substantial, though seemingly irregular, amount from core to core. Even with the qualification that the anion of 1 is not strictly comparable to these TcOS_4 and TcOS_2O_2 complexes because of the aromaticity of the ligand, it is evident that the structural parameters of $\text{TcOS}_x\text{O}_{(4-x)}$ complexes do not vary systematically with the value of x.

There does seem to be a systematic variation in the Tc=O stretch across the series. As sulfurs are replaced by oxygens, the band shifts to higher energy, at least for the ethanedithiolato-2-mercaptoethanolato-catecholato series. That this frequency shift is correlated with the polarizability of the ligating atoms is supported by the values of

Table 15
Comparative Structural and Infrared Parameters
of Four Oxotechnetium(V) Complexes

	$\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2$ ⁻¹⁷	$\text{TcO}(\text{SCH}_2\text{COS})_2$ ^{-1a}	$\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2$ ⁻²	$\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2$ ⁻
d(Å) Tc-O _t	1.64(1)	1.672(8)	1.662(5)	1.622(7)
d(Å) Tc-S(av)	2.300(13)	2.320(4)	2.290(3)	---
d(Å) Tc-O(av)	---	---	1.950(6)	1.954(7)
Tc-to-basal plane	0.761(2)	0.791	0.720(1)	0.707
$\nu(\text{Tc-O})$ (cm ⁻¹)	940	950	948	970

$\nu(\text{Tc=O})$ for the following series: $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ (940 cm^{-1})¹³, $\text{TcO}(\text{SCH}_2\text{COS})_2^-$ (950 cm^{-1})^{1a}, $\text{TcO}(\text{SOCCOS})_2^-$ (972 cm^{-1})^{1b}. As electron-withdrawing carbonyl oxygens are added to the dithiolato ligand in this series, the sulfurs become "harder", less polarizable, and $\nu(\text{Tc=O})$ shifts to higher frequencies.

The results in this chapter establish that stable bis(1,2-diolato) oxotechnetium(V) complexes can be prepared and are resistant to hydrolysis in the presence of excess diol. They clearly suggest that the same type of core structure can exist in ^{99m}Tc-radiopharmaceuticals with oxygen-donor ligands.

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CHAPTER 4

Ligand Exchange Reactivity Patterns of
Oxotechnetium(V) Complexes

INTRODUCTION

In the previous chapters, the synthesis and characterization of a number of oxotechnetium(V) complexes with core structures $TcOS_xO_{(4-x)}$ ($x = 0, 2, 4$) have been reported. X-ray structural studies of at least one member of the series for each value of x have shown square pyramidal coordination of Tc to be the rule. Each of these Tc(V) complexes has been prepared from aqueous solution, or has been shown ($x = 0$) to be stable in aqueous solution in the presence of excess ligand, as would be found in a radiopharmaceutical synthesis. The conjecture¹ that all ^{99m}Tc -radiopharmaceuticals probably contain Tc(IV) has been shown to be implausible.

The preparation of citrate² and gluconate³ complexes of Tc(V) has been reported. These complexes, prepared in situ by Sn(II) reduction of TcO_4^- in the presence of an excess of ligand, or by reaction of the ligand with $TcOCl_4^-$, have not been isolated. Further, spectroscopic evidence⁴ indicates the formation of a 2:1 dimercaptosuccinate : Tc complex by the reaction of dimercaptosuccinic acid with a solution of the Tc-gluconate complex. Also, the known compound $(Et_4N)[TcO(mnt)_2]$ ($mnt =$ maleonitriledithiolate) has been similarly prepared⁵ and isolated. These reports of ligand exchange on what are presumably oxotechnetium(V) complexes with oxygen-donor ligands has prompted this investigation of the reactivity of $TcO(OCH_2CH_2O)_2^-$ and $TcO(O_2C_6H_4)_2^-$, whose preparation and identification were described in the previous chapter. This investigation has also been extended to $TcO(SCH_2CH_2O)_2^-$, first described⁶ in Chapter 2. Spectrophotometric evidence will be presented to show the lability of all oxotechnetium(V) species having oxygen donor ligands

(i.e., TcOO_4 and TcOS_2O_2 cores) toward displacement of these ligands by 1,2-ethanedithiol.

The reactivity of TcOCl_4^- towards 1,2-dithiols is, of course, well-established,⁷ and reaction with 1,2-diols to form TcOO_4 complexes has been demonstrated in Chapter 3. During the course of an investigation of the formation of the diolato-complexes, an optical titration of TcOCl_4^- with 1,2-ethanedithiol was undertaken to evaluate the usefulness of this technique in determining ligand-co-metal stoichiometry. The surprising formation of the intermediate $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{S})_3$, the investigation of this reaction using other dithiols, and the implications of these findings for radiopharmaceutical science are also discussed in this chapter.

In a paper on the identification of $^{99\text{m}}\text{Tc}$ -radiopharmaceuticals by electrophoresis, Burns and Marzilli⁸ reported that $\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2^-$ was converted to $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ in the presence of 1,2-ethanedithiol under certain conditions. The remarkable possibility that some TcOS_4 complexes share in the lability heretofore thought reserved to TcOS_2O_2 and TcOO_4 complexes was also explored. A description of these results concludes this chapter on the ligand exchange reactivity patterns of oxotechnetium(V) complexes.

EXPERIMENTAL

Water was passed through a Barnstead D8904 cartridge for removal of organics, a Corning 3508-B demineralizer cartridge, and then distilled using a Corning Mega-Pure still. All reagents were used as received, except as otherwise noted. Aqueous $\text{NH}_4^{99}\text{TcO}_4$ was obtained from New England Nuclear. The concentration was determined by a literature method⁹.

Ethanedithiol, 3,4-toluenedithiol, 1,3-propanedithiol, sodium 2,3-dimercaptopropanesulfonate and catechol were obtained from Aldrich; citric acid and ethylene glycol from Fisher; and 3-mercaptoethanol from Eastman.

$(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ was prepared by the reaction of TcO_4^- with concentrated HCl as described¹⁰ in Chapter 1. $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2]$ was prepared by the published¹¹ procedure, and was recrystallized by concentrating a methanolic solution of the amorphous product. $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$ and $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$ were prepared by reacting the appropriate ligand with TcOCl_4^- , as described in Chapter 3. $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ was prepared⁶ by dithionite reduction of TcO_4^- , as detailed in Chapter 2.

Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia. Electronic spectra were obtained with a Cary Model 17 spectrophotometer. Infrared spectra were obtained with a Perkin Elmer 180 grating spectrophotometer as KBr pellets.

Preparation of $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{S})_3$

A solution of 24 μL 1,2-ethanedithiol (0.29 mmol) in 7 mL of MeOH was added dropwise to a stirred solution of 0.09447 g $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$

(0.19 mmol) in 20 mL of MeOH. A dark orange-red crystalline precipitate appeared immediately. This was filtered from the reaction mixture, washed with 3x10 mL portions of Et₂O, and air-dried. The electronic, infrared, and field desorption mass spectra of this material were identical to authentic samples prepared by Orvig¹².

Preparation of (TcO)₂(SCH₂CH₂CH₂S)₃

A stirred solution of 0.6691 g (n-Bu₄N)[TcOCl₄] (1.34 mmol) in 40 mL of MeOH was treated with 0.3 mL of 1,3-propanedithiol (2.99 mmol). A dark precipitate appeared immediately, which was filtered from the reaction mixture, and extracted with three 10 mL portions of CH₂Cl₂. The combined filtered extracts were taken to dryness on a rotary evaporator. The solid residue was extracted with three 10 mL portions of MeOH, and the extracts discarded. The remaining solid was extracted with 10 mL of CH₂Cl₂. The filtered extract was treated dropwise with MeOH until a large mass of crystals had formed. These were filtered from the mother liquor, washed with a few mL of MeOH, and dried in vacuo. The yield of brick red (TcO)₂(SCH₂CH₂CH₂S)₃ was 0.10546 g; 14% based on Tc.

Analysis, C₉H₁₈O₂S₆Tc₂, calcd: C, 19.70; H, 3.31; S, 35.07

found: C, 20.13; H, 3.17; S, 34.87

Optical Titration of Na[TcO(OCH₂CH₂O)₂] with 1,2-Ethanedithiol

A solution of 0.03266 g Na[TcO(OCH₂CH₂O)₂] in 100 mL MeOH was prepared volumetrically. A 2.5 mL aliquot of this was diluted to 10 mL (c = 3.16 x 10⁻⁴ M). The electronic spectrum of this solution from 550 to 350 nm was recorded, as was the baseline (MeOH vs. MeOH). A solution containing 51 μL of 1,2-ethanedithiol in 100 mL of MeOH was prepared

($c = 6.09 \times 10^{-3}$ M). Aliquots of 50 μ L (3.043×10^{-7} moles; 0.1 equivalent based on Tc) were added to the diluted solution of $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$, and its spectrum recorded after each addition.

Optical Titration of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$ with 1,2-Ethanedithiol

A solution of 0.01669 g of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$ in 100 mL MeOH was prepared volumetrically ($c = 2.909 \times 10^{-4}$ M). The electronic spectrum of this solution from 500 to 340 nm was recorded, as was the baseline (MeOH vs. MeOH). A solution of 48.8 μ L of 1,2-ethanedithiol in 10 mL MeOH was prepared ($c = 5.82 \times 10^{-2}$ M). Aliquots of 50 μ L (2.91×10^{-6} moles; 0.1 equivalent based on Tc) were added to the solution of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$ and its spectrum recorded after each addition.

Reaction of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ with 1,2-Ethanedithiol

A. A solution of 0.01846 g of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ in 100 mL of MeOH was prepared ($c = 2.84 \times 10^{-4}$ M), and its visible spectrum recorded. A solution of 48 μ L of 1,2-ethanedithiol in 1 mL of MeOH was prepared ($c = 5.73 \times 10^{-1}$ M), and 100 μ L of this (5.73×10^{-5} moles; 2 equivalents, based on Tc) added to the $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ solution. The spectrum of the reaction mixture was recorded every 30 minutes for 3.5 hours.

B. A solution of 0.5358 g of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ in 100 mL of MeCN was prepared ($c = 8.24 \times 10^{-4}$ M). A 5 mL aliquot of this solution was diluted to 15 mL ($c = 2.75 \times 10^{-4}$ M) and its visible spectrum recorded. Approximately 3 minutes after the addition of 70 μ L of neat 1,2-ethanedithiol (8.35×10^{-4} moles; 203 equivalents based on Tc) to the diluted solution, its spectrum was rescanned, and the spectrum of the intermediate observed.

Optical Titration of (n-Bu₄N)[TcOCl₄] with Citric Acid

A solution of 0.04819 g of (n-Bu₄N)[TcOCl₄] in 10 mL of MeOH was prepared volumetrically ($c = 9.66 \times 10^{-3}$ M) and the electronic spectrum of this solution from 800 to 500 nm recorded. A solution of 3.1907 g of citric acid monohydrate in 25 mL of MeOH was prepared ($c = 0.607$ M). Aliquots of 16 μ L (9.7×10^{-6} moles; 0.1 equivalent based on Tc) were added to the solution of (n-Bu₄N)[TcOCl₄], and its spectrum recorded after each addition.

Reaction of 1,2-Ethanedithiol with Tc-Citrate Complex

A. To a stirred solution of 0.4786 g (n-Bu₄N)[TcOCl₄] (0.1 mmol) in 7 mL of MeOH was added a solution of 0.21148 g of citric acid·H₂O (1 mmol) in 7 mL of MeOH. The reaction mixture was diluted to 25 mL with MeOH and the visible spectrum of an aliquot recorded. A broad λ_{\max} at 693 nm was observed, $\epsilon = 33 \text{ L mol}^{-1} \text{ cm}^{-1}$. One milliliter of this solution (3.8×10^{-3} mmol) was combined with 1.6 μ L of 1,2-ethanedithiol (1.9×10^{-2} mmol) and diluted to 10 mL. The resulting spectrum was that of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$, and using $\epsilon(400 \text{ nm}) = 3000 \text{ L mol}^{-1} \text{ cm}^{-1}$, a spectrophotometric yield of 90% was calculated.

B. To a solution of 0.05109 g of (n-Bu₄N)[TcOCl₄] (0.1 mmol) in a few mL of MeOH was added 0.24406 g citric acid·H₂O (1.2 mmol), followed by 0.96 mL of 0.625 M NaOH (0.6 mmol), after which the reaction was diluted to 10 mL. The visible spectrum of this mixture has λ_{\max} at 490 nm ($\epsilon = 55 \text{ L mol}^{-1} \text{ cm}^{-1}$). A 250 μ L aliquot (2.5×10^{-3} mmol) of the mixture was diluted to 25 mL with MeOH and 1.1 μ L of 1,2-ethanedithiol (1.3×10^{-2} mmol) added. The spectrum of the resulting solution was that of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$, with a spectrophotometric yield of 84%.

Optical Titration of Tc-Citrate Complex with 2,3-Dimercaptopropanesulfonate

To a solution of 0.05863 g of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ (0.12 mmol) in 25 mL of MeOH was added 0.3520 g of sodium citrate $\cdot 2\text{H}_2\text{O}$ (1.2 mmol). A 0.5 mL aliquot of this solution was diluted to 10 mL with H_2O ($c = 2.4 \times 10^{-4}$ M). The electronic spectrum of this solution from 500 to 300 nm was recorded, as was the baseline (H_2O vs. H_2O). A solution of 0.26655 g of sodium 2,3-dimercaptopropanesulfonate (1.27 mmol) was dissolved in 2 mL of H_2O . One milliliter of this solution was diluted to 20 mL with H_2O ($c = 3.18 \times 10^{-2}$ M). Aliquots of 21 μL (0.28 equivalent, based on Tc) of this ligand solution were added to the diluted Tc-citrate solution, the spectrum of which was recorded after each addition. A 20 minute lag was noted between the addition of the ligand aliquot and the stabilization of the spectrum. The final spectrum was the same as that of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$, and the spectrophotometric yield, assuming the same extinction coefficient as the ethanedithiol complex, was 94%.

Optical Titration of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ with 1,2-Ethanedithiol

A solution of 0.02032 g of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ (0.04 mmol) in 100 mL MeOH was prepared volumetrically ($c = 4.1 \times 10^{-4}$ M). The visible spectrum of this solution from 500 to 300 nm was recorded, as was a baseline (MeOH vs. MeOH). A solution of 0.34 mL 1,2-ethanedithiol (4.1 mmol) in 10 mL MeOH was prepared ($c = 0.41$ M). Aliquots of 10 μL (4.1×10^{-3} mmol; 0.1 equivalent based on Tc) of the dithiol solution were added to the solution of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$, and its spectrum was recorded after each addition.

Optical Titration of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ with 1,3-Propanedithiol

A solution of 0.02633 g of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ (0.05 mmol) in 10 mL of MeOH was prepared, and 5.3 mL of it (0.03 mmol) were diluted to 100 mL

with MeOH ($c = 3.0 \times 10^{-4}$ M). The visible spectrum of this solution from 550 to 350 nm was recorded, as was the baseline (MeOH vs. MeOH). A solution of 56.5 μ L of 1,3-propanedithiol (0.56 mmol) in 100 mL of MeOH was prepared ($c = 5.6 \times 10^{-3}$ M). A 10 mL aliquot of the $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ solution (3.0×10^{-6} moles) was treated with successive 100 μ L aliquots (6×10^{-7} moles; 0.2 equivalent based on Tc) of the dithiol solution, and the spectrum of the reaction mixture recorded after each addition.

Optical Titration of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ with 3,4-Toluenedithiol

A solution of 0.02220 g of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ (4.4×10^{-2} mmol) in 50 mL of MeOH was prepared, and 6.9 mL of this solution (6.1×10^{-3} mmol) diluted to 100 mL with MeOH ($c = 6.1 \times 10^{-5}$ M). A solution of 0.21952 g of 3,4-toluenedithiol (1.4 mmol) in 10 mL of MeOH was prepared, and 4.4 mL of this (6.2×10^{-1} mmol) diluted to 10 mL with MeOH ($c = 6.2 \times 10^{-2}$ M). The visible spectrum of the diluted TcOCl_4^- solution from 500 to 300 nm was recorded, as was the baseline (MeOH vs. MeOH). Aliquots of 10 μ L of the dithiol solution (6.2×10^{-4} mmol; 0.1 equivalent based on Tc) were added to the solution of TcOCl_4^- , and the spectrum of the reaction mixture recorded after each addition.

Reaction of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2]$ with 1,2-Ethanedithiol

A. The spectrum of a solution of 0.02623 g of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2]$ in 100 mL of MeOH ($c = 3.7 \times 10^{-4}$ M) was recorded. A 25 mL aliquot of this solution was diluted to 50 mL and treated with 77 μ L of 1,2-ethanedithiol (0.9 mmol ligand:0.009 mmol complex). The spectra of aliquots of this mixture were recorded at 1.5 hours and 30 days. A 5 mL aliquot of the mixture (at $t = 0$) was treated with ca. 10 μ L of 2N HCl, and its spectrum recorded after 0.5 hours.

B. A solution of 0.01353 g of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2]$ (1.0×10^{-2} mmol) in 100 mL of MeOH was prepared. Aliquots of 20 mL were treated with 32 μL of 1,2-ethanedithiol (100 equivalents ligand:Tc) and enough 0.2N HCl or 2.0N HCl to produce a $\text{H}^+:\text{Tc}$ ratio of 1 (19 μL of 0.2N), 2 (38 μL of 0.2N), 4 (76 μL of 0.2N), or 10 (19 μL of 2.0N). The visible spectra of these reaction mixtures were monitored periodically.

Kinetic Study of the Reaction of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2]$ with 1,2-Ethanedithiol

A stock solution of 3.16×10^{-4} M $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2]$ was prepared. There were three kinetic runs during which the absorbance at 475 nm was continually monitored. The compositions of the runs were as follows: #1, 25 mL stock solution + 66 μL 1,2-ethanedithiol + 0.79 mL of 0.2N HCl (1 Tc:100 dithiol:20 HCl); #2, 12.5 mL of stock solution + 33 μL 1,2-ethanedithiol + 1.2 mL of 0.2N HCl (1 Tc:100 dithiol:30 HCl); #3, 10 mL stock solution + 79 μL 1,2-ethanedithiol + 0.32 mL of 0.2N HCl (1 Tc:298 dithiol:20 HCl). The absorbance at 120 minutes was taken as A_∞ . A plot of $\ln(A - A_\infty)$ vs. time was linear over the first hour (correlation coefficient = 0.9997). To test for second-order behavior, the same data were plotted as $(A - A_\infty)^{-1}$ vs. time. The best straight line fitting the first hour's data had a correlation coefficient of only 0.978. The slopes of the three first-order plots and the initial concentration data were used to calculate the reaction order of the dithiol and HCl.

RESULTS AND DISCUSSION

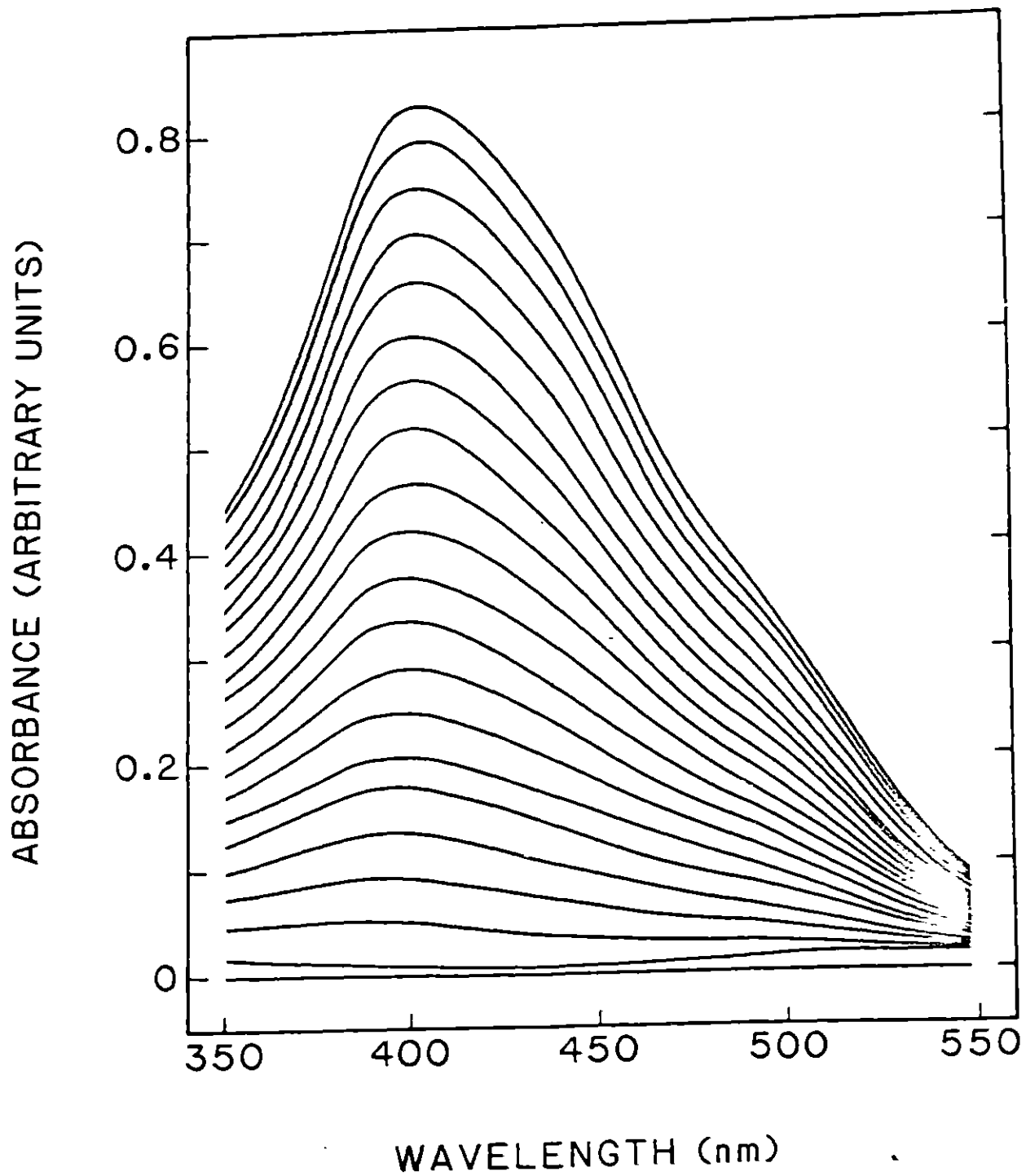
The affinity of the Tc(V)O^{3+} moiety for dithiolate ligands was first demonstrated¹³ in the fortuitous synthesis of $\text{TcO}(\text{SCH}_2\text{COS})_2^-$ from the dithiol contaminant in thioglycolic acid (HSCH_2COOH). This affinity was later highlighted in studies⁷ of the reactions of 1,2-dithiols (and 1,2-dithiolates) with the extremely labile TcOCl_4^- ion, to form a variety of bis(1,2-dithiolato)oxotechnetium(V) species. The formation of $\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2^-$ and $\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2^-$, described in the previous chapter, extended the list of ligands that stabilize the Tc(V)O^{3+} group to include 1,2-diolates. Literature reports²⁻⁵ of labile, uncharacterized complexes of Tc with oxygen donors led to the investigation of the reactivity of the already-characterized (1,2-diolato)oxotechnetium(V) complexes by UV-visible spectrophotometry, taking advantage of the clear-cut spectral differences among the species with $\text{TcOS}_x\text{O}_{(4-x)}$ ($x = 0, 2, 4$) cores. It was hypothesized that there is an order of relative affinity for Tc(V)O^{3+} among these ligands, and the experimental results thus far have borne this out.

Scanning the optical spectrum of a methanolic solution of $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$ after successive additions of 0.1 mole-equivalent aliquots of 1,2-ethanedithiol (Figure 15) shows the simple ingrowth of the spectrum of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$. The limiting spectrum is attained after the addition of 1.9 equivalents of the dithiol. This apparently one-step reaction is in marked contrast to the reaction of TcOCl_4^- with substoichiometric amounts of 1,2-ethanedithiol to form the intermediate $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{S})_3$, discussed later in this chapter.

When $\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2^-$ (the catecholato complex) was similarly titrated with twenty 0.1 equivalent aliquots of 1,2-ethanedithiol, the spectrum

Figure 15

Optical Titration of $\text{Na}[\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2]$
with 1,2-Ethanedithiol (in MeOH)



that developed initially was not that of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ ($\lambda_{\text{max}} = 400 \text{ nm}$) but rather exhibited λ_{max} at 370 nm, barely resolved from the strong tailing absorption at shorter wavelengths. Addition of 20 μL of neat dithiol to a 5 mL aliquot of this mixture shifted the maximum to 390 nm and enhanced its resolution considerably. After 24 hours, the spectra of both the sample containing excess dithiol and the sample containing the stoichiometric amount of dithiol had developed fully into the spectrum¹¹ of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$.

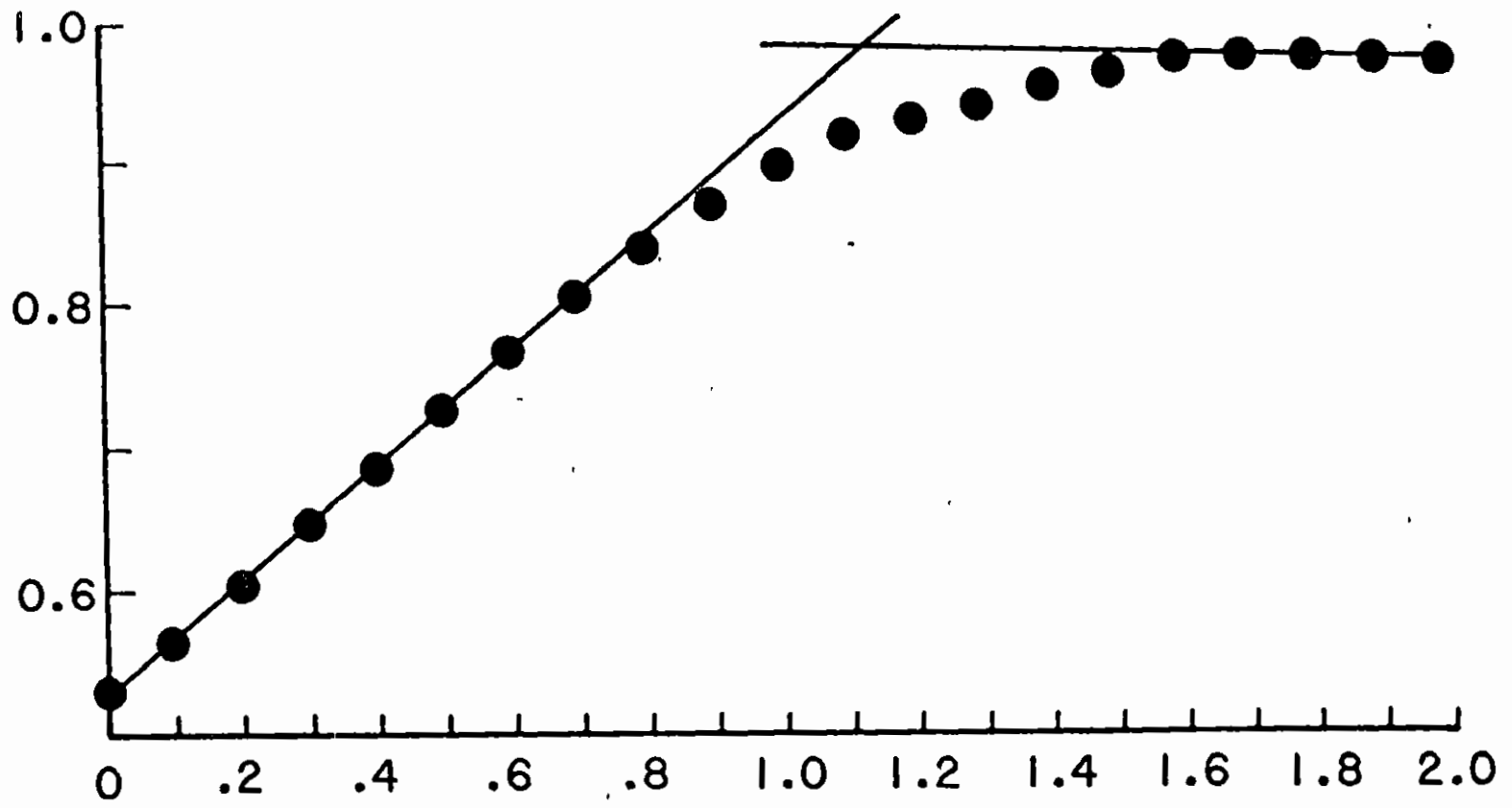
The observation of the species with λ_{max} at 370 nm is a kinetic artifact. As no alteration of the intermediate spectrum of the stoichiometric system had been observed during or shortly after the titration, the rate of reaction from starting material to intermediate was seen to be much greater than the rate of reaction from intermediate to final product, and so a mole-ratio plot¹⁴ was constructed. The plot (Figure 16) suggests that the intermediate contains one molecule of ethanedithiol per atom of technetium. A mixed (catecholato)(1,2-ethanedithiolato)oxotechnetium complex seems possible, and is supported by the fact that the 370 nm absorbance maximum is intermediate between that of the bis(catecholato) complex (280 nm) and the bis(ethanedithiolato) complex¹⁵ (400 nm).

When a methanolic solution of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ was treated with 2 equivalents of 1,2-ethanedithiol, the spectrum of a new species slowly grew in. A series of nine scans over a 3.5 hour period showed a family of spectra with isosbestic points at 323 and 375 nm. An absorption maximum at about 408 nm seemed to be developing during this time. After 18 hours, the solution spectrum was fully that of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ ($\lambda_{\text{max}} = 400 \text{ nm}$). This final spectral curve did not intersect the isosbestic

Figure 16

Mole-Ratio Plot, Reaction of $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{O}_2\text{C}_6\text{H}_4)_2]$
with 1,2-Ethanedithiol (in MeOH)

ABSORBANCE AT 370 nm



EQUIVALENTS DITHIOL ADDED

points. In an experiment where approximately 200 equivalents of 1,2-ethanedithiol were added to the bis(2-mercaptoethanolato) complex, an absorption maximum at 422 nm rapidly developed (Figure 17). The trace of this spectrum intersected that of the starting complex at 323 and 378 nm. The maximum began to decrease in absorption soon after it developed. These observations suggest that the reaction of 1,2-ethanedithiol with $\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2^-$ proceeds via a single intermediate with λ_{max} at 422 nm, and that further reaction to $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ proceeds at a roughly comparable rate.

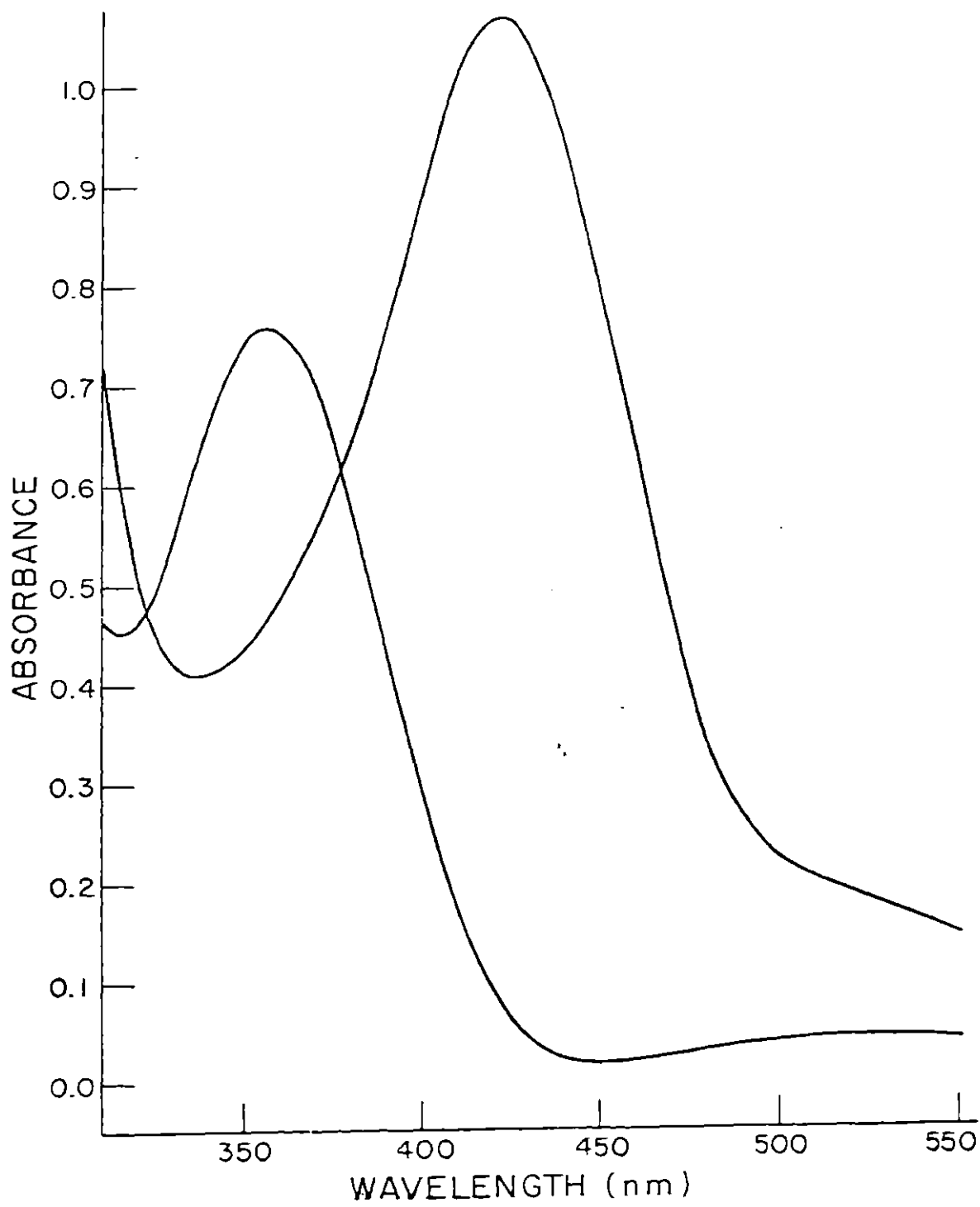
Because the initial step of the reaction is slow, a titration to determine the composition of the intermediate by the mole-ratio method was not attempted. The progression of λ_{max} to lower energy has been noted in the spectra of these oxotechnetium(V) complexes as ligand oxygens are replaced by ligand sulfurs (vide supra). The position of λ_{max} of this intermediate is anomalous if it is assumed to be the mixed ligand monomer $\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})(\text{SCH}_2\text{CH}_2\text{S})^-$. However, the spectral similarity among the intermediate and the dimer complexes $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{S})_3$ ($\lambda_{\text{max}} = 425 \text{ nm}$) and $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_3$ ($\lambda_{\text{max}} = 440 \text{ nm}$) (vide infra) suggests a structurally similar dimerized intermediate. It is not possible at this time to speculate further on the nature of the intermediate species in this reaction.

The foregoing results suggest the variety of ways in which structurally similar oxotechnetium complexes can react with a given ligand to form the same product: sometimes with no apparent intermediate, sometimes with a monomeric intermediate, and sometimes with a dimeric intermediate.

There have been reports of complexes of technetium with citrate and gluconate that undergo ligand exchange with 1,2-dithiols. Münze produced²

Figure 17

Electronic Spectrum of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ ($\lambda_{\text{max}} = 355 \text{ nm}$)
and Transient Intermediate ($\lambda_{\text{max}} = 422 \text{ nm}$) Formed on
Addition of 200 Equivalents of 1,2-Ethanedithiol (in MeOH)



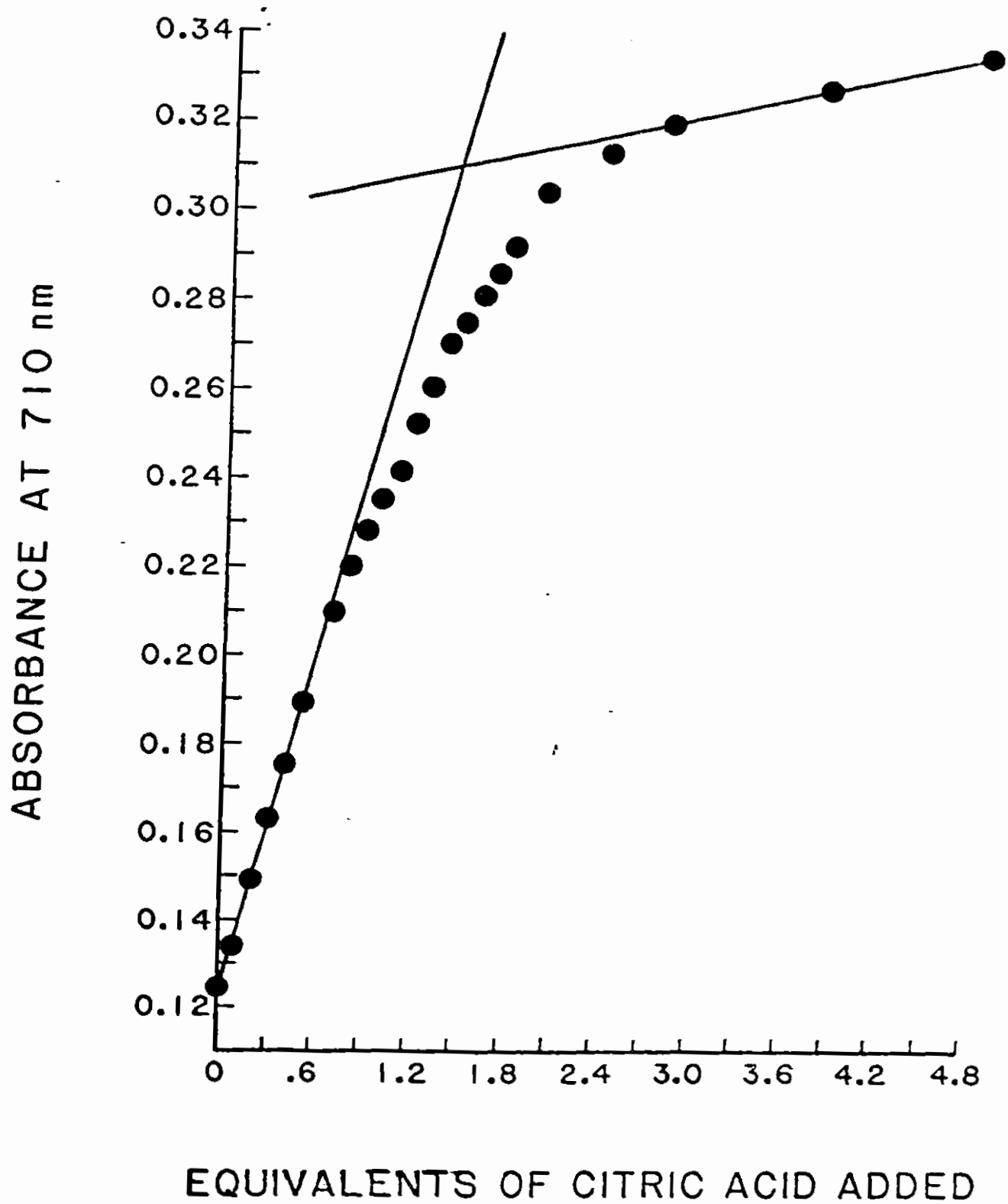
the citrate complex by stannous ion reduction of TcO_4^- in the presence of a large excess of citrate, or by addition of an excess of citric acid to a solution¹⁶ of TcOCl_4^- in concentrated hydrochloric acid. The gluconate complex was prepared³ by the same methods. Johannsen, et al, titrated¹⁹ a solution of the Tc-gluconate complex with a solution of 2,3-dimercaptopropanesulfonate (DMPS), a water-soluble analog of 1,2-ethanedithiol. They observed the uncomplicated ingrowth of a spectrum identical to that of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$, presumably the spectrum of the bis(DMPS) analog of this characterized complex.

These results have been verified and extended. A solution of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ in methanol was titrated with a solution of citric acid $\cdot\text{H}_2\text{O}$ in methanol. A mole-ratio plot¹⁴ was constructed (Figure 18), and extrapolations of the early and late parts of the curve intersect at a citrate-to-Tc ratio of 1.5. A solution of this complex was prepared by reacting 10 equivalents of citric acid $\cdot\text{H}_2\text{O}$ with 1 equivalent of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$. Addition of 5 equivalents of 1,2-ethanedithiol to this solution gave a 90% (spectrophotometric) yield of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$.

Although the 3:2 ligand-to-metal ratio experimentally indicated is unusual in light of the previously described TcOO_4 complexes, the multidentate nature of the citrate ion opens up novel possibilities for coordination. Also, the pH-dependence of the state of protonation of a tricarboxylic acid complicates the structural analysis, and a Tc-citrate complex of a given composition should not be assumed to exist at all pH values. Nevertheless, Tc-citrate preparations undergo the ligand exchange reaction with 1,2-ethanedithiol almost equally well over a range of acidities, with yields ranging from 90% in the citric acid- TcOCl_4^- system described above, to 84% in a similar system to which six

Figure 18

Mole-Ratio Plot, Reaction of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$
with Citric Acid (in MeOH)



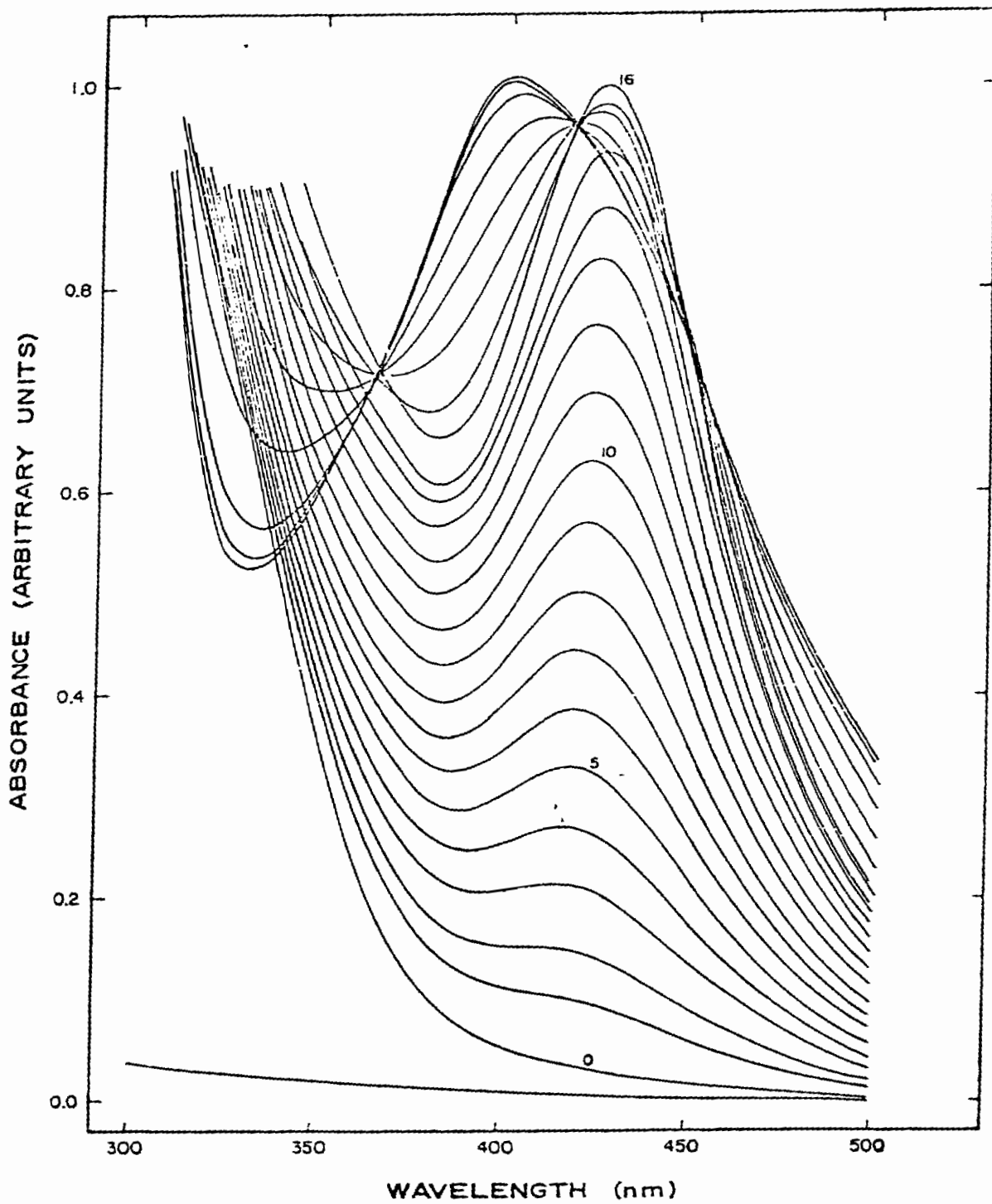
equivalents of sodium hydroxide have been added for each equivalent of technetium.

In another experiment, a methanolic Tc-citrate preparation was diluted with water without observable hydrolysis. This was titrated with an aqueous solution of DMPS, and its spectrum was scanned repeatedly during the course of the titration. The final spectrum was identical to that of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$, as expected, and no intermediates were observed. This is directly analogous to the titration of $\text{TcO}(\text{OCH}_2\text{CH}_2\text{O})_2^-$ with 1,2-ethanedithiol, previously described, and to the results of Johannsen's titration¹⁹ of Tc-gluconate with DMPS, and shows that the Tc-citrate complex can be stabilized against hydrolysis while being reactive toward ligand exchange in water.

It can be concluded from these observations that the reaction of 1,2-ethanedithiol and DMPS with the general class of complexes of technetium with aliphatic oxygen-donor ligands proceeds rapidly and without the formation of an observable intermediate.

It might be anticipated that the reaction of 1,2-ethanedithiol with the extremely labile (and hydrolytically sensitive) TcOCl_4^- would proceed directly to $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$. An optical titration revealed that this is not true. The family of spectra generated when a methanolic solution of TcOCl_4^- was titrated with 0.1 equivalent aliquots of 1,2-ethanedithiol (Figure 19) increased in absorbance monotonically as the first 1.5 equivalents of dithiol were added, but λ_{max} was at 420-425 nm, instead of the expected¹⁵ 400 nm for $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$. Addition of further aliquots of dithiol thereafter caused the peak at 425 nm to decrease, and the 400 nm maximum of the expected final product to grow in with isosbestic points at 450, 418, and 365 nm; the spectrum stabilized

Figure 19
Optical Titration of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ with
1,2-Ethanedithiol (in MeOH)



when a total of 2 equivalents of dithiol had been added.

The experimental results are most easily explained by positing an intermediate of composition $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{S})_3$, which can be formed from two square pyramids sharing an edge, this edge being bridged by one of the dithiolate ligands. To verify this, a crystalline sample of the intermediate was prepared by reacting 1.5 equivalents of 1,2-ethanedithiol with 1 equivalent of $(\text{Bu}_4\text{N})[\text{TcOCl}_4^-]$ in MeOH; the crystalline product was deposited from the concentrated reaction mixture. This compound was shown to be identical to an unidentified product isolated by Orvig¹² from the reaction of bis(acetamidomethyl)ethanedithiol with TcOCl_4^- , by comparison of their electronic and infrared spectra, and their field desorption mass spectra²⁰. In this way, the definitive identification of this compound as $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{S})_3$ was made. It was further shown that a suspension of the isolated compound in methanol, when treated with 0.5 equivalent (based on Tc) of 1,2-ethanedithiol, reacts to form $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$.

While the formation of this dimer intermediate is surprising, it might be thought to have little relevance to reactions of TcOCl_4^- with large excesses of dithiols. However, the observation¹² that only the dimer is formed in the reaction between TcOCl_4^- and excess amounts of the acetamidomethyl-protected dithiol raised the question of steric factors in the reaction that takes the intermediate to the final product. In this case, molecular models suggest that the protected thiol cannot approach the empty sixth coordination site of either of the Tc atoms because of steric hindrance. On the hypothesis that critical steric hindrance could be supplied by the dithiolate ligand itself, we reacted TcOCl_4^- with excess 1,3-propanedithiol in MeOH. A brick-red product

immediately precipitated, which was recrystallized from $\text{CH}_2\text{Cl}_2/\text{MeOH}$.

Smith, et al, isolated¹¹ the complex $\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2^-$ as its Ph_4As^+ salt, and this was soluble in MeOH. The insolubility of the ligand-exchange product in methanol, and a detailed comparison of the electronic spectra of it and $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2]$ in CH_2Cl_2 ($\lambda_{\text{max}} = 440 \text{ nm}$ for the new material vs. 452 nm for the monomer, and the bandshapes are distinctively different) confirms that a new species has been formed. The infrared spectrum is similar to that of $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{S})_3$, and its elemental analysis is consistent with the dimer $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_3$. Further confirmation of this formulation is given by the mole-ratio plot¹⁴ of a titration of TcOCl_4^- with 1,3-propanedithiol (Figure 20). Linear regression analysis of the curve indicates a ligand-to-Tc ratio of 1.3, which is more consistent with a dimer than a monomer.

Inspection of a molecular model of the compound shows that the extra methylene groups effectively block access to the otherwise-vacant sixth coordination sites of the Tc atoms, and explains the lack of reactivity of this substance even in the presence of excess dithiol. The discovery of this relatively unreactive dimer has ramifications for radiopharmaceutical science. The compound dihydrothioctic acid $[\text{HSCH}_2\text{CH}_2\text{CH}(\text{SH})(\text{CH}_2)_4\text{COOH}]$ is used²¹ as a ligand for the preparation of a $^{99\text{m}}\text{Tc}$ -hepatobiliary agent. Whether this ligand forms a monomer product (like Smith's¹¹ $\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2^-$), or a dimer product (like our $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_3$), may well depend on the mechanistic details of the radiopharmaceutical synthesis employed, and different synthetic methods may lead to products with different biodistributions.

This study was extended to aromatic dithiols, and it was discovered that titration (Figure 21) of TcOCl_4^- in MeOH with 3,4-toluenedithiol led

Figure 20

Mole-Ratio Plot, Reaction of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$
with 1,3-Propanedithiol (in MeOH)

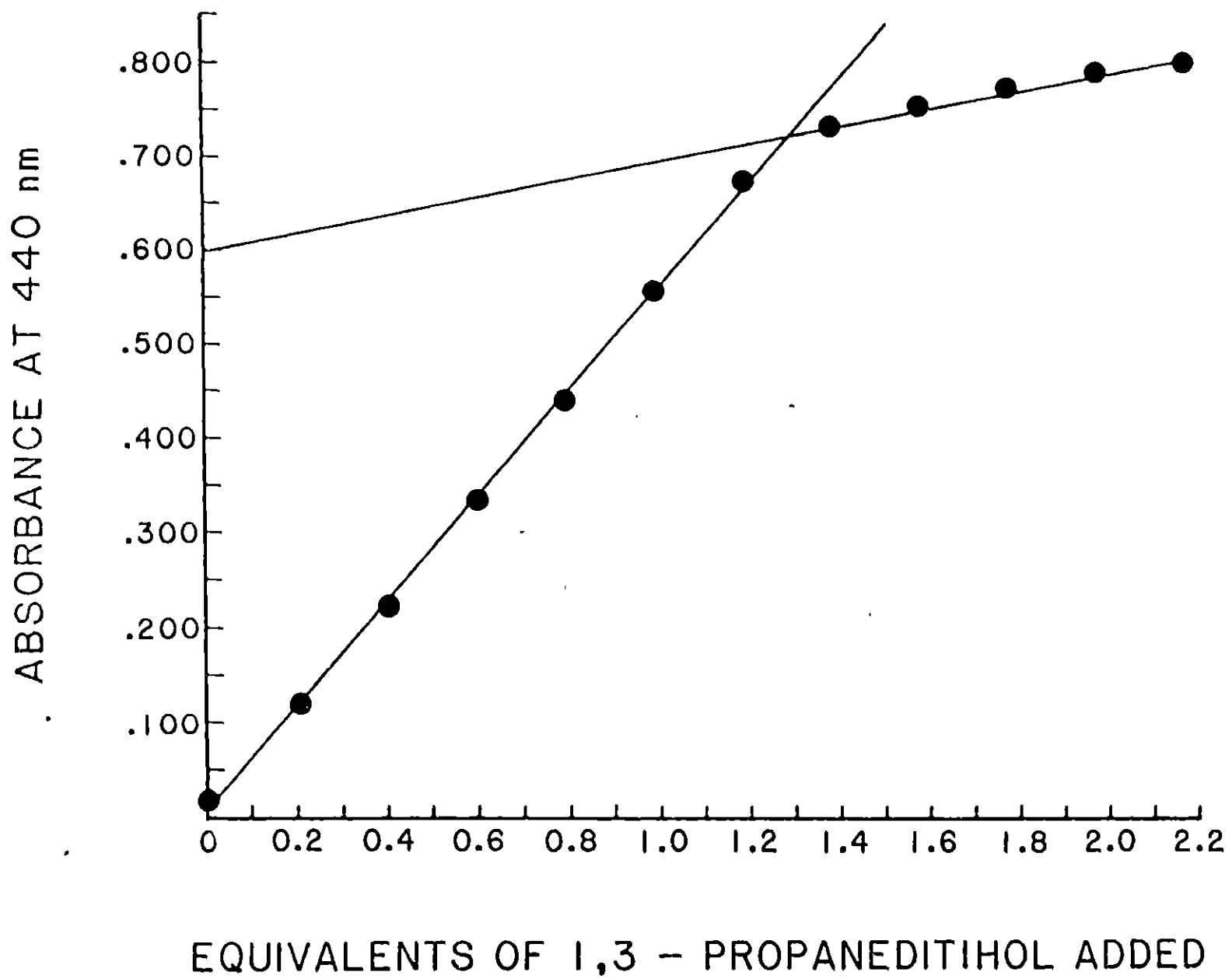
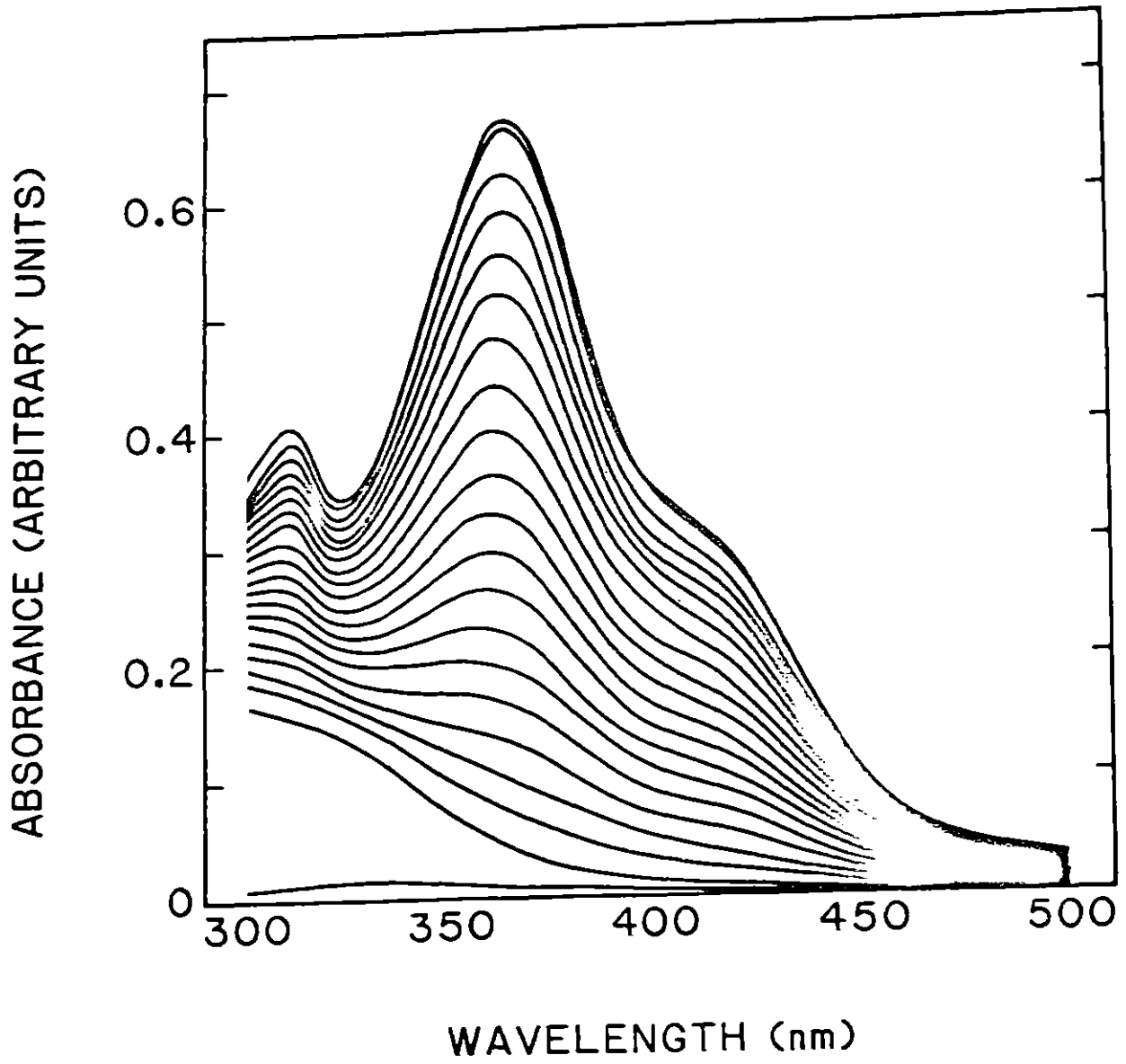


Figure 21

Optical Titration of $(n\text{-Bu}_4\text{N})[\text{TcOCl}_4]$ with
3,4-Toluenedithiol (in MeOH)



directly to the bis(dithiolato) monomer $\text{TcO}(\text{S}_2\text{C}_6\text{H}_3(\text{CH}_3))_2^-$, without formation of an intermediate! The reasons for this behavior are not clear at this point, but could involve factors that destabilize the (hypothetical) intermediate or stabilize the final monomer. It is interesting to note that the interligand S-S distances in $\text{TcO}(\text{SCH}_2\text{COS})_2^-$ (see Table 4 in Chapter 1) are 3.041 and 3.016 Å, close to the average value of 3.05 Å noted by Gray, et al²², in the crystal structures of several tris-dithiolene complexes. This relatively short distance was taken to be indicative of some interligand bonding interaction of the sulfur atoms in the dithiolene complexes, and such an interaction may be operative in stabilizing $\text{TcO}(\text{S}_2\text{C}_6\text{H}_3(\text{CH}_3))_2^-$ relative to the unobserved dimer.

The results of this series of experiments with dithiols and TcOCl_4^- demonstrate how the mechanism and the final product of their reaction depends sensitively on the detailed structure of the dithiol species. It is this type of information that will be useful in designing highly selective reactions for $^{99\text{m}}\text{Tc}$ -radiopharmaceutical syntheses.

In a paper describing a new electrophoretic method for determining ligand:Tc stoichiometry in $^{99\text{m}}\text{Tc}$ -radiopharmaceuticals, Marzilli, et al, observed⁸ ligand exchange between $^{99\text{m}}\text{Tc}$ -complexes of 1,3-dithiols with added 1,2-ethanedithiol. The reactions were monitored by examining the electrophoretic mobility of the products, which could not be isolated, since only tracer amounts of $^{99\text{m}}\text{Tc}$ were used.

The possibility of ligand exchange between $\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2^-$ and 1,2-ethanedithiol was studied spectrophotometrically. A methanolic solution of $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2]$ was incubated with a 100-fold excess of 1,2-ethanedithiol for 1.5 hours, and its electronic spectrum was

observed to be identical to that of the starting material. One month later, however, the solution spectrum had become that of the ligand-exchange product, $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ (97% yield). In a parallel experiment, a small amount of 2N HCl was added to an aliquot of the same 100:1 ethanedithiol : $\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2^-$ reaction mixture, and the spectrum of $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ was observed after only 24 hours.

To investigate the course of the H^+ -catalyzed reaction in its early stages, a number of 100:1 ethanedithiol : $\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2^-$ samples were prepared, each with \underline{n} equivalents (based on Tc) of HCl added ($n = 1, 2, 4, 10$). At $n = 10$, the reaction proceeded at a rate fast enough to permit serial spectrophotometric scans at 1-2 hour intervals. A new maximum developed at 422 nm, with an isosbestic point at 435 nm. Another set of serial scans at 24, 48, and 72 hours gave a family of spectra that did not pass through the isosbestic point, and were converging to a maximum at 400 nm.

These results are in agreement with the observations of Marzilli, et al⁸, regarding the existence of a ligand exchange reaction between (1,3-dithiolato)oxotechnetate(V) species and 1,2-ethanedithiol. It is known²³ that transition metal chelates with five-membered rings are generally more stable than similar complexes with six-membered rings. While there is obviously a mechanistic pathway for this to occur in pure methanol solution, a significant catalytic effect is observed when HCl is added. The position of λ_{max} of the intermediate species is again similar to that of $(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{S})_3$, but caution should be exercised in speculating on the nature of the intermediate, since a 1,3-dithiol is now involved. Indeed, the λ_{max} at 422 nm for the intermediate is almost exactly the average of the values for $\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2^-$ (400 nm) and

$\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2^-$ (445 nm), suggesting it is a mixed (1,2-dithiolato) (1,3-dithiolato) complex.

A simple kinetic study was done to illuminate the matter. The reaction of 1,2-ethanedithiol with $\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2^-$ was monitored at 475 nm. The incoming ligand and HCl were present in excess (100 to 300-fold ligand : Tc, 20 to 30-fold HCl:Tc). Excellent straight lines were produced in every case when the data were plotted assuming a first order dependence on the initial technetium complex. Variation of the concentrations of the entering ligand and HCl led to the following empirical rate law:

$$\text{Rate} = \frac{k_{\text{OBS}}[\text{TcO}(\text{SCH}_2\text{CH}_2\text{CH}_2\text{S})_2^-][\text{HSCH}_2\text{CH}_2\text{SH}]^{0.78}}{[\text{HCl}]^{3.5}}$$

This rate law suggests the intermediate is indeed monomeric, and the inverse order in HCl suggests preliminary protonation before the rate-determining step²⁴. All this is consistent with protonation of the 1,3-propanedithiolate ligands as a prelude to their displacement by 1,2-ethanedithiols.

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Appendix 1

Positional and Thermal Parameters for $(n\text{-Bu}_4\text{N})[\text{TcO}(\text{SCH}_2\text{COS})_2]$

POSITIONAL AND THERMAL PARAMETERS AND THEIR ESTIMATED STANDARD DEVIATIONS.

ATOM	WEIGHT	X	Y	Z	B(1,1)	B(2,2)	B(3,3)	B(1,2)	B(1,3)	B(2,3)
TC		0,0000(0)	0,0000(0)	0,0000(0)	0,0112(1)	0,00674(6)	0,00585(9)	0,0000(0)	0,0051(2)	0,0000(0)
S1		0,1760(4)	0,1023(3)	0,1340(5)	0,0107(3)	0,0066(2)	0,0191(5)	-0,0006(4)	0,0031(6)	0,0005(6)
S2		-0,1494(4)	0,1015(3)	0,0358(5)	0,0104(3)	0,0034(2)	0,0195(5)	0,0045(4)	0,0105(6)	0,0013(6)
O1		-0,026(2)	0,000(0)	-0,178(1)	0,026(2)	0,0126(11)	0,003(1)	0,000(0)	0,010(2)	0,000(0)
O2		0,170(2)	0,260(1)	0,239(2)	0,029(2)	0,0094(8)	0,035(3)	0,004(2)	0,016(4)	-0,005(3)
H1		0,638(1)	0,0000(0)	0,430(1)	0,010(1)	0,0054(7)	0,007(1)	0,0000(0)	0,004(2)	0,0000(0)
C1		0,094(2)	0,199(1)	0,154(2)	0,022(2)	0,0050(7)	0,023(2)	-0,003(2)	0,019(3)	-0,001(2)
C2		-0,059(2)	0,205(1)	0,077(2)	0,014(2)	0,0075(8)	0,026(3)	0,007(2)	0,014(3)	0,005(3)
C11	0,5	0,541(3)	0,078(2)	0,439(3)	4,9(5)					
C12	0,5	0,600(3)	0,129(2)	0,589(3)	5,2(6)					
C13	0,5	0,400(4)	0,187(3)	0,585(4)	7,4(9)					
C14	0,5	0,551(4)	0,150(3)	0,741(5)	9,0(11)					
C21	0,5	0,662(3)	0,076(2)	0,542(3)	4,8(6)					
C22	0,5	0,528(3)	0,115(2)	0,551(3)	5,4(6)					
C23	0,5	0,505(4)	0,196(2)	0,640(4)	6,5(7)					
C24	0,5	0,426(7)	0,110(4)	0,669(8)	12,6(17)					
C31	0,5	0,700(3)	-0,043(2)	0,455(3)	4,8(5)					
C32		0,000(3)	0,000(0)	0,436(3)	0,0(7)					
C33	0,5	1,026(3)	-0,020(2)	0,474(3)	5,8(7)					
C34	0,5	1,139(4)	-0,034(2)	0,479(5)	7,2(9)					
C41	0,5	0,564(3)	0,030(1)	0,272(3)	4,2(5)					
C42		0,525(3)	0,000(0)	0,142(4)	8,5(7)					
C43	0,5	0,467(2)	-0,028(1)	0,000(3)	4,5(6)					
C44	0,5	0,440(3)	0,030(2)	-0,143(3)	5,3(7)					

THE FORM OF THE ANISOTROPIC THERMAL PARAMETER IS:

$$U_{ij} = \{B(1,1)X_iX_j + B(2,2)Y_iY_j + B(3,3)Z_iZ_j + B(1,2)X_iX_j + B(1,3)X_iZ_j + B(2,3)Y_iZ_j\}$$

Appendix 2

Final Positional and Thermal Parameters for $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$

Table of Positional and Thermal Parameters and Their Estimated Standard Deviations.

Atom	<u>x</u>	<u>y</u>	<u>z</u>	<u>ρ(1,1)</u>	<u>ρ(2,2)</u>	<u>ρ(3,3)</u>	<u>ρ(1,2)</u>	<u>ρ(1,3)</u>	<u>ρ(2,3)</u>
TU	0.56015(5)	0.46646(4)	0.29263(4)	0.00416(4)	0.00202(2)	0.00250(2)	0.00004(5)	-0.00076(5)	-0.00126(4)
AS	0.40006(5)	0.16575(4)	0.45728(4)	0.00297(4)	0.00100(2)	0.00163(2)	-0.00005(5)	-0.00010(5)	-0.00002(4)
S1	0.7013(2)	0.4270(1)	0.3143(1)	0.0047(1)	0.0034(1)	0.0032(1)	0.0015(2)	0.0000(2)	-0.0002(1)
S2	0.5223(2)	0.4116(2)	0.3950(2)	0.0071(2)	0.00410(10)	0.00339(11)	0.0031(2)	0.0047(2)	0.0011(2)

Atom	<u>x</u>	<u>y</u>	<u>z</u>	<u>B, Å²</u>	Atom	<u>x</u>	<u>y</u>	<u>z</u>	<u>B, Å²</u>
O1	0.6200(4)	0.5521(3)	0.2355(3)	4.5(1)	C14	0.3154(7)	-0.0740(5)	0.4037(5)	4.7(2)
O2	0.4000(4)	0.5417(3)	0.3249(3)	4.3(1)	C15	0.2771(7)	-0.0230(5)	0.5261(5)	5.2(2)
O3	0.5171(5)	0.4201(4)	0.2266(4)	6.3(2)	C16	0.3044(6)	0.0512(5)	0.5190(5)	4.0(2)
C1	0.7111(8)	0.5449(6)	0.2935(6)	6.7(3)	C17	0.5002(5)	0.1703(4)	0.4066(4)	2.0(2)
C2	0.7692(9)	0.4909(7)	0.2709(7)	7.9(3)	C18	0.5755(6)	0.2197(5)	0.4331(5)	3.7(2)
C3	0.4275(7)	0.5049(6)	0.3066(6)	5.6(2)	C19	0.6030(6)	0.2327(5)	0.3949(5)	4.5(2)
C4	0.4154(8)	0.4006(7)	0.4072(6)	6.8(3)	C20	0.6604(7)	0.2014(5)	0.3293(5)	4.7(2)
C5	0.3006(5)	0.2122(4)	0.4047(4)	2.6(2)	C21	0.5929(6)	0.1607(5)	0.3017(5)	1.3(2)
C6	0.2200(6)	0.1920(4)	0.4102(4)	3.5(2)	C22	0.5144(6)	0.1470(4)	0.3300(4)	3.1(2)
C7	0.1024(6)	0.2201(5)	0.3791(5)	4.5(2)	C23	0.4050(5)	0.2160(4)	0.3446(4)	2.7(2)
C8	0.1757(6)	0.2000(5)	0.3320(5)	4.4(2)	C24	0.3966(6)	0.2909(5)	0.5417(4)	3.6(2)
C9	0.2650(6)	0.3023(5)	0.3200(5)	4.4(2)	C25	0.3907(6)	0.3297(5)	0.6046(5)	4.0(2)
C10	0.3305(6)	0.2666(5)	0.3004(4)	3.6(2)	C26	0.4110(6)	0.2940(5)	0.6660(5)	4.3(2)
C11	0.3706(5)	0.0667(4)	0.4716(4)	2.8(2)	C27	0.4200(6)	0.2199(5)	0.6602(5)	4.0(2)
C12	0.4100(6)	0.0130(5)	0.4301(5)	3.7(2)	C28	0.4100(5)	0.1790(4)	0.6066(4)	3.1(2)
C13	0.3029(7)	-0.0507(5)	0.4306(5)	4.9(2)					

The form of the anisotropic thermal parameter is:
 $\exp[-(\rho(1,1)h^2 + \rho(2,2)k^2 + \rho(3,3)l^2 + \rho(1,2)hk + \rho(1,3)hl + \rho(2,3)kl)]$.

Estimated standard deviations in the least significant digits are shown in parentheses

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sink.

BIOGRAPHICAL NOTE

The author was born in the Bronx, New York, on February 3, 1951. He received his primary education at All Hallows Grammar School. After a distinguished high school career at Fordham Preparatory School, he entered Yale University, where he did his senior chemistry project under the guidance of Professor John W. Faller. He graduated cum laude with a Bachelor of Science degree in chemistry in 1972. He pursued graduate studies in inorganic chemistry under Professor Richard H. Holm both at the Massachusetts Institute of Technology and Stanford University, and received the Master's degree in chemistry from the former institution in 1976. After a sobering period of unemployment, he assumed a position with Stat Toxicology Service of Boston, Inc., and soon rose to a position of supervisory responsibility. At the urging of Professor Alan Davison of M.I.T., he began working at the Shields Warren Radiation Laboratory in late 1976, under the immediate guidance of Alun G. Jones and Michael A. Davis. There he did the research that formed the basis of this thesis. He received the degree of Doctor of Philosophy in inorganic chemistry from M.I.T. in June, 1981, and plans for the immediate future to continue his research in the chemistry of technetium.