Figure 3. Comparison of log K_{ex} of various lanthanides to log K_{ex} of Eu: (O) HPMDP; (●) HPMOP; (△) HPMPPP; (▲) HPMPAP; (◇) HPMBBP; (◆) HPMBP.[7]

enhances lanthanide extraction ($K_{ex}' > K_{ex}$). The values of K_{ex}', like those of K_{ex}, increase with increasing atomic number. Closer examination reveals that this reflects an override of the influence of β_3, referred to earlier, because the values of K_{ex}'/K_{ex} (from eq 5) show a reverse trend, namely that the fourth ligand anion, as reflected in K_{ex}'/K_{ex}, becomes less favored with increasing atomic number, possibly because of crowding around smaller metal ions.

It is interesting to observe that the K_{ex} values of the lanthanides for each of the reagents studied exhibit the well-known increase with reciprocal ionic radius of the metal ion (Figure 1), which probably reflects the importance of the stability constant, β_3, of the acylpyrazolones studied; the K_{ex}

values for HPMBP are largest, probably because its relatively low pK_a (4.1) translates into the largest proton displacement constant. In the other members of the series, which are almost equally acidic, HPMBBP displays the highest K_{ex}, possibly because of the higher distribution constants of its chelates.

Logarithmic plots of K_{ex} for the extractants in this series vs. that for HPMBP (Figure 2) result in a series of converging lines which indicate that the greatest change in extraction constant from one acylpyrazolone to another occurs with the metal ion having the lowest K_{ex} (i.e. with La). The K_{ex} value increases with the atomic number, but the difference from one reagent is the series to another decreases.

How structural changes affect selectivity can best be seen by a series of log–log plots comparing log K_{ex} values for Eu with those of the other lanthanides (Figure 3). The lines describing the behavior of La and Pr are essentially parallel to one another as well as to that for Eu, indicating a selectivity in this group that is insensitive to structure modifications. The slope of the line for Yb, however, is significantly different from the others, and one can observe that selectivity (as Δ log K_{ex}) is highest at low K_{ex} values (i.e. with HPMDP).

In the presence of phen, however, the behaviors of Yb, Eu, and Pr shown by a similar plot are more nearly parallel with the differences for La becoming more pronounced. With TOPO, on the other hand, the separation of Yb from the other lanthanides becomes significantly larger. Finally, the use of the quaternary ammonium ion shifts the K_{ex} values to favor a greater separation for La from the other three.

This study demonstrates the usefulness of the acylpyrazolones as extractants for separation of the lanthanides as well as the need to carefully specify the pair of metal ions involved when one tries to characterize "reagent selectivity".

Ligand-Exchange Reactivity Patterns of Oxotechnetium(V) Complexes

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The ligand-exchange reactions of various oxotechnetium(V) complexes with 1,2-dithiols have been investigated. The complexes $[TcO(OCH_2CH_2O)_2]^-$ (1), $[TcO(O_2C_6H_4)_2]^-$ (2), and $[TcO(SCH_2CH_2O)_2]^-$ (3) all react with 2 equiv of 1,2-ethanedithiol to ultimately form $[TcO(SCH_2CH_2S)_2]^-$ (4). However, different mechanisms and/or intermediates are observed in each case. The reaction of 1 proceeds without evidence for the formation of intermediates. In the reaction of 2, an intermediate is detected, which is probably a mixed-ligand oxotechnetium monomer; and in the reaction of 3 the spectrum of the intermediate formed is similar to that of the dimer species $[(TcO)_2(SCH_2CH_2S)_3]$ (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 $[(TcO)_2(SCH_2CH_2CH_2S)_3]$, which does not react with further amounts of ligand to form the bis(1,3-dithiolato) monomer, as would be anticipated from the sequential formation of 4 from 5 in the reaction of $[TcOCl_4]^-$ with 1,2-ethanedithiol.

We have previously reported the synthesis and characterization[2] of a number of oxotechnetium(V) complexes with core structures $TcOS_xO_{4-x}$ (x = 0, 2, 4). 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, the situation occurring in radiopharmaceutical kits.[3] The conjecture[4] that all ^{99m}Tc radiopharmaceuticals probably contain Tc(IV) has been shown to be unlikely.

The preparation of citrate[5] and gluconate[6] 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

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(2) (a) DePamphilis, B. V.; Jones, A. G.; Davis, M. A.; Davison, A. *J. Am. Chem. Soc.* **1978**, *100*, 5570. (b) Davison, A.; Orvig, C.; Trop, H. S.; Sohn, M.; DePamphilis, B. V.; Jones, A. G. *Inorg. Chem.* **1980**, *19*, 1988. (c) Davison, A.; Jones, A. G.; DePamphilis, B. V. *Ibid.* **1981**, *20*, 1617. (d) Davison, A.; DePamphilis, B. V.; Franklin, K.; Jones, A. G.; Lock, C. J. L., in preparation.

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of ligand or by reaction of the ligand with $[TcOCl_4]^-$, have not been isolated. Further, spectroscopic evidence[7] indicates the formation of a 2:1 dimercaptosuccinate:Tc complex by the reaction of dimercaptosuccinic acid with a solution of the Tc–gluconate complex. The known[2b] compound $[Et_4N]$-$[TcO(mnt)_2]$ (mnt = maleonitriledithiolate) has been similarly prepared[8] and isolated. These reports of ligand exchange on what are presumably oxotechnetium(V) complexes with oxygen-donor ligands have prompted this investigation of the reactivity of $[TcO(OCH_2CH_2O)_2]^-$, $[TcO(O_2C_6H_4)_2]^-$,[2d] and $[TcO(SCH_2CH_2O)_2]^-$.[2c] 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 $[TcOCl_4]^-$ with 1,2-dithiols is, of course, well established,[2b] and reaction with 1,2-diols to form $TcOO_4$ complexes has been demonstrated.[2d] During the 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-to-metal stoichiometry. The surprising formation of the intermediate $[(TcO)_2(SCH_2CH_2S)_3]$, the investigation of this reaction using other dithiols, and the implications of these findings for radiopharmaceutical chemistry are discussed.

Experimental Section

Water was passed through a Barnstead D8904 cartridge for removal of organics and a Corning 3508-B demineralizer cartridge and then distilled by means of a Corning Mega-Pure still. All reagents were used as received, except as noted. Aqueous $NH_4[^{99}TcO_4]$ was obtained from New England Nuclear and its concentration determined by a literature method.[9]

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

$[n\text{-}Bu_4N][TcOCl_4]$ was prepared by the reaction of $[TcO_4]^-$ with concentrated HCl as previously described.[2b,10] $[Ph_4As][TcO\text{-}(SCH_2CH_2S)_2]$ was synthesized by the published[11] procedure and was recrystallized by concentrating a methanolic solution of the amorphous product. $[n\text{-}Bu_4N][TcO(O_2C_6H_4)_2]$ and $Na[TcO(OC\text{-}H_2CH_2O)_2]$ were prepared by reacting the appropriate ligand with $[TcOCl_4]^-$,[2d] and $[Ph_4As][TcO(SCH_2CH_2O)_2]$ was prepared by dithionite reduction of $[TcO_4]^-$.[2c]

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

Preparation of $[(TcO)_2(SCH_2CH_2S)_3]$. A solution of 24 μL of 1,2-ethanedithiol (0.29 mmol) in 7 mL of MeOH was added dropwise to a stirred solution of 0.094 47 g of $[n\text{-}Bu_4N][TcOCl_4]$ (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 three 10-mL portions of Et_2O, and air-dried. The electronic, infrared, and field desorption mass spectra of this material were identical with those of authentic samples prepared by Orvig et al.[12]

Preparation of $[(TcO)_2(SCH_2CH_2CH_2S)_3]$. A stirred solution of 0.669 10 g of $[n\text{-}Bu_4N][TcOCl_4]$ (1.3 mmol) in 40 mL of MeOH was treated with 0.30 mL of 1,3-propanedithiol (3.0 mmol). A dark precipitate appeared immediately, which was filtered from the reaction mixture and extracted with three 10-mL portions of CH_2Cl_2. The combined filtered extracts were taken to dryness on a rotary evaporator. The solid residue was washed with three 10-mL portions of MeOH,

and the filtrates were discarded. The remaining solid was extracted with 10 mL of CH_2Cl_2. 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 milliliters of MeOH, and dried in vacuo. The yield of brick red $[(TcO)_2(SCH_2CH_2CH_2S)_3]$ was 0.105 46 g, 14% based on Tc.

Anal. Calcd for $C_9H_{18}O_2S_6Tc_2$: C, 19.70; H, 3.31; S, 35.07. Found: C, 20.13; H, 3.17; S, 34.87.

Optical Titration of $Na[TcO(OCH_2CH_2O)_2]$ with 1,2-Ethanedithiol. A solution of 0.032 66 g of $Na[TcO(OCH_2CH_2O)_2]$ in 100 mL of MeOH was prepared volumetrically. A 2.5-mL aliquot of this was diluted to 10 mL (c 3.2 × 10⁻⁴). The electronic spectrum of this solution from 550 to 350 nm was recorded, as was the base line (MeOH vs. MeOH). A solution containing 51 μL of 1,2-ethanedithiol in 100 mL of MeOH was prepared (c 6.1 × 10⁻³). Aliquots of 50 μL (3.0 × 10⁻⁷ mol; 0.1 equiv based on Tc) were added to the diluted solution of $Na[TcO(OCH_2CH_2O)_2]$, and its spectrum was recorded after each addition.

Optical Titration of $[n\text{-}Bu_4N][TcO(O_2C_6H_4)_2]$ with 1,2-Ethanedithiol. A solution of 0.016 69 g of $[n\text{-}Bu_4N][TcO(O_2C_6H_4)_2]$ in 100 mL of MeOH was prepared volumetrically (c 2.9 × 10⁻⁴). The electronic spectrum of this solution from 500 to 340 nm was recorded, as was the base line (MeOH vs. MeOH). A solution of 49 μL of 1,2-ethanedithiol in 10 mL of MeOH was prepared (c 5.8 × 10⁻²). Aliquots of 50 μL (2.9 × 10⁻⁶ mol; 0.1 equiv based on Tc) were added to the solution of $[n\text{-}Bu_4N][TcO(O_2C_6H_4)_2]$, and its spectrum was recorded after each addition.

Reaction of $[Ph_4As][TcO(SCH_2CH_2O)_2]$ with 1,2-Ethanedithiol. A. A solution of 0.018 46 g of $[Ph_4As][TcO(SCH_2CH_2O)_2]$ in 100 mL of MeOH was prepared (c 2.8 × 10⁻⁴) and its visible spectrum recorded. A solution of 48 μL of 1,2-ethanedithiol in 1 mL of MeOH was prepared (c 5.7 × 10⁻¹), and 100 μL of this (5.7 × 10⁻⁵ mol; 2 equiv based on Tc) was added to the $[Ph_4As][TcO(SCH_2CH_2O)_2]$ solution. The spectrum of the reaction mixture was recorded every 30 min for 3.5 h.

B. A solution of 0.053 58 g of $[Ph_4As][TcO(SCH_2CH_2O)_2]$ in 100 mL of MeCN was prepared (c 8.2 × 10⁻⁴). A 5-mL aliquot of this solution was diluted to 15 mL (c 2.7 × 10⁻⁴) and its visible spectrum recorded. Approximately 3 min after the addition of 70 μL of neat 1,2-ethanedithiol (8.4 × 10⁻⁴ mol; 203 equiv based on Tc) to the diluted solution, its spectrum was rescanned, and the spectrum of the intermediate was observed.

Optical Titration of $[n\text{-}Bu_4N][TcOCl_4]$ with Citric Acid. A solution of 0.048 19 g of $[n\text{-}Bu_4N][TcOCl_4]$ in 10 mL of MeOH was prepared volumetrically (c 9.7 × 10⁻³) and the electronic spectrum of this solution from 800 to 500 nm recorded. A solution of 3.190 70 g of citric acid monohydrate in 25 mL of MeOH was prepared (c 0.61). Aliquots of 16 μL (9.7 × 10⁻⁶ mol; 0.1 equiv based on Tc) were added to the solution of $[n\text{-}Bu_4N][TcOCl_4]$, and its spectrum was recorded after each addition.

Reaction of 1,2-Ethanedithiol with Tc–Citrate Complex. A. To a stirred solution of 0.047 86 g of $[n\text{-}Bu_4N][TcOCl_4]$ (0.1 mmol) in 7 mL of MeOH was added a solution of 0.211 48 g of citric acid monohydrate (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 (ϵ = 33 L mol⁻¹ cm⁻¹). One milliliter of this solution (3.8 × 10⁻³ mmol) was combined with 1.6 μL of 1,2-ethanedithiol (1.9 × 10⁻² mmol) and diluted to 10 mL. The resulting spectrum was that of $[TcO(SC\text{-}H_2CH_2S)_2]^-$, and with ϵ(400 nm) = 3000 L mol⁻¹ cm⁻¹, a spectrophotometric yield of 90% was calculated.

B. To a solution of 0.051 09 g of $[n\text{-}Bu_4N][TcOCl_4]$ (0.1 mmol) in a few milliliters of MeOH was added 0.244 06 g of citric acid monohydrate (1.2 mmol), followed by 0.96 mL of 0.625 M NaOH (0.6 mmol), after which the solution was diluted to 10 mL. The visible spectrum of this mixture has λ_{max} at 490 nm (ϵ = 55 L mol⁻¹ cm⁻¹). A 250-μL aliquot (2.5 × 10⁻³ mmol) of the mixture was diluted to 25 mL with MeOH and 1.1 μL of 1,2-ethanedithiol (1.3 × 10⁻² mmol) added. The spectrum of the resulting solution was that of $[TcO(S\text{-}CH_2CH_2S)_2]^-$, with a spectrophotometric yield of 84%.

Optical Titration of Tc–Citrate Complex with 2,3-Dimercaptopropanesulfonate. To a solution of 0.058 63 g of $[n\text{-}Bu_4N][TcOCl_4]$ (0.12 mmol) in 25 mL of MeOH was added 0.352 00 g of sodium citrate dihydrate (1.2 mmol). A 0.5-mL aliquot of this solution was diluted to 10 mL with H_2O (c 2.3 × 10⁻⁴). The electronic spectrum of this solution from 500 to 300 nm was recorded, as was the base

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(12) Davison, A.; DePamphilis, B. V.; Faggiani, R.; Jones, A. G.; Lock, C. J. L.; Orvig, C., in preparation.

line (H₂O vs. H₂O). A solution of 0.266 55 g of sodium 2,3-di-mercaptopropanesulfonate (1.27 mmol) in 2 mL of H₂O was prepared. One milliliter of this solution was diluted to 20 mL with H₂O (c 3.2 × 10⁻²). Aliquots of 21 μL (0.28 equiv 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-min 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 [TcO(S-CH₂CH₂S)₂]⁻, and the spectrophotometric yield was 94%, if the same extinction coefficient as that of the ethanedithiol complex was assumed.

Optical Titration of [n-Bu₄N][TcOCl₄] with 1,2-Ethanedithiol. A solution of 0.020 32 g of [n-Bu₄N][TcOCl₄] (0.04 mmol) in 100 mL of MeOH was prepared volumetrically (c 4.1 × 10⁻⁴). The visible spectrum of this solution from 500 to 300 nm was recorded, as was the base line (MeOH vs. MeOH). A solution of 0.34 mL of 1,2-ethanedithiol (4.1 mmol) in 10 mL of MeOH was prepared (c = 0.41 M). Aliquots of 10 μL (4.1 × 10⁻³ mmol; 0.1 equiv based on Tc) of the dithiol solution were added to the solution of [n-Bu₄N][TcOCl₄], and its spectrum was recorded after each addition.

Optical Titration of [n-Bu₄N][TcOCl₄] with 1,3-Propanedithiol. A solution of 0.026 33 g of [n-Bu₄N][TcOCl₄] (0.05 mmol) in 10 mL of MeOH was prepared, and 5.3 mL (0.03 mmol) was diluted to 100 mL with MeOH (c 3.0 × 10⁻⁴). The visible spectrum of this solution from 550 to 350 nm was recorded, as was the base line (MeOH vs. MeOH). A solution of 56.5 μL of 1,3-propanedithiol (0.56 mmol) in 100 mL of MeOH was prepared (c 5.6 × 10⁻³). A 10-mL aliquot of the [n-Bu₄N][TcOCl₄] solution (3.0 × 10⁻⁶ mol) was treated with successive 100-μL aliquots (5.6 × 10⁻⁷ mol; 0.2 equiv based on Tc) of the dithiol solution and the spectrum of the reaction mixture recorded after each addition.

Optical Titration of [n-Bu₄N][TcOCl₄] with 3,4-Toluenedithiol. A solution of 0.022 20 g of [n-Bu₄N][TcOCl₄] (4.4 × 10⁻² mmol) in 50 mL of MeOH was prepared, and 6.9 mL of this solution (6.1 × 10⁻³ mmol) was diluted to 100 mL with MeOH (c 6.1 × 10⁻⁵). A solution of 0.219 52 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 × 10⁻²). The visible spectrum of the diluted [TcOCl₄]⁻ solution from 500 to 300 nm was recorded, as was the base line (MeOH vs. MeOH). Aliquots of 10 μL of the dithiol solution (6.2 × 10⁻⁴ mmol; 0.1 equiv based on Tc) were added to the solution of [TcOCl₄]⁻, and the spectrum of the reaction mixture was recorded after each addition.

Results and Discussion

The affinity of the Tc^{V}O³⁺ moiety for dithiolate ligands was first demonstrated[2a] in the fortuitous synthesis of [TcO(SC-H₂COS)₂]⁻ from the dithiol contaminant in thioglycolic acid (HSCH₂COOH). This affinity was later highlighted in studies[2b] of the reactions of 1,2-dithiols (and 1,2-dithiolates) with the extremely labile [TcOCl₄]⁻ ion to form a variety of bis(1,2-dithiolato)oxotechnetium(V) species. The formation of [TcO(OCH₂CH₂O)₂]⁻ and [TcO(O₂C₆H₄)₂]⁻ [2d] extended the list of ligands that stabilize the Tc^{V}O³⁺ group to include 1,2-diolates. Literature reports[5–8] of labile, uncharacterized complexes of Tc with oxygen donors led to the investigation of the reactivity of the already characterized bis(1,2-diolato)oxotechnetium(V) complexes by UV–visible spectrophotometry, taking advantage of the clear-cut spectral differences among the species with TcOₓO₄₋ₓ (x = 0, 2, 4) cores. It was hypothesized that there is an order of relative affinity for Tc^{V}O³⁺ among these ligands and the experimental results thus far have borne this out.

Scanning the optical spectrum of a methanolic solution of Na[TcO(OCH₂CH₂O)₂] after successive additions of 0.1 mol equiv aliquots of 1,2-ethanedithiol (Figure 1) shows the simple ingrowth of the spectrum[11] of [TcO(SCH₂CH₂S)₂]⁻. The limiting spectrum is attained after the addition of 1.9 equiv of the dithiol. This apparently one-step reaction is in marked contrast to the reaction, to be discussed later, of [TcOCl₄]⁻ with substoichiometric amounts of 1,2-ethanedithiol to form the intermediate [(TcO)₂(SCH₂CH₂S)₃].[12]

When [TcO(O₂C₆H₄)₂]⁻ (the catecholato complex) was similarly titrated with twenty 0.1-equiv aliquots of 1,2-
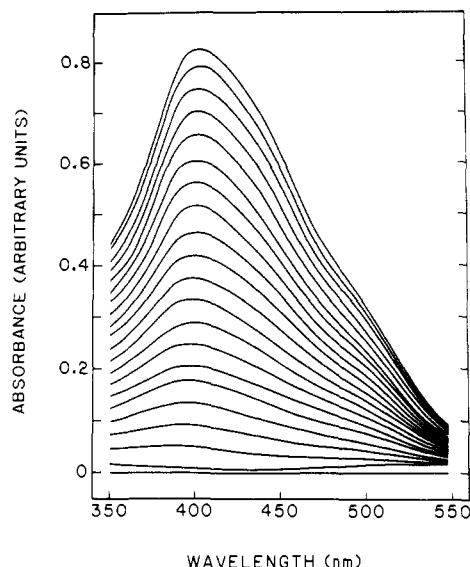
Figure 1. Optical titration of Na[TcO(OCH₂CH₂O)₂] with 1,2-ethanedithiol (in MeOH).
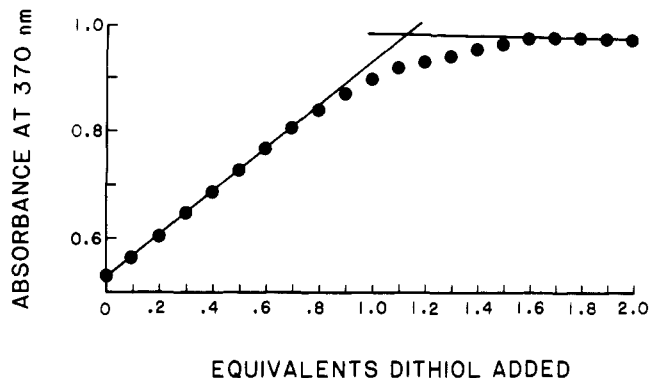
Figure 2. Mole ratio plot of the reaction of [n-Bu₄N][TcO(O₂C₆H₄)₂] with 1,2-ethanedithiol (in MeOH).

ethanedithiol, the spectrum that developed initially was not that of [TcO(SCH₂CH₂S)₂]⁻ (λ_{max} = 400 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 h, the spectra of both the sample containing excess dithiol and the sample containing the stoichiometric amount of dithiol had developed fully into the spectrum[11] of [TcO-(SCH₂CH₂S)₂]⁻.

The observation of the species with λ_{max} at 370 nm is a kinetic artifcat. 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 plot[13] was constructed. The plot (Figure 2) suggests that the intermediate contains one molecule of ethanedithiol per atom of technetium. A mixed (catecholato)(1,2-ethane-dithiolato)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) complex[14] (400 nm).

When a methanolic solution of [Ph₄As][TcO-(SCH₂CH₂O)₂] was treated with 2 equiv of 1,2-ethanedithiol,

(13) Skoog, D. A.; West, D. M. "Fundamentals of Analytical Chemistry", 3rd ed.; Holt, Rinehart, and Winston: New York, 1976; p 557.

(14) Although λ_{max} for [TcO(SCH₂CH₂S)₂]⁻ was reported[11] to be 390 nm, our repeated observation has been that λ_{max} is closer to 400 nm.
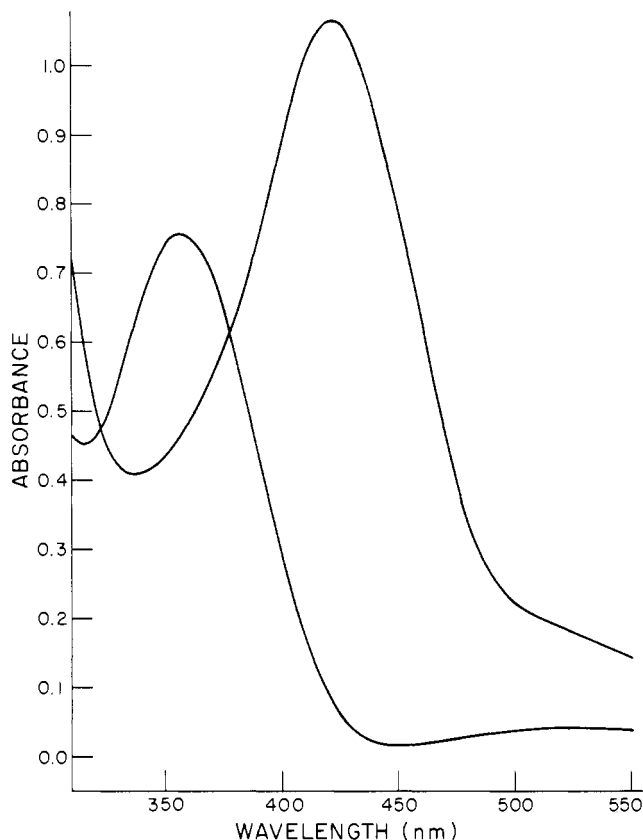
Figure 3. Electronic spectra of [Ph$_4$As][TcO(SCH$_2$CH$_2$O)$_2$] (λ_{max} = 355 nm) and the transient intermediate (λ_{max} = 422 nm) formed on addition of 200 equiv of 1,2-ethanedithiol (in MeOH).

Figure 4. Mole ratio plot of the reaction of [n-Bu$_4$N][TcOCl$_4$] with citric acid (in MeOH).

the spectrum of a new species slowly grew in. A series of nine scans over a 3.5-h 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 h, the solution spectrum was fully that of [TcO(S-CH$_2$CH$_2$S)$_2$]$^-$ (λ_{max} = 400 nm). This final spectral curve did *not* intersect the isosbestic points. In an experiment where approximately 200 equiv of 1,2-ethanedithiol was added to the bis(2-mercaptoethanolato) complex, an absorption maximum at 422 nm rapidly developed (Figure 3). 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 [TcO(SCH$_2$CH$_2$O)$_2$]$^-$ proceeds via a single intermediate with λ_{max} at 422 nm and that further reaction to [TcO(SCH$_2$CH$_2$S)$_2$]$^-$ occurs 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[2d] in the spectra of these oxotechnetium(V) complexes as ligand oxygens are replaced by ligand sulfurs. The position of λ_{max} of this intermediate is anomalous if it is assumed to be the mixed-ligand monomer [TcO(SCH$_2$CH$_2$O)(SCH$_2$CH$_2$S)]$^-$. However, the spectral similarity of the intermediate and the dimer complexes [(TcO)$_2$(SCH$_2$CH$_2$S)$_3$] (λ_{max} = 425 nm) and [(TcO)$_2$(SC-H$_2$CH$_2$CH$_2$S)$_3$] (λ_{max} = 440 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 inter-
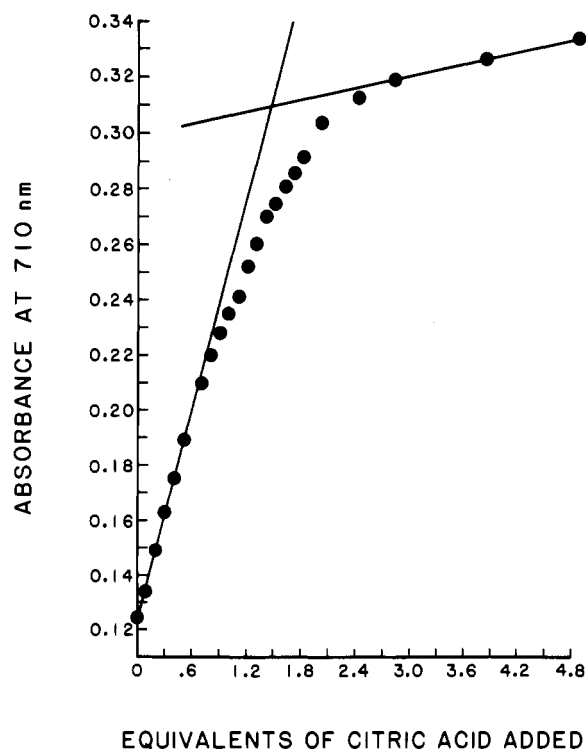
mediate, and sometimes with a dimeric intermediate.

There have been reports of complexes of technetium with citrate and gluconate that undergo ligand exchange with 1,2-dithiols. Münze produced[5] 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 solution[15] of [TcOCl$_4$]$^-$ in concentrated hydrochloric acid. The gluconate complex was prepared[6] by the same methods. Johannsen et al. titrated[18] a solution of the Tc–gluconate complex with a solution of 2,3-dimercaptopropanesulfonate (DMPS), a water-soluble analogue of 1,2-ethanedithiol. They observed the stepwise appearance of a spectrum identical with that of [TcO(SCH$_2$CH$_2$S)$_2$]$^-$, presumably the spectrum of the (DMPS)$_2$ analogue of this characterized complex.

These results have been verified and extended. A solution of [n-Bu$_4$N][TcOCl$_4$] in methanol was titrated with a solution of citric acid monohydrate in methanol. A mole ratio plot[13] was constructed (Figure 4), 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 equiv of citric acid monohydrate with 1 equiv of [n-Bu$_4$N][TcOCl$_4$]. Addition of 5 equiv of 1,2-ethanedithiol to this solution gave a 90% (spectrophotometric) yield of [TcO-(SCH$_2$CH$_2$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

(15) The reactive species in ref 5 is formulated as "[TcOCl$_5$]$^{2-}$", in accord with ref 16; its equivalence to TcOCl$_4^-$ has been demonstrated.[17]

(16) Jezowska-Trzebiatowska, B.; Baluka, M. *Bull. L'Acad. Pol. Sci., Ser. Sci. Chim.* **1965**, *13*, 1.

(17) Trop, H. S. Ph.D. Dissertation, Massachusetts Institute of Technology, Cambridge, MA, 1979.

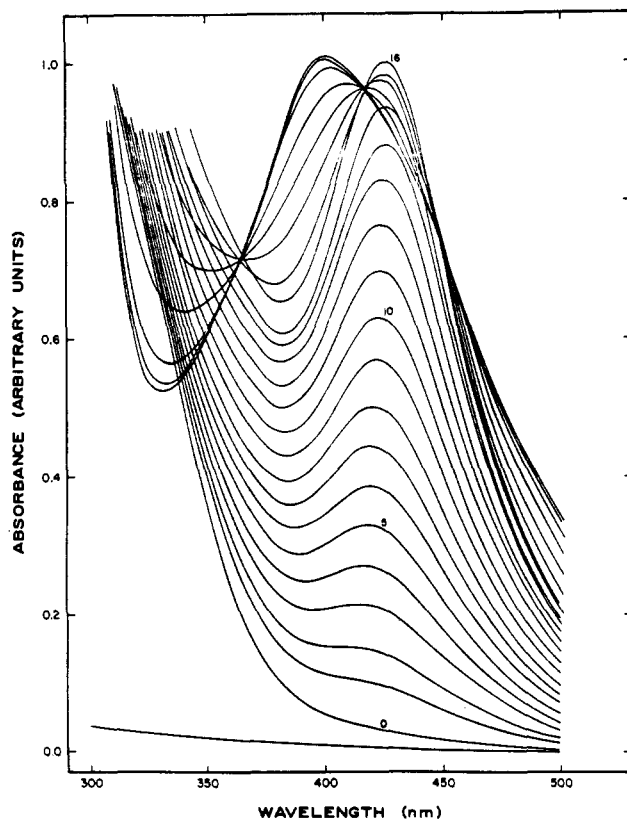(18) Vanlić-Razumenić, N.; Johannsen, B.; et al. *Int. J. Appl. Radiat. Isot.* **1979**, *30*, 661.

Figure 5. Optical titration of [n-Bu$_4$N][TcOCl$_4$] with 1,2-ethanedithiol (in MeOH).

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 6 equiv of sodium hydroxide has 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 with that of [TcO(SCH$_2$CH$_2$S)$_2$]$^-$, as expected, and no intermediates were observed. This is directly analogous to the titration of [TcO(OCH$_2$CH$_2$O)$_2$]$^-$ with 1,2-ethanedithiol, previously described, and to the results of Johannsen's titration[18] of technetium 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, 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 [TcO(SCH$_2$CH$_2$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-equiv aliquots of 1,2-ethanedithiol (Figure 5) increased in absorbance monotonically as the first 1.5 equiv of dithiol was added, but λ_{max} was at 420–425 nm, instead of the expected[14] 400 nm for [TcO(SCH$_2$CH$_2$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 when a total of 2 equiv of dithiol had been added.
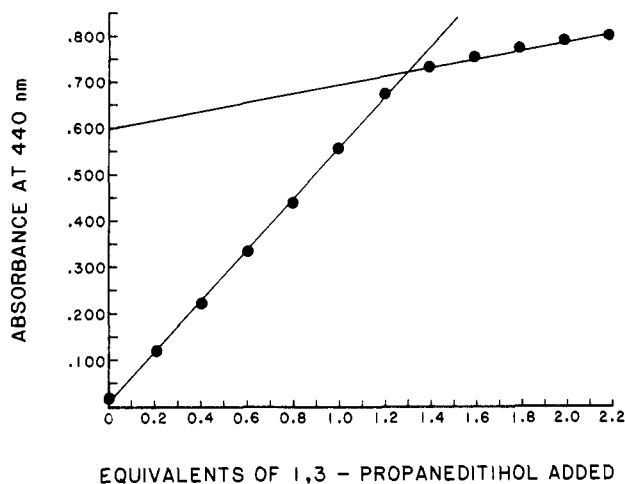

Figure 6. Mole ratio plot of the reaction of [n-Bu$_4$N][TcOCl$_4$] with 1,3-propanedithiol (in MeOH).

The experimental results were most easily explained by hypothesizing an intermediate of composition [(TcO)$_2$(SCH$_2$CH$_2$S)$_3$]. To verify this, a crystalline sample of the intermediate was prepared by reacting 1.5 equiv of 1,2-ethanedithiol with 1 equiv of [Bu$_4$N][TcOCl$_4$] in MeOH; the crystalline product was deposited from the concentrated reaction mixture. This compound was shown to be identical with the product isolated by Orvig et al.[12] from the reaction of bis(acetamidomethyl)ethanedithiol with [TcOCl$_4$]$^-$, by comparison of their electronic and infrared spectra and their field desorption mass spectra.[19] In this way, the definitive identification of this compound as [(TcO)$_2$(SCH$_2$CH$_2$S)$_3$] was made. It was further shown that a suspension of the isolated compound in methanol, when treated with 0.5 equiv (based on Tc) of 1,2-ethanedithiol, reacts to form [TcO(SCH$_2$CH$_2$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 observation[12] that *only* the dimer is formed in the reaction between [TcOCl$_4$]$^-$ and *excess* amounts of acetamidomethyl-protected 1,2-ethanedithiol 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 CH$_2$Cl$_2$/MeOH.

Smith et al. isolated[11] the complex [TcO(SCH$_2$CH$_2$CH$_2$S)$_2$]$^-$ as its [Ph$_4$As]$^+$ salt, and this was soluble in MeOH. The insolubility of the ligand-exchange product in methanol and a detailed comparison of its electronic spectra with that of [Ph$_4$As][TcO(SCH$_2$CH$_2$CH$_2$S)$_2$] in CH$_2$Cl$_2$ (λ_{max} = 440 nm for the new material vs. 452 nm for the monomer, and the band shapes are distinctively different) confirm that a new species has been formed. The infrared spectrum is similar to that of [(TcO)$_2$(SCH$_2$CH$_2$S)$_3$], and its elemental analysis is consistent with the dimer [(TcO)$_2$(SCH$_2$CH$_2$CH$_2$S)$_3$]. Further confirmation of this formulation is given by the mole ratio plot[13] of a titration of [TcOCl$_4$]$^-$ with 1,3-propanedithiol (Figure 6). 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.

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(19) Field desorption mass spectra were obtained by C. E. Costello, S. A. Carr, and K. Biemann of the Mass Spectrometry Laboratory of the Department of Chemistry, MIT.
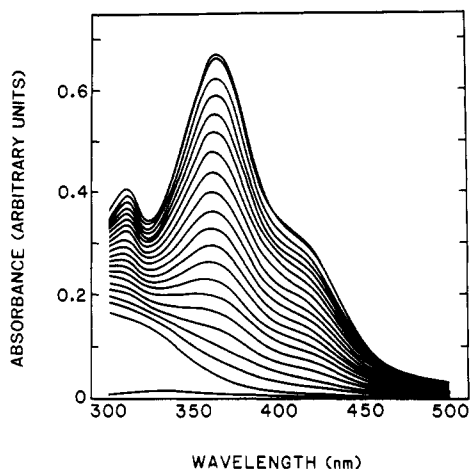
Figure 7. Optical titration of [*n*-Bu$_4$N][TcOCl$_4$] with 3,4-toluene-dithiol (in MeOH).

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 dimer has ramifications for radiopharmaceutical chemistry. The compound dihydrothioctic acid [HSCH$_2$CH$_2$CH(SH)(CH$_2$)$_4$CO-OH] is used[20] as a ligand for the preparation of a ^{99m}Tc he-

patobiliary agent. Marzilli et al. have shown[21] that the product of the stannous ion reduction of no-carrier-added ^{99m}TcO$_4^-$ in the presence of dihydrothioctic acid is the bis(ligand) *monomer*, not the dimer. This observation demonstrates the importance of reaction conditions in the synthesis of 1,3-dithiolato complexes of technetium.

This study was extended to aromatic dithiols, and it was discovered that titration (Figure 7) of [TcOCl$_4$]$^-$ in MeOH with 3,4-toluenedithiol led directly to the bis(dithiolato) monomer [TcO(S$_2$C$_6$H$_3$(CH$_3$))$_2$]$^-$ without formation of an intermediate. The reasons for this behavior are not clear but could involve factors that destabilize the (hypothetical) intermediate or stabilize the final monomer.

The results of this series of experiments with dithiols and [TcOCl$_4$]$^-$ demonstrate how the mechanism and the final product of their reaction depend 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 ^{99m}Tc-radiopharmaceutical syntheses.

Registry No. [(TcO)$_2$(SCH$_2$CH$_2$S)$_3$], 86119-88-2; [*n*-Bu$_4$N][TcOCl$_4$], 71341-65-6; [(TcO)$_2$(SCH$_2$CH$_2$CH$_2$S)$_3$], 86119-89-3; Na[TcO(OCH$_2$CH$_2$O)$_2$], 86119-90-6; [*n*-Bu$_4$N][TcO(O$_2$C$_6$H$_4$)$_2$], 86119-92-8; [Ph$_4$As][TcO(SCH$_2$CH$_2$O)$_2$], 86119-94-0; [Ph$_4$As]-[TcO(SCH$_2$CH$_2$S)$_2$], 70177-06-9; [TcO(SCH$_2$CH$_2$O)(SCH$_2$CH$_2$S)]$^-$, 86119-95-1; [TcO(O$_2$C$_6$H$_4$)(SCH$_2$CH$_2$S)]$^-$, 86119-96-2.

(20) Tonkin, A. K.; DeLand, F. H. *J. Nucl. Med.* **1974**, *15*, 539.

(21) Marzilli, L. G.; Worley, P.; Burns, H. D. *J. Nucl. Med.* **1979**, *20*, 871.

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Hydrolysis of Cations. Formation Constants and Standard Free Energies of Formation of Hydroxy Complexes

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The formation constants and standard free energies of formation of both mononuclear and polynuclear hydroxy complexes of metal ions throughout the periodic table have been examined. Some empirical correlations are presented that make it possible to predict rough values for these constants. For mononuclear complexes the equation is $\Delta G_f°\{M(OH)_y\} = \Delta G_f°\{M\} + By + Cy^2 + D/y$, where B, C, and D are empirical parameters and y is the number of coordinated hydroxide ions. These parameters are subject to constraints that limit acceptable values. For example, B, C, and electronegativity are interrelated. This equation can be rearranged to define a new function, U, that is linearly related to y. This allows the interpolation of unmeasured free energies and hence formation constants. For mononuclear complexes predicted values of log K_{1y} have an uncertainty of about ±0.5. For polynuclear hydroxy complexes a relation previously proposed by Baes and Mesmer has been slightly modified and used to predict unknown formation constants with an uncertainty in log K_{xy} of about ±0.5y. Mercury(II) and silver(I), which form especially stable "linear" complexes, do not follow the above correlations because of the structure change that occurs upon going from the M(OH)$_2$ to the M(OH)$_3$ species. The tetrahedrally coordinated Be^{2+}(aq) ion is more acidic than expected when compared with octahedrally coordinated aquo ions of divalent metals. Each hydrogen must carry a somewhat greater portion of the positive charge than it would in an octahedral complex, and this makes the removal of a proton easier. Aqueous Sn^{2+} is also unusually acidic, and it is suggested that it too has fewer water molecules in the primary coordination sphere than one would expect for a "normal" octahedrally coordinated metal ion. A reason is suggested for the experimental difficulty previous investigators have encountered in determining the formation constants for polynuclear hydroxy complexes of certain metal ions such as bismuth(III), cerium(IV), and zirconium(IV).

Metal ions in aqueous solution generally hydrolyze to form a series of mononuclear and polynuclear hydroxy complexes. The general equation is

$$xM^{n+} + yH_2O \underset{}{\overset{K_{xy}}{\rightleftharpoons}} M_x(OH)_y^{n-y} + yH^+ \qquad (1)$$
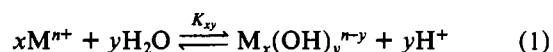
Iron(III), for example, forms FeOH^{2+}, Fe(OH)$_2^+$, Fe(OH)$_3$(aq), Fe(OH)$_4^-$, Fe$_2$(OH)$_2^{4+}$, and probably other polynuclear species. In the last four decades much effort has gone into the identification of the species present in aqueous

solutions and the measurement of their formation constants. The work up to 1974 has been critically reviewed and summarized by Baes and Mesmer.[1] Despite the large number of equilibrium constants that have been measured, there are still a number of cases in which data are conflicting or absent. In some of these the formation constants are experimentally difficult to determine because equilibrium is reached very

(1) Baes, C. F.; Mesmer, R. E. "The Hydrolysis of Cations"; Wiley-Interscience: New York, 1976.