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Synthesis and Characterization of a Series of Isomeric Oxotechnetium(V) Diamido Dithiolates

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The diamido dithiolato technetium complexes $[TcO(SCH_2CONCH_2CONCH_2CH_2S)]^-$ and $[TcO(SCH_2CH_2NCO)_2]^-$ have been prepared both via dithionite reduction of TcO_4^- and by ligand exchange from $[TcO(OCH_2CH_2O)_2]^-$. The synthesis and characterization of the complexes and their precursor ligands are presented. The highly stereoselective deuterium exchange of the active methylenes of $[TcO(SCH_2CONCH_2CONCH_2CH_2S)]^-$ is discussed. The application of this chemistry to radiopharmaceuticals is considered.

The importance of the metastable isomer (^{99m}Tc, γ = 140 keV, $t_{1/2}$ = 6 h) in the practice of nuclear medicine has led to intensive studies of the basic chemistry of this element using macroscopic quantities of the long-lived radionuclide ^{99}Tc, a β^- emitter ($t_{1/2} = 2.12 \times 10^5$ years). A significant portion of this work has been directed toward the synthesis of kinetically stable complexes that can be prepared easily in aqueous media by the reduction of the pertechnetate ion in the presence of a suitable ligand. Our previous work has demonstrated that there is a diverse chemistry associated with oxotechnetium(V) centers. The systematics of the chemistry of these diamagnetic (d^2 spin paired) kinetically inert complexes has been recently reviewed.[2]

Our early findings led to the concept of a tetradentate ligand that would be capable of stabilizing technetium in the +5 oxidation state. The initial series of ligands[3] were chosen to exploit the geometrical preferences of the TcO^{3+} core by spanning the basal plane of a square pyramid, thus avoiding the geometrical isomerism possible with unsymmetrical bidentate ligands.

The ligands selected were a homologous series of symmetrical diamide dithiols. One of the resultant complexes, the oxo[*N*,*N*′-ethylenebis(2-mercaptoacetamido)]technetate(V) anion showed rapid renal clearance both in animals[4] (our findings have been confirmed by Fritzberg[5] and co-workers) and in humans, as shown by Klingensmith.[6] We have also shown, by using a combination of high-pressure liquid chromatography and field desorption mass spectrometry, that the anion is excreted unchanged into both urine and bile.[4]

The present study was undertaken to investigate the synthesis and stability of the isomeric complexes that result from the permutation of the amide carbonyls of the ligand backbone. This paper demonstrates that a range of complexes based on the oxo-(diamido dithiolato) technetium(V) system are readily synthesized. In principle, from readily available synthons, analogous compounds with a wide variety of side chains, capable of directing a specific biological distribution, can be prepared.

Experimental Section

Technetium as $NH_4^{99}TcO_4$ was obtained as a gift from New England Nuclear, Billerica, MA. All manipulations were carried out in laboratories approved for low-level radioactivity (^{99}Tc is a weak β emitter with a half-life of 2.12×10^5 years and a particle energy of 0.292 MeV). All precautions were as detailed previously.[7,8] Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA.

Melting points were obtained with a Mel-Temp apparatus and are uncorrected. Infrared spectra, obtained as KBr pellets, were recorded in the range 4000–200 cm^{-1} on a Perkin-Elmer PE180 or 283B grating infrared spectrometer. Electronic spectra, λ in nm (ϵ in L mol^{-1} cm^{-1}), were obtained in CH_3CN on a Cary 17 or Perkin-Elmer 330 spectrometer. High-field proton NMR were recorded on a Bruker 250- or 270-MHz spectrometer, while routine spectra were obtained with a Varian T-60. The carbon-13 NMR spectra were recorded on a Brucker 250 MHz spectrometer at 68 MHz. All NMR spectra are reported as downfield shifts from internal Me_4Si, and $CDCl_3$ was used as solvent unless otherwise specified. Field desorption (FDMS) and fast atom bombardment mass spectra (FABMS), in positive or negative ion mode, were measured on a Varian MAT 731 instrument described elsewhere.[9,10] Electrochemistry was carried out in dry acetonitrile solution (10^{-3} M complex, 0.09 M TBAP supporting electrolyte) under Ar on a Princeton Applied Research Model 174 polarographic analyzer with a Pt disk as the working electrode, a Pt wire as the counter-electrode, and a SCE as the reference.

Thin-layer chromatography (TLC) was carried out on E. Merck silica gel 60 F 254 plates developed in 5% methanol/CH_2Cl_2. Reverse-phase thin-layer chromatography (RPTLC) was carried out on Whatman MKC18 plates developed in 50% methanol/50% 0.5 M aqueous sodium chloride.

Prior to use, distilled water was passed through a Barnstead Ultrapure D8902 cartridge, followed by redistillation in a Corning AG-1 water still. Peroxide-free DME was used throughout. All other chemicals were of reagent grade, used without further purification, unless otherwise indicated.

2-((Triphenylmethyl)thio)acetic Acid (I). A mixture of distilled mercaptoacetic acid (20.87 g, 0.23 mol), triphenylmethanol (60.0 g, 0.23 mol), and glacial acetic acid (200 mL) was heated to 70 °C. Boron trifluoride etherate (32 mL, 0.25 mol) was added, and the resulting brown mixture was stirred for 45 min at room temperature. The reaction mixture was then poured into water (500 mL), depositing a buff, granular solid that was filtered off, washed well with water then ether, and dried to give I, 49.67 g (67%). A further crop (12.27 g (16%)) was recovered from the ether washings, purified by recrystallization from benzene/hexanes. Both crops were homogeneous by TLC.

Mp: 158.5–160 °C (lit.[11] mp 160–163 °C). Anal. Calcd for $C_{21}H_{18}O_2S$: C, 75.42; H, 5.43; S, 9.59. Found: C, 75.37; H, 5.42; S, 9.49. IR: ν_{max} 3000, 1705, 1480, 1440, 1270, 1145, 740, 680 cm^{-1}. ^1H NMR: δ 2.98 (s, 2 H, CH_2), 7.25 (m, 15 H, aryl), 10.2 (s, 1 H, COOH).

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Succinimido 2-((Triphenylmethyl)thio)acetate (II). To a cooled solution of I (33.4 g, 0.10 mol) and *N*-hydroxysuccinimide (11.5 g, 0.10 mol) in DME (250 mL) was added a solution of DCC (22.7 g, 0.11 mol) in DME (50 mL) such that the temperature remained below 0 °C. The resulting mixture was stored at 5 °C overnight and then filtered. The residue was washed well with CH_2Cl_2, and the combined filtrate and washings were concentrated in vacuo, giving II as a white precipitate that was filtered off, washed with ether, and dried. The filtrate and ether washings gave a further crop (combined yield 36.53 g (85%)) homogeneous by TLC. Recrystallization from ethyl acetate/hexanes gave an analytically pure sample.

Mp: 178.5–179.5 °C. Anal. Calcd for $C_{25}H_{21}NO_4S$: C, 69.59; H, 4.91; N, 3.25; S, 7.43. Found: C, 69.56; H, 4.98; N, 3.24; S, 7.35. IR: ν_{max} 3400, 1810, 1780, 1735, 1440, 1210, 1180, 1060, 740, 690 cm^{-1}. ^1H NMR: δ 2.67 (s, 4 H, CH_2CH_2), 3.08 (s, 2 H, CH_2), 7.17 (m, 15 H, aryl).

[2-((Triphenylmethyl)thio)acetyl]glycine (III). To a solution of active ester II (30.0 g, 70 mmol) in DME (300 mL) and DMF (150 mL) was added a solution of glycine (5.25 g, 70 mmol) and $NaHCO_3$ (11.76 g, 140 mmol) in water (150 mL). The resulting solution was stirred at room temperature for 45 min and then concentrated in vacuo to remove the DME. Dilution with water (300 mL) and treatment with 50% aqueous citric acid (60 mL) gave III as a white solid that was recrystallized from ethyl acetate; yield 24.07 g (88%).

Mp: 160.5–162.5 °C. Anal. Calcd for $C_{23}H_{21}NO_3S$: C, 70.56; H, 5.41; N, 3.58; S, 8.19. Found: C, 70.40; H, 5.47; N, 3.53; S, 8.17. IR: ν_{max} 3315, 2900, 1730, 1620, 1525, 1485, 1385, 1245, 1220, 1210, 740, 730, 695, 640 cm^{-1}. ^1H NMR: δ 3.12 (s, 2 H, $COCH_2S$), 3.63 (d, J = 6 Hz, 2 H, $COCH_2N$), 6.58 (m, 1 H, NH), 7.25 (m, 15 H, aryl), 13.63 (s, 1 H, COOH).

[2-((Triphenylmethyl)thio)acetyl]glycine, *N*-Hydroxysuccinimido Ester (IV). To a solution of acid III (9.48 g, 24 mmol) and *N*-hydroxysuccinimide (2.79 g, 24 mmol) in DME (200 mL), cooled to −5 °C, was added DCC (5.69 g, 28 mmol) in DME (20 mL), such that the temperature remained below 0 °C, and the resulting mixture was stored at 5 °C overnight. The precipitate was filtered off and washed well with CH_2Cl_2, and the filtrate and washings were evaporated to a pale yellow solid. Recrystallization of the latter from ethyl acetate gave IV, 10.48 g (89%).

Mp: 179–182 °C. Anal. Calcd for $C_{27}H_{24}N_2O_5S$: C, 66.38; H, 4.95; N, 5.73; S, 6.56. Found: C, 66.15; H, 5.00; N, 5.70; S, 6.49. IR: ν_{max} 3400, 3200, 3060, 1820, 1780, 1745, 1655, 1210, 1105, 735, 695 cm^{-1}. ^1H NMR: δ 2.78, (s, 4 H, CH_2CH_2), 3.15 (s, 2 H, $COCH_2S$), 3.98 (d, J = 5 Hz, 2 H, $COCH_2N$), 6.33 (m, 1 H, NH), 7.28 (m, 15 H, aryl).

2-((Triphenylmethyl)thio)ethylamine (V). A mixture of 2-mercaptoethylamine hydrochloride (11.45 g, 0.10 mol) and triphenylmethanol (26.23 g, 0.10 mol) in trifluoroacetic acid (100 mL) was stirred at room temperature for 30 min and then evaporated to a brown oil. Trituration of the oil with ether (500 mL) (complete color discharge) gave the trifluoroacetate salt of V as a white precipitate that was filtered off and washed with ether. The washings were cooled to give a second crop, combined yield 30.8 g (70%). The trifluoroacetate salt of V (14.0 g, 32 mmol) was partitioned between 1 M aqueous NaOH and ether. Evaporation of the ether phase and recrystallization (ether/hexanes) gave V, 9.07 g (88%).

Mp: 93–94 °C (lit.[12] mp 90–93 °C). Anal. Calcd for $C_{21}H_{21}NS$: C, 78.95; H, 6.63; N, 4.38; S, 10.04. Found: C, 78.88; H, 6.65; N, 4.35; S, 10.11. IR (ν_{max}): 3400, 3050, 1480, 1435, 750, 735, 695 cm^{-1}. ^1H NMR: δ 1.05 (s, 2 H, NH_2), 2.45 (m, 4 H, CH_2CH_2), 7.23 (m, 15 H, aryl).

***N*-[2-((Triphenylmethyl)thio)acetyl]-*N'*-[2-((triphenylmethyl)-thio)ethyl]glycinamide (VI).** A solution of ester IV (2.45 g, 5.0 mmol) and amine V (1.61 g, 5.0 mmol) in CH_2Cl_2 (70 mL) was stirred at room temperature for 3 h and then stored at −5 °C overnight. The precipitated VI was filtered off, washed well with cold CH_2Cl_2, and dried; yield 2.50 g (72%). From the filtrate (washed with 5% aqueous $NaHCO_3$, dried over $MgSO_4$, evaporated, and recrystallized from CH_2Cl_2) a further crop was obtained; combined yield 3.11 g (90%).

Mp: 191–193 °C. Anal. Calcd. for $C_{44}H_{40}N_2O_2S_2$: C, 76.27; H, 5.82; N, 4.04; S, 9.25. Found: C, 75.88; H, 6.13; N, 3.99; S, 9.20. IR: ν_{max} 3250, 3050, 1640, 1565, 1550, 1470, 1440, 740, 690 cm^{-1}. ^1H NMR (270 MHz): δ 2.36 (three-line m, 2 H, CH_2S), 3.01 (four-line m, 2 H, CH_2N), 3.10 (s, 2 H, $COCH_2S$), 3.45 (d, J = 5 Hz, 2 H, $COCH_2N$), 5.90 (br t, 1 H, NH), 6.49 (br t, 1 H, NH), 7.2–7,4 (m, 30 H, aryl).

***N*-(2-Mercaptoacetyl)-*N'*-(2-mercaptoethyl)glycinamide (VII).** To a solution of the bis(*S*-triphenylmethyl) derivative VI (5.40 g, 7.8 mmol) in trifluoroacetic acid (30 mL) cooled in an ice bath was added triethylsilane (2.6 mL, 16.3 mmol). Immediate color discharge and formation of a white precipitate was observed. The mixture was diluted with hexanes (40 mL) and water (40 mL); the aqueous phase was separated, washed with several portions of hexane, filtered through celite, and evaporated to a colorless oil. Trituration of the oil with 2-propanol gave VII as a white solid that was recrystallized from 2-propanol; yield 1.50 g (92%). A further recrystallization from $CHCl_3$ gave an analytically pure sample.

Mp: 128–130 °C. Anal. Calcd for $C_6H_{12}N_2O_2S_2$: C, 34.60; H, 5.81; N, 13.45; S, 30.79. Found: C, 34.83; H, 5.81; N, 13.33; S, 30.68. IR: ν_{max} 3300, 3080, 1640, 1560 cm^{-1}. ^1H NMR (270 MHz): δ 2.40 (four-line m, 1 H, SH), 2.51 (four-line m, 2 H, CH_2S), 2.76 (t, J = 8 Hz, 1 H, SH), 3.15 (d, J = 8 Hz, 2 H, $COCH_2S$), 3.22 (four-line m, 2 H, CH_2N), 3.69 (d, J = 5.5 Hz, 2 H, $COCH_2N$), 8.05 (br t, 1 H, NH), 8.27 (br t, 1 H, NH). ^{13}C NMR: δ 23.5 (CH_2S), 27.1 ($COCH_2S$), 42.1 (CH_2N), 42.3 ($COCH_2N$), 168.7 (CO), 169.9 (CO).

***N,N'*-Bis(2-mercaptoethyl)oxamide (VIII).** To a stirred suspension of 2-mercaptoethylamine hydrochloride (4.43 g, 40 mmol) in freshly distilled CH_3CN (60 mL), cooled to −5 °C under Ar, was added diisopropylethylamine (16.0 mL, 92 mmol). After 5 min, chlorotrimethylsilane (6.6 mL, 52 mmol) was added in one portion, causing the complete solution of all suspended material. After 10 min, a solution of oxalyl chloride (1.76 mL, 20 mmol) in CH_3CN (10 mL) was added dropwise, such that the temperature remained below 0 °C, followed by diisopropylethylamine (7.0 mL, 40 mmol), again such that the temperature remained below 0 °C. The resulting soluton was allowed to stir for 30 min at or below 0 °C and then allowed to warm to room temperature over 2 h. The solution was then poured into ice/water (150 mL), immediately depositing the crude product VIII as a white precipitate that was collected, washed well with water, and dried in vacuo (18 h at room temperature followed by 12 h at 67 °C); yield 3.5 g (87%). This material (soluble only in Me_2SO, trifluoroacetic acid, and aqueous alkali) was normally used without purification. Analytically pure material was obtained as follows.

With rigorous exclusion of oxygen, an Ar-purged solution of sodium hydroxide (144 mg, 3.6 mmol) in doubly distilled deionized water (50 mL) was added to the crude dithiol (1.009 g, 4.85 mmol). The mixture was stirred for 30 min followed by removal of a small amount of undissolved material by anaerobic filtration. To the filtrate was added 12 M aqueous HCl (2.0 mL, 24 mmol), giving an immediate white precipitate that was collected, washed with distilled, deionized water (50 mL), and dried in vacuo at 67 °C: yield 300 mg of pure VIII; mp 167 °C.

Anal. Calcd for $C_6H_{12}N_2O_2S_2$: C, 34.60; H, 5.81; N, 13.45; S, 30.78. Found: C, 34.70; H, 5.73; N, 13.31; S, 30.64. IR: ν_{max} 3290, 2920, 2550, 1650, 1440, 860 cm^{-1}. ^1H NMR (250 MHz, Me_2SO-d_6): δ 2.17 (three-line m, 2 H, SH), 2.24 (four-line m, 4 H, CH_2S), 2.95 (four-line m, 4 H, CH_2N), 8.56 (br t, 2 H, NH). ^{13}C NMR (68 MHz, Me_2SO-d_6): δ 22.40 (CH_2S), 41.79 (CH_2N), 170.51 (CO). Positive-ion FDMS (m/z): 208 (100), 209 (51), 210 (20), [$C_6H_{12}N_2O_2S_2$ mol wt 208].

The Oxobis(1,2-ethanediolato)technetate(V) Ion (IX). Solutions of this complex were prepared by the following modification to the procedure of DePamphilis.[13]

To a pale green solution of $Bu_4NTcOCl_4$[8] (107 mg, 0.21 mmol) in methanol (2 mL) containing ethylene glycol (0.10 mL, 1.79 mmol) was slowly added a methanolic solution of sodium acetate (0.75 M, 2 mL, 1.5 mmol). The color of the solution passed from green through dark blue to the clear, stable, deep purple characteristic of oxo-bis(diolato) technetium(V) complexes. The resulting solution was thus approximately 0.05 M in the oxobis(1,2-ethanediolato)technetate ion (IX).

Tetraphenylarsonium Oxo[*N*-(2-mercaptoacetyl)-*N'*-(2-mercaptoethyl)glycinamido]technetate(V) (Ph_4As(X)). Method 1. To a warm (70 °C) solution of $NH_4{}^{99}TcO_4$ (1 mL of a 0.42 M aqueous solution, 0.42 mmol) and dithiol VII (131 mg, 0.63 mmol) in 0.2 M aqueous

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NaOH (40 mL, 8 mmol) was added sodium dithionite (155 mg, 0.98 mmol), giving a dark orange solution. RPTLC analysis showed only the technetium complex X. Upon stirring for 10 min at 70 °C, a clear orange solution was obtained. Tetraphenylarsonium chloride hydrate (0.32 g, 0.73 mmol) was added, giving $Ph_4As(X)$ as a yellow precipitate that was filtered off, washed with water, dried, and recrystallized (acetone/water); yield 246 mg (83%).

Mp: 232–235 °C. Anal. Calcd for $C_{30}H_{28}AsN_2O_3S_2Tc$: C, 51.29; H, 4.02; N, 3.99; S, 9.13. Found: C, 51.34; H, 4.03; N, 3.97; S, 9.08. Electronic spectrum (λ_{max}, nm (ϵ)): 285 (sh), 361 (4500), 435 (sh). IR: ν_{max} 1630, 1610 (CO), 945 (TcO). ^1H NMR (270 MHz): δ 3.28 (m, 2 H, CH_2S), 3.76 (AB q, J = 17 Hz, 2 H, $COCH_2S$), 3.79 (m, 2 H, CH_2N), 4.07 (m, 2 H, CH_2N), 4.43 (AB q, J = 18 Hz, 2 H, $COCH_2N$), 7.6–7.9 (m, 20 H, aryl). ^{13}C NMR (68 MHz): δ 37.0 (CH_2S), 37.6 (CH_2S), 54.9 (CH_2N), 57.9 (CH_2N), 120.2, 131.4, 132.8, 135.0 (aryl), 186.4, 186.6 (CO). High-resolution positive ion FABMS (Na^+ salt of the complex; m/z): 320.9192 [$(C_6H_8N_2O_3S_2Tc{\cdot}2H)^+$ mol wt 320.9191]. E_{pc} vs. SCE (V): −1.86, −2.11.

Method 2. To a colorless solution of VII (50 mg, 0.24 mmol) in 0.2 M aqueous NaOH (20 mL) was slowly added a deep purple, methanolic solution of the technetium complex IX (0.20 mmol in 3.5 mL, prepared as described above) to give a clear, golden yellow solution. The addition of tetraphenylarsonium chloride hydrate (0.12 g, 0.27 mmol) gave a yellow precipitate of $Ph_4As(X)$, which was filtered off, washed with water, and dried; yield 127 mg (91%).

Tetraphenylarsonium Oxo[*N*,*N*′-bis(2-mercaptoethyl)oxamido]technetate(V) (Ph_4As(XI)). Method 1. To a warm (60 °C) stirred solution of $NH_4{}^{99}TcO_4$ (0.52 mL of a 0.38 M solution, 0.20 mmol) and dithiol VIII (164 mg, 0.8 mmol) in ethanol (50 mL) and 2 M aqueous NaOH (50 mL) was slowly added a solution of sodium dithionite (100 mg, 0.60 mmol) in 2 M aqueous NaOH (5 mL). During the addition, the reaction mixture turned yellow, then brown, and, upon further heating, orange. After the volume was allowed to reduce to approximately 40 mL, the reaction mixture was allowed to cool to room temperature. The addition of a solution of tetrabutylammonium bromide (483 mg, 1.7 mmol) in water (5 mL) gave an immediate yellow precipitate that was collected, washed with water, and dried in vacuo to give 150 mg of impure product contaminated with pertechnetate (IR analysis). Since purification by recrystallization was unsuccessful, reverse-phase chromatography using a C_{18} SEP-PAK[14] was employed.

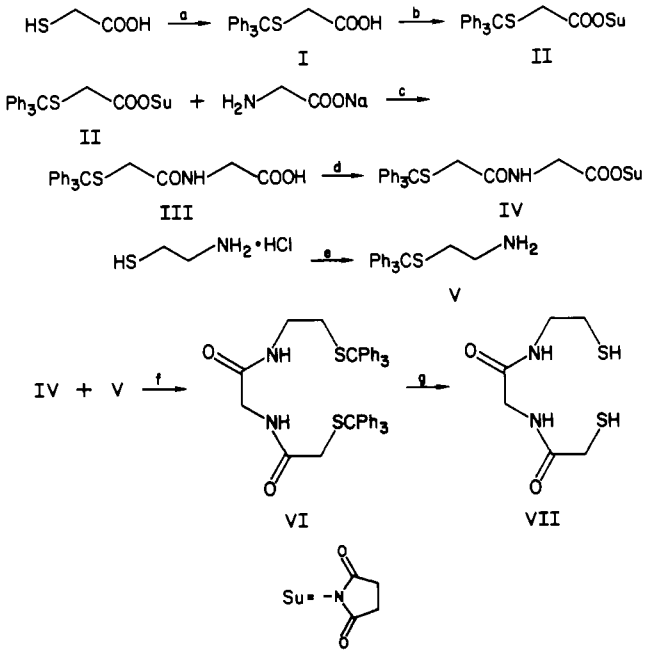
A C_{18} SEP-PAK was equilibrated with methanol (10 mL) followed by 0.05 M aqueous ammonium sulfate (10 mL). Crude product, dissolved in 15 mL of 25% acetone in water, was applied to an equilibrated C_{18} SEP-PAK in 0.5–1.5-mL portions. Elution with 0.05 M aqueous ammonium sulfate (10 mL) completely removed the pertechnetate. Subsequent elution with methanol (5 mL) gave a yellow solution. The methanolic fractions were combined, evaporated, redissolved in acetone and water, and treated with tetraphenylarsonium chloride hydrate (0.25 g, 57 mmol) to give Ph_4As(XI) as an orange precipitate. The precipitate was collected, washed with water then ether, and dried in vacuo; yield 30 mg (21%).

Anal. Calcd for $C_{30}H_{28}AsN_2O_3S_2Tc$: C, 51.29; H, 4.02; N, 3.99; S, 9.13. Found: C, 51.36; H, 4.05; N, 3.77; S, 8.63.

Method 2. A purple, methanolic solution of IX (0.22 mmol in 10 mL, prepared as described above) was added dropwise to a warm (50–60 °C) colorless solution of dithiol VIII (166 mg, 0.8 mmol) in ethanol (75 mL) and 3 M aqueous NaOH (75 mL). The resulting clear yellow solution was further heated to reduce the volume to 50 mL and then allowed to cool to room temperature. A solution of tetraphenylarsonium chloride hydrate (0.25 g, 0.57 mmol) in water (5 mL) was added, and the resulting solution was allowed to stand overnight, depositing Ph_4As(XI) as small orange needles that were collected, washed with water, and dried in vacuo; yield 127 mg (82%). Recrystallization from CH_2Cl_2/hexanes gave dark gold/orange blocks, mp 227–228 °C.

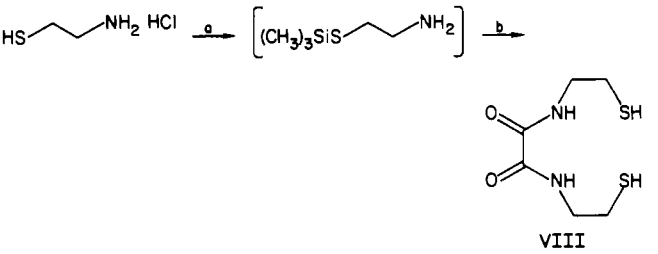
Anal. Calcd for $C_{30}H_{28}AsN_2O_3S_2Tc$: C, 51.29; H, 4.02; N, 3.99; S, 9.13. Found: C, 51.54; H, 4.01; N, 3.77; S, 8.67. Electronic spectrum (λ_{max}, nm (ϵ)): 307 (sh), 358 (2800), 473 (sh). IR: ν_{max} 1650 (CO), 940 (TcO) cm^{-1}. ^1H NMR (250 MHz): δ 2.9–3.0 (m, 2 H, CH_2S), 3.2–3.3 (m, 2 H, CH_2S), 3.8–3.9 (m, 2 H, CH_2N), 4.1–4.2 (m, 2 H, CH_2N), 7.5–7.9 (m, 20 H, aryl). ^{13}C NMR (68 MHz): δ 35.24 (CH_2S), 54.41 (CH_2N), 120.25, 131.35, 132.83, 134.94 (aryl), 170.51 (CO). Negative ion FDMS (m/z): 319 (100), 320 (12), 321 (12) [$[C_6H_8N_2O_2S_2Tc]^-$ mol wt 319]. E_{pc} vs. SCE (V): −1.82.

Scheme I[a]



[a] Key: (a) Ph_3COH, BF_3OEt_2, CH_3COOH; (b) HOSu, DCC, DME; (c) $NaHCO_3$, DME, H_2O; (d) HOSu, DCC, DME, DMF; (e) Ph_3COH, CF_3COOH; (f) CH_2Cl_2; (g) Et_3SiH, CF_3COOH.

Scheme II[a]



[a] Key: (a) $(CH_3)_3SiCl$, i-Pr_2NEt, CH_3CN; (b) (i) $(COCl)_2$, i-Pr_2NEt, CH_3CN (ii) H_2O.

Tetraphenylarsonium Oxo[*N*,*N*′-ethylenebis(2-mercaptoacetamido)]technetate(V) (Ph_4As(XIII)).[3] A deep purple methanolic solution of IX (0.20 mmol in 7 mL, prepared as described above) was added to a colorless solution of *N*,*N*′-ethylenebis(2-mercaptoacetamide) (XII)[15] (50 mg, 0.24 mmol) in 0.2 M aqueous NaOH (20 mL) to give a clear yellow solution. RPTLC analysis showed only XIII. The addition of excess tetraphenylarsonium chloride hydrate gave Ph_4As(XIII) as a yellow precipitate that was filtered off, washed with water, and dried; yield 115 mg (78%). E_{pc} vs. SCE (V): −1.86, −2.11.

Deuterium Exchange of X, XI, and XIII. The tetraphenylarsonium salts of complexes X, XI, and XIII were dissolved in $CDCl_3$ (0.025 M solution). An equivalent volume of 0.024 M sodium tetraphenylborate in D_2O containing 0.1% DSS was added, and the two layers were shaken, resulting in almost complete extraction of the (yellow) sodium salts of the complexes into the D_2O layer. Deuterium exchange was carried out by the addition of NaOD in D_2O (1 M, 0.1 mL, 0.1 mmol) to 0.5 mL (0.012 mmol) of the complex solution, which raised the pH to 13. Exchange was terminated by the addition of DCl/D_2O (0.99 M, 0.11 mL, 0.11 mmol) in the cases of X and XI or CD_3COOD/D_2O (0.99 M, 0.11 mL, 0.11 mmol) in the case of XIII.

^1H NMR (250 MHz) spectra (Figure 1) were recorded after exchange had been halted and were compared with the spectra of the

(14) Waters Associates Inc., Milford, MA.

(15) Atkinson, E. R.; Handrick, G. R.; Bruni, R. J.; Grandelli, F. E. *J. Med. Chem.* **1965**, *8*, 29.

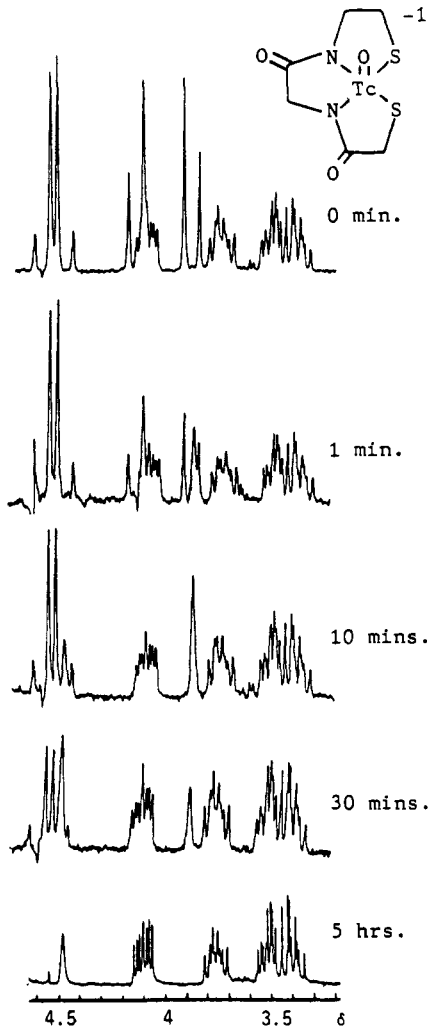


Figure 1. ^{1}H NMR (250 MHz) of complex X at selected stages of deuterium exchange.

unexchanged complexes. In order to obtain mass spectra, the neutralized D_2O solution was adsorbed onto a equilibrated Sep-Pak, washed with D_2O (to remove NaCl), eluted with CH_3OD, and evaporated to dryness.

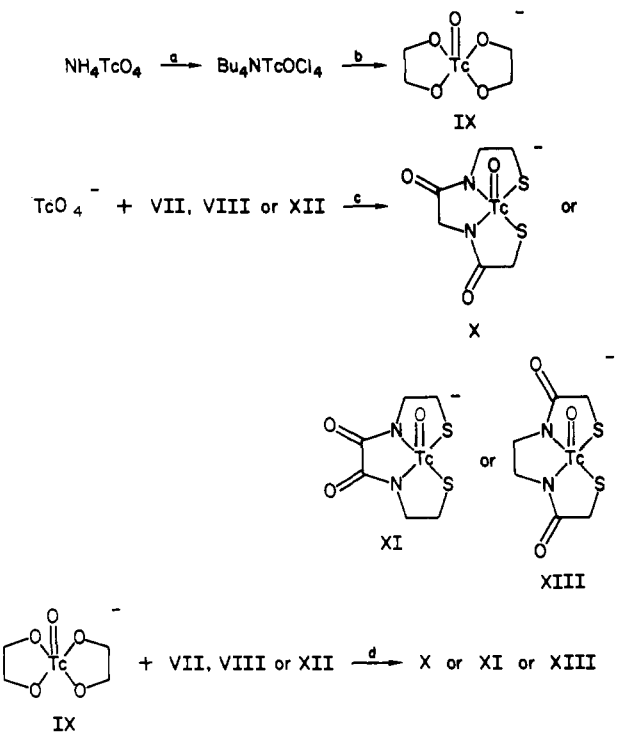
Results

The syntheses of the amide thiols VII and VIII are shown in Schemes I and II.

The synthesis of ligand VIII required protection of the thiol of 2-mercaptoethylamine during reaction with oxalyl chloride. This was conveniently carried out by in situ silylation,[16] the protecting groups being removed upon aqueous workup (see Scheme II). Since preparation of the asymmetric ligand VII required a stepwise reaction sequence, the more stable *S*-triphenylmethyl protecting group was used. A conventional peptide-type synthesis gave the bis(*S*-triphenylmethyl) derivative VI, which was deprotected by a novel method using triethylsilane in trifluoroacetic acid[17] (see Scheme I).

The asymmetric complex X could be prepared by dithionite reduction of pertechnetate in alkali in the presence of ligand VII, as has been reported for complex XIII.[3] However, due to its instability toward dithionite, only poor yields of complex XI could be obtained under such conditions. We thus developed an alternative, ligand-exchange procedure, using the oxobis(ethanediolato)technetate(V) anion IX,[18] which gave

Scheme III[a]



[a] Key: (a) (i) 12 M HCl, (ii) Bu_4NCl; (b) (i) HO⌒OH, (ii), NaOAc; (c) H_2O, OH^-, $Na_2S_2O_4$; (d) H_2O, CH_3OH, OH^-.

high yields of all three complexes X, XI, and XIII (see Scheme III), isolated as their tetraphenylarsonium salts.

The tetraphenylarsonium salts of the complexes X, XI, and XIII are air-stable yellow-orange crystalline salts that are readily soluble in polar nonaqueous solvents. The three isomeric complexes show the characteristic absorption due to the TcO stretch in their infrared spectra in the range 940–945 cm^{-1}.

The negative ion FDMS of XI shows a strong peak at m/z 319 that serves to characterize the anion. The high-resolution positive-ion FABMS of X gives a strong peak at m/z 320.9191 (anion + 2 H)$^+$. The compounds are diamagnetic and show ^{1}H and ^{13}C NMR spectra consistent with their formulations as square-pyramidal five-coordinate complexes. Under alkaline conditions the complexes X and XIII undergo stereoselective deprotonation–reprotonation (see Discussion).

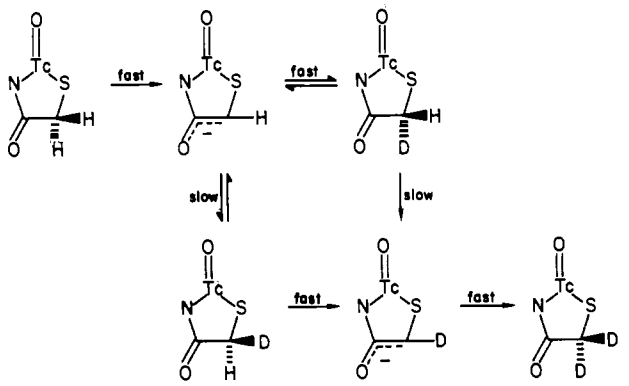
Discussion

The new amide thiol ligands VII and VIII are isomers of the ligand *N,N'*-ethylenebis(2-mercaptoacetamide) (XII). These ligands were selected to demonstrate the versatility of the diamido dithiolato tetradentate ligand system. These ligands, like XII, form the very stable, five-coordinate oxotechnetium anions X and XI, whose properies are quite similar to those of the structurally characterized complex XIII.

The deprotonated ligand, having imido nitrogen and thiolato sulfurs, presumably spans the basal positions of a square pyramid, the apex of which is the oxo group of the low-spin d^2 $[Tc^VO]^{3+}$ core. The complex X, which results from the unsymmetrical ligand VII, is a racemate. Because low yields of the complex XI (ca. 20%) resulted from the reaction of VIII with TcO_4^- and $Na_2S_2O_4$ in basic aqueous–ethanol, a modified ligand-exchange procedure was developed. Basic aqueous ethanolic solutions of the ligands XII, VII, and VIII reacted with the oxobis(ethanediolato)technetate ion (IX) under strictly anaerobic conditions to give high yields of the com-

(16) Shinkai, I.; Liu, T.; Reamer, R.; Sletzinger, M. *Synthesis* **1980**, 924.
(17) Brenner, D.; Davison, A.; Jones, A. G.; Lister-James, J., to be submitted for publication.
(18) DePamphilis, B. V.; Jones, A. G.; Davison, A. *Inorg. Chem.* **1983**, *22*, 2292.

Scheme IV[a]



[a] E.g. for faster anti exchange (partial structures).

plexes X, XI, and XIII. The oxygen-free atmosphere prevents both the oxidation of the ligands and the oxidation of IX to TcO_4^-, which is rapid in basic solution.

The electronic spectra (strong absorption in the range 355–360 nm) and the only slight variation in the TcO stretching frequencies suggest that the isomeric complexes are virtually identical electronically (b_2^2–$^1A_1$ ground state for idealized C_{4v} symmetry).

None of the complexes are readily oxidized or reduced electrochemically, but although the complees X and XIII are stable to reducing agents, the complex XI is unstable to dithionite in alkali. All three complexes are stable for extended periods of time in both acidic (pH ~0) and basic (pH ~14) solutions (vide infra). They are kinetically robust and do not undergo substitution or ligand-exchange reactions with other thiols. These new complexes extend the types of backbones that can give rise to $TcON_2S_2$ chelates.

The presence of the apical oxygen makes the methylene protons in the complexes diastereotopic. The complexes X and XIII, which have methylene groups adjacent to a carbonyl function in a five-membered ring, undergo highly stereoselective deprotonation–reprotonation reactions. This exchange was observed by using deuterium labeling in D_2O/NaOD solution and does not occur in either neutral or acidic solutions at a detectable rate. Significantly, the oximido complex XI does not have active methylene groups because no exchange was observed under identical conditions.

The course of the deuterium exchange of the complexes X and XIII was followed by ^1H NMR. For the complex XIII, the acyl methylene hydrogens initially appeared as an AB quartet δ 4.04 and 4.23 (J_{AB} = 17.5 Hz). When it was treated with NaOD in D_2O, the lower field resonances disappeared and the higher field resonances collapsed to a singlet at δ 4.03. The latter signal had a maximum intensity at ca. 3 min, corresponding to approximately 90% monodeuteration (all anti or all syn) at each acyl methylene position and approximately 10% dideuteration. Over a further 2 h, complete deuteration had occurred and at no time was a singlet at δ 4.20 observed. The mercaptoacyl hydrogens of complex X were observed to exchange on a similar time scale to those of XIII. The initial AB quartet δ 3.90 and 4.15 (J_{AB} = 17.5 Hz) collapsed to a singlet at δ 3.89, maximum intensity ca. 3 min, which then disappeared over 2 h. The glycyl hydrogens of X exchanged more slowly but again stereoselectively. The initial AB quartet δ 4.50 and 4.58 (J_{AB} = 17.5 Hz) collapsed to a singlet at δ 4.52, maximum intensity at 1 h, which disappeared over a further 12 h. The positive-ion FABS of the complex after 48 h confirmed the sole presence of tetradeuterated X.

For comparative purposes, the water-soluble oxidatively stable bis(*S*-acetamidomethyl) derivatives of the ligands VII and XII were similarly treated with D_2O/NaOD. All of the acyl hydrogens of both derivatives exchanged within 5 min. When the OD^- to compound ratio was reduced from 8:1 (the value used for the compounds X and XIII to 1:10, the mercaptoacetyl hydrogens of both derivatives still fully exchanged within 5 min but the glycyl protons of the bis(*S*-acetamidomethyl) derivative of VII were only 50% exchanged in 24 h. Thus, all the acyl methylenes of complexes X and XIII exhibit highly stereoselective deuterium exchange either syn or anti to the Tc=O group.

The most plausible explanation of such stereoselectivity requires both stereoselective deproton(deuteron)ation and stereoselective redeuteration from the same side (face of the enolic intermediate), as shown in Scheme IV.

Slower deproton(deuteron)ation, or redeuteration of the enolic intermediate, from the less favored side then accounts for the subsequent formation of the dideuteriomethyene moiety.

All of the faster exchanging hydrogens have their ^1H NMR resonances downfield of the slower exchanging hydrogens. This suggests that they are all syn *or* all anti to the Tc=O bond. However, only structural characterization will allow assignment as to which is which. Clearly, the deuterium exchange of the complexes was much slower than that of the ligands. While charge repulsion (of the anionic complexes and OD^-) may account for some rate change, a more significant effect may be unfavorable enolization of the more rigid triple-ring system of the complexes.

As previously reported for complex XIII, the two new complexes X and XI also undergo rapid renal excretion. Details of their biodistribution will be reported elsewhere.

Registry No. I, 34914-36-8; II, 91425-31-9; III, 91425-32-0; IV, 91425-33-1; V, 1095-85-8; VI, 91425-34-2; VII, 91425-35-3; VII, bis(*S*-acetamidomethyl) derivative, 91425-37-5; VIII, 91425-36-4; IX, 91443-59-3; Ph_4As(X), 91443-61-7; Ph_4As(XI), 91443-63-9; XII, bis(*S*-acetamidomethyl) derivative, 91425-38-6; $Bu_4NTcOCl_4$, 71341-65-6; Ph_4As(XIII), 75949-45-0; NH_4TcO_4, 14333-20-1; mercaptoacetic acid, 68-11-1; triphenylmethanol, 76-84-6; *N*-hydroxysuccinimide, 6066-82-6; glycine, 56-40-6; 2-mercaptoethylamine hydrochloride, 156-57-0; oxalyl chloride, 79-37-8; hydrogen, 1333-74-0.