SYNTHESIS AND STUDY OF TECHNETIUM(V) COMPLEXES OF TETRADENTATE NITROGEN-, SULFUR-DONOR LIGANDS

by
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ABSTRACT

CHAPTER 1. The synthesis of several new diamine-dithiol ligands with N-alkyl substituents (methyl, benzyl, p-[2-(4,4-dimethyl-2-oxazolino)]benzyl) is described. These compounds (DADT-R) readily ligand exchange with $Na[TcO(eg)_2]$ (eg = 1,2-ethanediolato) to give neutral complexes [TcODADT-R]. Comparisons with other [TcODADT-R] complexes are made.

CHAPTER 2. General methods for the preparation of a new series of N-alkylated N_2S_2 ligands of the type $ZS(CH_2)_2NH(R)CH_2C(O)NH(CH_2)_2SZ$, R-aa$(aetZ)_2$ (Z = H, benzamidomethyl, and acetamidomethyl, R = H, benzyl, 4-(carboxy)benzyl, and 4-(carboxy)benzyl esters), are described. Ligand exchange with both oxotechnetium and oxorhenium starting materials yields stable neutral oxometal complexes. Two complexes [TcO(Benzyl-aa$(aet)_2$)] and [ReO(Benzyl-aa$(aet)_2$)] are partially structurally characterized. Crystal data for the technetium compound are: space group $R\overline{3}$(h), a = 26.012(6) Å, c = 12.412(2) Å, V = 7273(4) $Å^3$, Z = 18, R = 0.057, R_w = 0.076. Crystal data for the rhenium compound are: space group $R\overline{3}$(h), a = 26.022(3) Å, c = 12.418(4) Å, V = 7291 (3)$Å^3$, Z = 18, R = 0.052, R_w = 0.053.

CHAPTER 3. Two anionic nitridotechnetium complexes of diamide-thiol-thioether ligands are synthesized and compared with the analogous neutral oxotechnetium complexes. Instabilities of these anionic complexes to a variety of conditions were noted. Attempts at synthesizing neutral nitridotechnetium complexes with diamide-dithioether (N_2S_2) and diimine-diol (N_2O_2) ligands were made.

APPENDIX I. Development of the amine-amide-dithiol complexes for use as radiolabeling bifunctional chelating agents was attempted. General synthetic details of the peptide coupling activation reactions are detailed. No successful radiolabeling procedure was found.

APPENDIX II. Partial crystal structure of [TcO(Bzl-DADT)]. Crystal data for the compound are: space group I2/a, a = 24.586 (2) Å, b = 7.045 (5) Å, β = 111.46°, V = 3821 (5) $Å^3$, Z = 8, R = 0.150, R_w = 0.210. Due to disorder in the benzyl carbons the structure could not be further refined. Structural data can only be used to indicate that the structure is the syn isomer.

Thesis Supervisor: Dr. Alan Davison
Title: Professor of Chemistry

To Penny for showing me what life is all about.

THIS BRIDGE

This bridge will only take you halfway there
To those mysterious lands you long to see:
Through gypsy camps and swirling Arab fairs
And moonlit woods where unicorns run free.
So come and walk awhile with me and share
The twisting trails and wondrous worlds I've known.
But this bridge will only take you halfway there -
The last few steps you'll have to take alone.

Shel Silverstein
A Light in the Attic

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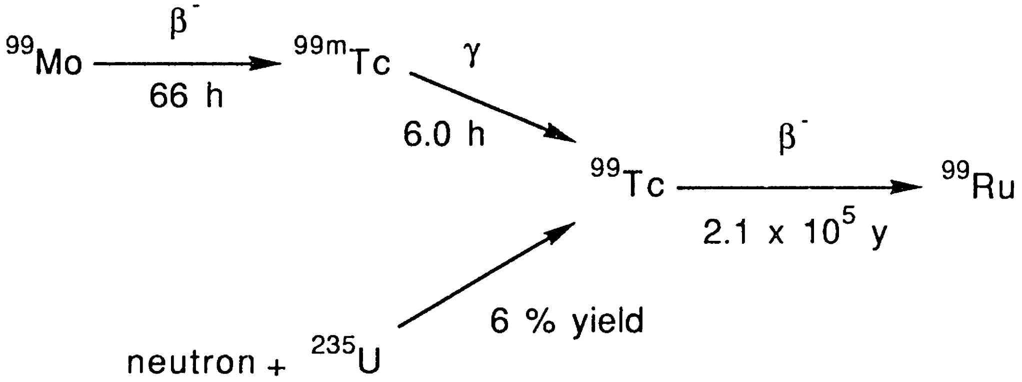
INTRODUCTION

While the existence of element 43 had been predicted by Mendeleev in 1869, it was not until 1937 that Perrier and Segrè[1, 2] isolated technetium from transmutation reactions with molybdenum. Technetium is not naturally abundant; though it is formed as 6% of yield of uranium fission. Based on this yield there is now more technetium in the world than rhenium, its naturally occuring congener. Unfortunately most of the world's supply of technetium is contained within spent uranium fission rods as long-lived nuclear waste.[3]

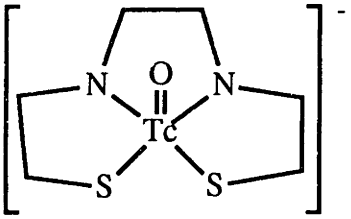


There are two isotopes of technetium which are of current interest to those studying this element's chemistry. Technetium-99 is a long-lived isotope ($t_{1/2}$=2.1 x 10^5 years) with a low level beta emission(β^-= 292 keV). This isotope is regularly used for studying technetium's inorganic chemistry due to its long-term stability and limited precautions for use.[4] The second isotope of interest is technetium-99m. This is a metastable isotope which is regularly used in diagnostic nuclear medicine. It has a 6 hour half-life and emits a gamma photon(140 keV). Technetium-99m can be readily isolated from a molybdenum-99 generator which makes it highly practical for hospital use.

The ongoing goal of the Davison group is to probe the inorganic chemistry of technetium and pursue new nuclear medicine applications (radiopharmaceuticals). Unfortunately, the rational design of practical radiopharmaceuticals is much more difficult than the task of uncovering new and interesting technetium chemistry.[5, 6]

The pursuit of new technetium radiopharmaceuticals is complicated by the conditions required for success. The starting material for all technetium-99m radiopharmaceuticals is aqueous pertechnetate ($^{99m}TcO_4^-$) at very low concentrations (10^{-6}-10^{-9}M). Reactions which yield different products dependent upon concentration are thus problematic. Finally, the 99m isotope has a six hour half-life, which restricts reactions to those which are completed in short periods of time. Therefore, a successful radiopharmaceutical is one which forms from pertechnetate in aqueous or aqueous/alcoholic solution, is not stoichiometrically dependent in its formation, and has a very high yield(>95%) within a short period of time.

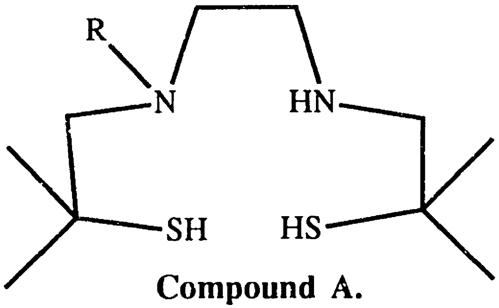
Technetium radiopharmaceuticals are inorganic complexes which have been found to localize in important parts of the human body. Though some of these radiopharmaceuticals were designed, many of them were discovered serendipitously. Nonetheless there has always been an interest in being able to develop, by way of rational synthesis, a radiopharmaceutical system that can target specific areas of the body. Recent research[7, 8] has been centered upon the development of bifunctional chelating agents. This involves the synthesis of chelating ligands for technetium which contain a second functionality capable of binding to biological molecules.


Oxotechnetium(V) Anion

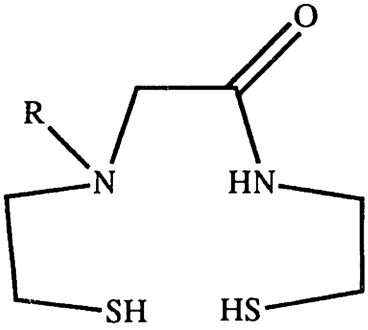
For technetium, the use of tetradentate S,N,N,S-donor ligands (N_2S_2's) is one of the best for simple metal complexation. Technetium has a very high affinity for sulfur ligands, and the N_2S_2 ligands have been found to form very stable technetium(V) oxo complexes.[9] Several anionic N_2S_2 complexes have shown strong renal clearance, and some of a series of neutral complexes have been shown to cross the blood-brain barrier.[3] This ability to have some control over biodistribution by variation of the overall charge and lipophilicity is very important in the development of radiopharmaceuticals.

The work that follows details the development of new N_2S_2 ligands and the resulting technetium and rhenium complexes. An emphasis has been placed on the synthesis of neutral oxotechnetium(V) complexes which have applications towards labeling of biological molecules. Chapter one discusses the synthesis and study of new diamine-dithiol (DADT)[10, 11] ligands (Figure 1, Compound A). Chapter two details work with an amine-amide-dithiol (AADT) [12] ligand (Figure 1, Compound B) which undergoes mono-N-alkylation more readily than that of the DADT system. Chapter three details some monoanionic complexes of a diamide-thiol-thioether (EMA)[13] ligand (Figure 1, Compound C) system with the nitridotechnetium core. Appendix one details some attempted work towards applying the AADT ligand system to the development of bifunctional chelating agents.

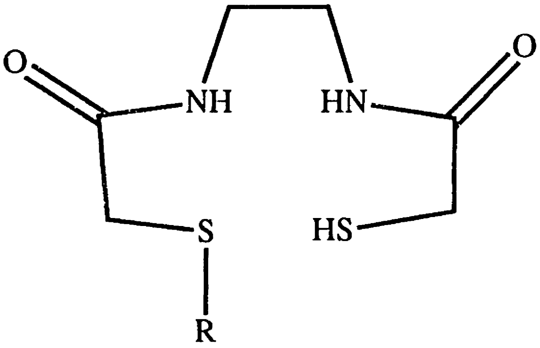
Figure I.1 Functionalized N_2S_2 Ligand Structures



Compound A.
Diamine-dithiol (DADT)



Compound B.
Amine-amide-dithiol (AADT)



Compound C.
Diamide-thiol-thioether (EMA)

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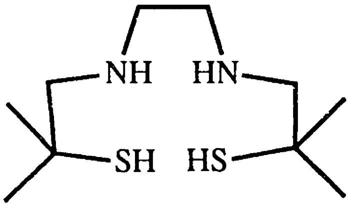
CHAPTER 1.

COMPLEXES OF DIAMINE-DITHIOL CHELATING LIGANDS

INTRODUCTION

While many different types of technetium complexes have been synthesized in the pursuit of new radiopharmaceuticals, complexes with sulfur containing ligands have been of particular interest.[1, 2] Specifically, the use of tetradentate S,N,N,S-donor ligands has been well studied. These N_2S_2 ligands form very stable square pyramidal technetium(V) oxo compounds. Of the many N_2S_2 ligands developed to date, the diamine-dithiol (DADT, N_2S_2) system has been widely studied by researchers.[3] Various derivatives of the basic DADT ligand have been synthesized by alkylation of one or more of the atoms within the basic ligand framework. Applications for such derivatized technetium DADT complexes have varied from those of Kung,[4] which cross the blood-brain barrier, to those of Lever,[5, 6] which suggest applications in the labeling of biological molecules.



Diamine-Dithiol (DADT)

Based on published methods[5, 7, 8] several mono-N-substituted 2,2,9,9-tetramethylethylene-N,N'-bis(aminoethanethiol) (DADT) ligands were synthesized by N-alkylation of 1,1,4,4-tetramethylimidazolino[1,2-d]dithiazepine[8] followed by lithium aluminum hydride reduction. The use of methyl iodide provided methyl-DADT (**2**), benzyl chloride provided benzyl-DADT (**4**), and 2-[(p-chloromethyl)phenyl]-4,4-dimethyl-2-oxazoline (**7**) provided a protected carboxylic acid DADT derivative (**9**). The corresponding technetium(V) oxo complexes (**10, 11, 12**) were synthesized by ligand exchange with technetium(V) oxo starting materials.

Work completed by Lever et al.[9, 10] since the start of this work has subsequently reported the synthesis and study of a methyl-DADT oxotechnetium complex. Comparisons made between this complex and **10** indicate that the two compounds are identical.

EXPERIMENTAL

CAUTION: ^{99}Tc is a weak β^--emitting isotope with a half-life of 2.12 x 10^5 years. All manipulations involving technetium were carried out in laboratories approved for low-level radioactivity and the precautions followed were detailed previously.[2, 11]

General. Ammonium pertechnetate was supplied as a gift by DuPont Biomedical Products. Flash chromatography was performed using either Kieselgel TLC grade silica or ICN Biomedical neutral alumina, as indicated. The column was pressurized using a hand-powered blower (Fisher). Thin layer chromatography was performed using EM Science Silica Gel 60 F-254 TLC plates which were developed using 0.05% $PdCl_2$ in 0.24 M HCl to identify S-containing compounds. Melting points were obtained with a Mel-Temp apparatus and are uncorrected. IR spectra were measured from 4000 to 400 cm^{-1} on a Mattson Cygnus 100 FT-IR spectrometer. Potassium bromide pellets were used unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer. UV-visible absorption spectra were recorded with a Hewlett-Packard 8451A photodiode array spectrophotometer. Fast atom bombardment mass spectra (FABMS), in positive or negative mode, were measured on a MAT 731 mass spectrometer equipped with an Ion Tech B11N FAB gun operating at an accelerating voltage of 8keV. The FAB gun produced a beam of 6-8 keV xenon neutrals. Samples were dissolved in a p-nitrobenzylalcohol matrix unless otherwise indicated. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

The following compounds were made from literature preparations: sodium oxobis(1,2-ethanediolato)technetate,[12, 13] tetra-n-butylammonium oxotetrachlorotechnetate,[14] 2,2'-dithiobis(2-methylpropanol),[15] 3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene,[15] and 1,1,4,4-tetramethylimidazolino[1,2-d]dithiazepine.[8] Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Distilled water was run through a Barnstead Ultrapure D8902 cartridge, followed by redistillation in a Corning AG-1 water still. All other chemicals and solvents were of reagent grade and used as received.

(1) - 1,1,4,4,9-pentamethylimidazolino[1,2-*d*]dithiazepine - (Me-bicyclic) subsequently reported by Lever[5]

$C_{11}H_{22}N_2S_2$ MW = 246

A solution of of 1,1,4,4-tetramethylimidazolino[1,2-d]dithiazepine (5 g, 22 mmole) in 40 ml acetonitrile was cooled in an ice bath and tetramethylguanidine (3 ml, 28 mmole) was added. After slow addition of iodomethane (Aldrich, 4 ml, 65 mmole), the ice bath was removed and the solution was refluxed for 2 hours. The resulting solution was concentrated under reduced pressure and partitioned between ether and aqueous base. The organic layer was concentrated and dried over anhydrous potassium carbonate. Ether was added and the resulting solution was filtered. Removal of the ether under reduced pressure yielded an oil which was chromatographed (Silica gel using a 1-10% methanol in methylene chloride eluant gradient). Forty fractions were collected and solvent was removed under reduced pressure to yield **1** as a white solid. Yield 3.72 g (15.12 mmole, 69%).

MP =25-28°C.

^{1}H-NMR ($CDCl_3$) δ 1.23 (s, 6H, CH_3's), 1.29 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.47 (s, 3H, N-CH_3), 2.6-3.4 (multiplets, 7H, CH_2's).

FABMS$^+$ m/z= 247 $(M + H)^+$, 231 $(MH - CH_4)^+$, 204 $(M\text{-}C(CH_3)_2)^+$, 188 $(M\text{-}CH_3CH(CH_3)_2)^+$,171 $(M\text{-} (CH_3)_2C\text{-}SH)^+$.

IR: vmax 1710, 1471, 1365, 1119, 1044, 805 cm^{-1}.

(2) - 2,2,4,9,9-pentamethylethylene-N,N'-bis(aminoethanethiol) - (Me-DADT) - subsequently reported by Lever[5]

$C_{11}H_{26}N_2S_2$ MW= 250

Tetrahydrofuran (THF) was slowly added to lithium aluminum hydride powder (2.576 g, 67.93 mole) under a nitrogen atmosphere. A second solution of the bicyclic amine **1** (5.044 g, 20.10 mmole) in THF was slowly added to the lithium aluminum hydride slurry. When the addition was completed the solution was stirred and refluxed under nitrogen for 60 hours. Reflux was stopped and the solution was allowed to cool to room temperature. The flask was placed in an ice bath, and distilled water was added slowly (exothermic reaction). Solvent was removed under reduced pressure. Ethyl acetate was added to the remaining grey solid, and the solution was refluxed for 45 minutes. The solution was filtered, and the grey solid was washed with another portion of ethyl acetate. The ethyl acetate layers were combined, and the solvent was removed under reduced pressure to yield **2** as a purplish oil. Yield 2.26 g (9.04 mmole. 45%)

^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 6H, 2 CH_3's), 1.38 (s, 6H, 2 CH_3's), 1.9-2.1 (br s, 3H, NH, 2SH's), 2.38 (s, 3H, CH_3-N), 2.48 (s, 2H, N-CH_2), 2.63 (s, 2H, N-CH_2), 2.65-2.78 (m, 4H, N-CH_2-CH_2-N).

(3) - 9-Benzyl-1,1,4,4-tetramethylimidazolino[1,2-*d*]dithiazepine - (Bzl-bicyclic)

$C_{17}H_{26}N_2S_2$ MW= 322.5

To a solution of 1,1,4,4-tetramethylimidazolino[1,2-*d*]dithiazepine (3.95 g, 17 mmole) in 40 ml acetonitrile was added tetramethylguanidine (2.5 ml, 20 mmole). Benzyl chloride (3 ml, 26 mmole) was added, and the solution was refluxed for 10 hours. The solvent was removed and the remaining yellowish oil was partitioned between ether and aqueous base. The ether layer was dried over anhydrous potassium carbonate. Filtration and concentration under reduced pressure yielded a solid which was chromatographed (Silica gel, 1-5% methanol in methylene chloride eluant gradient). Sulfur containing fractions were combined and **3** was isolated as a white solid by trituration of the methylene chloride/methanol solution with water. Yield 3.51g (10.88 mmole, 64%).

MP =72-75°C.

^{1}H-NMR (CD_2Cl_2) δ 1.22 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.5-3.1 (m's, 6H, CH_2's), 3.30(,1H, s, CH_2-Ph), 3.80 (s, 1H, CH), 3.83(,1H, CH_2- Ph), 7.2-7.4 (m, 5H, aromatic).

FABMS$^+$ m/z= 323 $(MH)^+$, 270 $(M-C(CH_3)_2)^+$, 264 $(M-CH_3CH(CH_3)_2)^+$, 248 $(M-(CH_3)_2C-SH)H^+$, 233 $(M-C_7H_7)H_2^+$, 215 $(M-(CH_3)_2CSH-SH)H^+$, 175 $(215 - C(CH_3)_2)H_2^+$, 160 $(175 - CH_3)^+$.

IR νmax 1456, 1359, 1125, 1044, 720 cm^{-1}.

Anal Calculated for $C_{17}H_{26}N_2S_2$: C, 63.31; H, 8.13; N, 8.69; S, 32.06.
Found: C, 63.35; H, 8.20; N, 8.64.

(4) - 4-benzyl-2,2,9,9-tetramethylethylene-N,N'-bis(aminoethanethiol) - (Bzl-DADT)

$C_{17}H_{30}N_2S_2$ MW= 326.5

Lithium aluminum hydride (0.51 g, 13 mmole) was weighed into a round bottom flask. The round bottom flask was placed in an ice bath and

THF was slowly added under a nitrogen atmosphere. A THF solution of the bicyclic amine **3** (0.516 g, 16 mmole) was added slowly through a pressure-equalizing addition funnel. When the addition was completed the ice bath was removed and the solution was allowed to stir and reflux under nitrogen for 60 hours. At that time reflux was stopped and the solution was allowed to cool to room temperature. A 40% solution of Rochelle's salt (sodium potassium tartrate in distilled water) was added slowly while the flask was cooled in an ice bath. Solvent was removed under reduced pressure. Ethyl acetate was added to the resulting white solid and the mixture refluxed. The solution was filtered and the solid washed with ethyl acetate. The ethyl acetate layers were combined and the solvent was removed under reduced pressure to yield **4** as an orange/white oil. Yield 2.09 g (6.4 mmole, 40 %).

(5) - p-(Chloromethyl)benzoyl chloride (α-chloro-p-toluyl chloride)

$C_8H_6Cl_2O$ MW = 189

A solution of 4-(chloromethyl)benzoic acid (Aldrich, 3.155g, 18.50 mmole) in thionyl chloride (Fluka, 10 ml) was stirred and refluxed for 12 hours. Removal of the excess thionyl chloride proceeded by repeated additions of benzene followed by solvent removal under reduced pressure. This yielded **5** quantitatively as a white solid.

MP =165-175°C.

^{1}H-NMR ($CDCl_3$) δ 4.68(s, 2H, CH_2), 7.58 (1/2 'A_2B_2' quartet, J=9 Hz, 2H, aromatic), 8.15 (1/2 'A_2B_2' quartet, J=9 Hz, 2H, aromatic).

IR νmax 1780, 1744, 1680 (CO), 1290, 1206, 1175, 711 cm^{-1}

(6) - N-(2,2-dimethyl-3-hydroxypropyl)-p-(chloromethyl) benzamide

$C_{12}H_{22}ClNO_2$ MW = 241.5

A methylene chloride solution of 2-amino-2-methyl-1-propanol (Aldrich, 4 ml, 42 mmole) was cooled in an ice bath. In an exothermic reaction, the acid chloride **5** (4g, 21 mmole) was added slowly. After stirring for two hours, a white solid (the amine salt of 2-amino-2-methyl-1-propanol) had precipitated. The solution was partitioned between methylene chloride and 0.1M acetic acid. The organic layer was dried over anhydrous potassium carbonate, and concentrated under reduced pressure to yield **6** as a white solid.

MP =76-81°C.

^{1}H-NMR ($CDCl_3$) δ 1.41, 1.42 (2s, 6H, CH_3's), 3.67 (s, 2H, $C(CH_3)_2$-$C\underline{H_2}$), 3.7 (v br s, 1H, OH), 4.60 (s, 2H, Cl-CH_2), 6.3 (br s, 1H, NH), 7.44 (1/2 'A_2B_2', J=9Hz, 2H, aromatic), 7.72(1/2 'A_2B_2', J=9Hz, 2H, aromatic).

FABMS$^+$ m/z= 483 $(M_2H)^+$, 447 $(M_2\text{-}Cl)^+$, 242 $(MH)^+$, 170 $(M\text{-}C(CH_3)_2CH_2OH)H_2^+$, 153 $(M\text{-}NHC(CH_3)_2CH_2OH)^+$, 91 $(C_7H_7)^+$.

(7) - 2-[(p-chloromethyl)phenyl]-4,4-dimethyl-2-oxazoline hydrochloride - (Oxazoline-Cl)

$C_{12}H_{20}ClNO$	MW = 229.5
$C_{12}H_{21}Cl_2NO$ (HCl salt)	MW = 266

Thionyl chloride was slowly added to a methylene chloride solution of compound **6**. This solution was allowed to stir under nitrogen for 12 hours. Benzene was added and the solution was concentrated under reduced pressure to a white/yellow solid. The solid (**7**) was filtered and washed with benzene. Net yield (Reactions **5**, **6**, and **7**) 9.81 g (42.7 mmole 73%) from 10 g of 4-(chloromethyl)benzoic acid.

MP =142-144°C.

^{1}H-NMR ($CDCl_3$) δ 1.80 (s, 6H, 2 CH_3's), 4.64 (s, 2H, CH_2), 4.71 (s, 2H, CH_2), 7.64 (1/2 'A_2B_2', J=9Hz, 2H, aromatic), 8.52 (1/2 'A_2B_2', J=9Hz, 2H, aromatic).

FABMS$^+$m/z= 483 $(M_2 + HCl)^+$447 $(M_2H)^+$, 377 $(M + NBA)^+$, 224 $(MH)^+$, 189 $(M\text{-}Cl)H^+$, 91 $(C_7H_7)^+$.

IR vmax 1641, 1633, 1613, 1475, 1451, 1365, 1195, 1111, 935, 876, 701cm^{-1}.

Anal Calc for $C_{12}H_{21}Cl_2NO$: C, 55.40; H, 5.81; N, 5.38; Cl, 27.25; O, 6.15.
(HCl Salt) Found: C, 55.27; H, 5.84; N, 5.33; Cl, 27.16.

(8) - 9-p-[2-(4,4-dimethyl-2-oxazolino)]benzyl-1,1,4,4-tetramethylimidazolino[1,2-*d*]dithiazepine - (Oxazoline-bicyclic)

$C_{22}H_{33}N_3OS_2$	MW = 419
$C_{22}H_{39}Cl_3N_3O_{2.5}S_2$ (HCl Salt)	MW = 556

Acetonitrile was added to a flask containing 1,1,4,4-tetramethylimidazolino[1,2-*d*]dithiazepine (8.776 g, 37.83 mmole), oxazoline compound **7** (8.58 g, 38.48 mmole), and potassium bicarbonate (4.258 g, 42.58 mmole). This solution was stirred and refluxed for 22 hours. The resulting white precipitate (potassium chloride) was removed and the solution was concentrated to a slightly yellowish oil. This oil was dissolved in methylene chloride and chromatographed (Silica gel, 1% methanol in methylene chloride eluant). One major sulfur containing band was collected and yielded a clear oil. This oil was redissolved in ether. Bubbling HCl(g) through this solution resulted in the precipitation of **8** as a hydrochloride salt (compound.3 HCl.3/2 H_2O). Yield 11.43g (20.63 mmole, 55%).

^{1}H-NMR ($CDCl_3$) δ 1.22 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.38 (s, 6H, 2 CH_3's), 1.46 (s, 3H, CH_3), 2.5-3.1 (m's, 6H, 3 CH_2's), 3.30 (1/2 AB quart, J=11.5Hz, 1H, CH_2-Ph), 3.81 (s, 1H, CH), 3.87 (1/2 AB quart, J=11.5 Hz, 1H, CH_2-Ph), 4.10 (s, 2H, O-CH_2), 7.38, 7.40 (1/2 'A_2B_2', J=6Hz, 2H, aromatic), 7.88, 7.90 (1/2 'A_2B_2', J=6Hz, 2H, aromatic).

FABMS$^+$ m/z= 420 $(MH)^+$, 361 $(M\text{-}CH_3CH(CH_3)_2)^+$, 345 $(M\text{-}(CH_3)_2CSH)^+$, 312 $(345\text{-}SH)^+$, 271 $(312\text{-}C(CH_3)_2)H_2^+$, 257 $(271\text{-}CH_2)^+$, 188 $(CH_2\text{-}Ph\text{-}Oxazoline)^+$.

IR vmax 1645, 1613, 1459, 1389, 1359, 1320, 1114 cm^{-1}.

Anal Calc. for $C_{22}H_{39}Cl_3N_3O_{2.5}S_2$: C, 47.52; H, 7.01; N, 7.55; Cl, 19.13;
(HCl Salt) O, 7.19; S, 11.53.
Found: C, 47.54; H, 7.21; N, 7.40; Cl, 18.82

(9) - 4-p-[2-(4,4-dimethyl-2-oxazolino)]benzyl-2,2,9,9-tetramethylethylene-N,N'-bis(aminoethanethiol) - (Oxazoline-DADT)

$C_{22}H_{37}N_3OS_2$ MW = 423

Lithium aluminum hydride (2.081 g, 54.88 mmole) was placed in a round bottom flask as a powder. The round bottom flask was placed in an ice bath and freshly distilled THF was slowly added. The resulting slurry was stirred under a nitrogen atmosphere. The N-alkylated bicyclic amine **8** (6.1 g, 10.97 mmole) was dissolved in THF and added to the lithium aluminum hydride slurry by use of a pressure-equalizing dropping funnel. When the addition was completed the ice bath was removed and the solution was allowed to stir and reflux under nitrogen for 60 hours. At that time reflux was stopped and the solution was allowed to cool to room temperature. The flask was placed in an ice bath and a 40% solution of Rochelle's salt (sodium potassium tartrate in distilled water) was added slowly . Solvent was removed under reduced pressure. Ethyl acetate was added to the resulting white solid and the mixture refluxed. The solution was filtered and the solid washed with ethyl acetate. The ethyl acetate layers were combined and the solvent was removed under reduced pressure to give a yellow oil. This oil was chromatographed (Silica gel, methanol in methylene chloride gradient) and the solvent was removed under reduced pressure to give **9** as a clear oil. Yield 0.462 g (1.09 mmole, 10%)

(10)- 4-N-methyl-2,9-dimethyl-4,7-diaza-2,9-decanedithiolato oxotechnetium - [TcO(Me-DADT)] Subsequently reported by Lever.[5]

$C_{11}H_{23}N_2OS_2Tc$ MW= 362

To a methanol solution of sodium oxobis(1,2-ethanediolato)technetate (21.9 mg, 0.0848 mmole) was added the methyl-DADT ligand **2** (25 mg, 0.1 mmole) in a sodium methoxide/methanol (25% w/w) solution. The solution stirred for one hour and was concentrated to a brown/yellow solid. This solid was redissolved in methylene chloride and chromatographed (Silica gel, 1% methanol/methylene chloride eluant). Compound **10**, as a mixture of isomers was isolated as a yellow/orange solid. Yield 26 mg (0.072 mmole, 85%).

^{1}H-NMR (syn isomer) ($CDCl_3$) δ 1.54 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 2.22 (ABCD, J=12Hz, J=6.7Hz, 1H, NCH_2CH_2N), 2.58 (AB, J=13Hz, CH_2), 3.05 (ABCD, J=3Hz, J=1Hz, NCH_2CH_2), 3.07 (AB, J=13Hz, CH_2), 3.39 (ABCD, J=5Hz, J=1Hz, NCH_2CH_2N), 3.46 (s, 3H, NCH_3), 3.82 (AB, J=12Hz, 1H, CH_2), 3.90 (AB, J=12Hz, CH_2), 3.39 (ABCD, J=13Hz, J=3Hz, NCH_2CH_2N).

^{1}H-NMR (anti isomer) ($CDCl_3$) δ 1.49 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.00 (s, 3H, NCH_3), 3.4-3.5 (overlapping multiplets, 4H, CH_2's), 3.6-3.9 (overlapping multiplets, 3H, CH_2's), 4.1 (ABCD, 1H, NCH_2CH_2N).

FABMS$^+$ m/z= 363 $(MH)^+$, 347 $(M-CH_3)^+$, 329 $(M-SH)^+$, 288 $(M-(CH_3)_2CSH)H^+$, 232 $(BAT-4H)^+$.

IR vmax 916 cm^{-1} (Tc=O, syn)[5]
924 cm^{-1} (Tc=O, anti)[5]

(11) - 4-N-benzyl-2,9-dimethyl-4,7-diaza-2,9-decanedithiolato oxotechnetium - [TcO(Bzl-DADT)]

$C_{17}H_{27}N_2OS_2Tc$ MW= 438

The procedure for formation of the oxotechnetium methyl-DADT complex (**10**) was repeated using the benzyl-DADT ligand (**4**). Silica chromatography (70% benzene/ 25% methylene chloride/ 5% acetonitrile as eluant) yielded **11** as a yellow/orange solid in 79% yield. Red/brown needles were isolated by slow diffusion of hexanes into a methylene chloride solution.

MP = 180-182° C.

^{1}H-NMR (syn isomer) ($CDCl_3$) δ 1.52 (s, 3H, CH_3), 1.60 (s, 3H, CH_3). 1.83 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.15 (1/2 AB quartet, J = 13.3 Hz, 1H, N-CH_2), 3.24 (1/4 ABCD, 1H, N-CH_2-CH_2-N), 3.35 (1/4 ABCD, 1H, N-CH_2-CH_2-N), 3.50 (1/4 ABCD, 1H, N-CH_2-CH_2-N), 3.64 (1/2 AB quartet, J = 13.3 Hz, 1H, N-CH_2), 3.91 (AB quartet, J = 10 Hz, 2H, N(Bzl)-CH_2), 4.67 (1/4 ABCD, 1H, N-CH_2-CH_2-N), 4.94 (1/2 AB quartet, J= 15 Hz, 1H, CH_2Ph), 5.28 (1/2 AB quartet, J= 15 Hz, 1H, CH_2Ph), 7.4-7.5 (m, 5H, aromatic).

^{13}C-NMR ($CDCl_3$) δ 28.16, 30.32, 31.26, 32.78, 55.81, 56.22, 61.23, 61.95, 63.17, 72.30, 81.90, 128.96, 129.39, 131.78, 132.73, 152.07.

FABMS$^+$ (NBA, mw. = 154) 1314 $(M_3)^+$, 878 $(M_2H_2)^+$, 439 $(MH)^+$, 364 (M-$(CH_3)_2$C-SH)H$^+$, 347(M-C_7H_7)$^+$, 323(Bzl-Bicyclic)$^+$, 248 (M-(TcO$(CH_3)_2$CSH)H)$^+$.

IR νmax 1453, 1084, 908 (TcO), 733, 701 cm^{-1}.

Anal Calculated for $C_{17}H_{27}N_2OS_2Tc$: C, 46.56; H, 6.21; N, 6.39; S, 14.62; O, 3.65; Tc, 22.58.

Found: C, 46.53; H, 6.15; N, 6.30; S, 14.62.

(12) - 4-N-p-[2-(4,4-dimethyl-2-oxazolino)]benzyl-2,9-dimethyl-4,7-diaza-2,9-decanedithiolato oxotechnetium - [TcO(Oxazoline-DADT)]

$C_{22}H_{34}N_3O_2S_2Tc$ MW = 535.5

The procedure for formation of the oxotechnetium methyl-DADT complex (**10**) was repeated using the oxazoline-DADT ligand (**9**). Silica chromatography (1% methanol in methylene chloride eluant) yielded **12** as a yellow/orange solid. Yield 62%.

MP = 170-173°C.

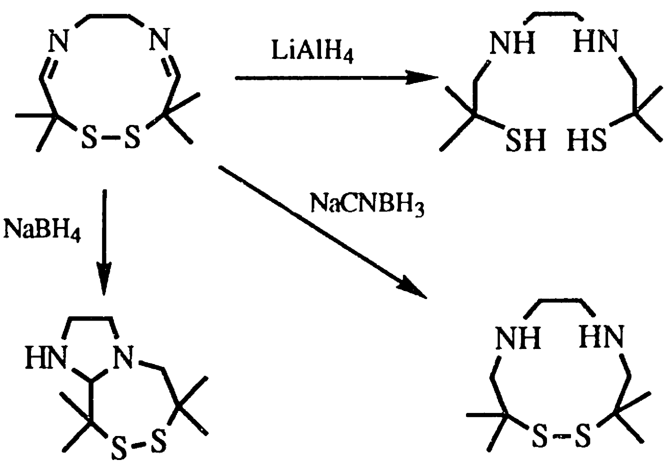
^{1}H-NMR (syn isomer) ($CDCl_3$) δ 1.20 (s, 6H, N-C$(CH_3)_2$), 1.51 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.14 (1/2 AB quartet, J= 13.2 Hz, 1H, N-CH_2), 3.23 (1/4 ABCD, 1H, N-CH_2-CH_2-N), 3.33 (1/4 ABCD, 1H, N-CH_2-CH_2-N), 3.61 (1/2 AB quartet, J= 13.2 Hz, 1H, N-CH_2), 3.71 (1/4 ABCD, 1H, N-CH_2-CH_2-N), 3.82 (s, 2H, CH_2-O), 3.91 (s, 2H, N(Bzl)-CH_2), 4.65 (1/4 ABCD, 1H, N-CH_2-CH_2-N), 4.90 (1/2 AB quartet, J = 14.1Hz, 1H, N-CH_2-Ph), 5.25 (1/2 AB quartet, J = 14.1Hz, 1H, N-CH_2-Ph), 7.40 (1/2 'A_2B_2' quartet, J = 8.1 Hz, 2H, aromatic), 7.50 (1/2 'A_2B_2' quartet, J = 8.1 Hz, 2H, aromatic).

IR νmax 1653 (C=N), 1457, 1084, 909 (Tc=O), 732, 701 cm^{-1}.

RESULTS AND DISCUSSION

The synthetic chemistry of the DADT ligands is fairly complex. The ligand has been prepared by a Schiff base condensation to form 3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene[15] followed by lithium aluminum hydride reduction of the two imine bonds and the one disulfide bond to form a diamine-dithiol compound (1-1). Changing the lithium aluminum hydride to milder reducing agents will yield slightly different products based upon which of the above three bonds (two imine, one disulfide) are reduced (1-1).

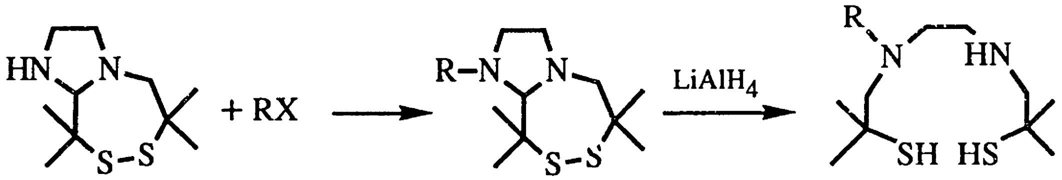
(1-1)



Of particular interest is the reduction by sodium borohydride. Under very mild reaction conditions sodium borohydride will reduce only one of the two imine bonds, and leave the disulfide bond intact. The second imine bond undergoes a stabilization reaction to form a bicyclic amine compound. This bicyclic amine (1,1,4,4-tetramethylimidazolino[1,2-d]dithiazepine)[8] contains two amine nitrogens of very different reactivities, and is the starting material of choice for the work that follows.

Mono-alkylation of the bicyclic amine is a relatively simple process. Reaction of the amine with an alkyl halide readily yields a mono-N-alkylated product. (1-2) After monoalkylation, the bicyclic amine is further reduced with lithium aluminum hydride to form the respective mono-N-alkylated diamine-dithiol ligand.

(1-2)



Over a period of days the free thiols of the DADT ligands will reoxidize to disulfides. This poses a problem since the disulfides are useless for chelation chemistry. Trityl and other sulfur-protecting groups have been regularly used with many N_2S_2 ligand systems to prevent disulfide formation.[16, 17] Unfortunately similar S-protection reactions with the DADT ligands proceed in much lower yield than for other N_2S_2 ligands. This drastic difference in yield is probably due to steric hindrance from the gem-dimethyl groups on the DADT ligand.

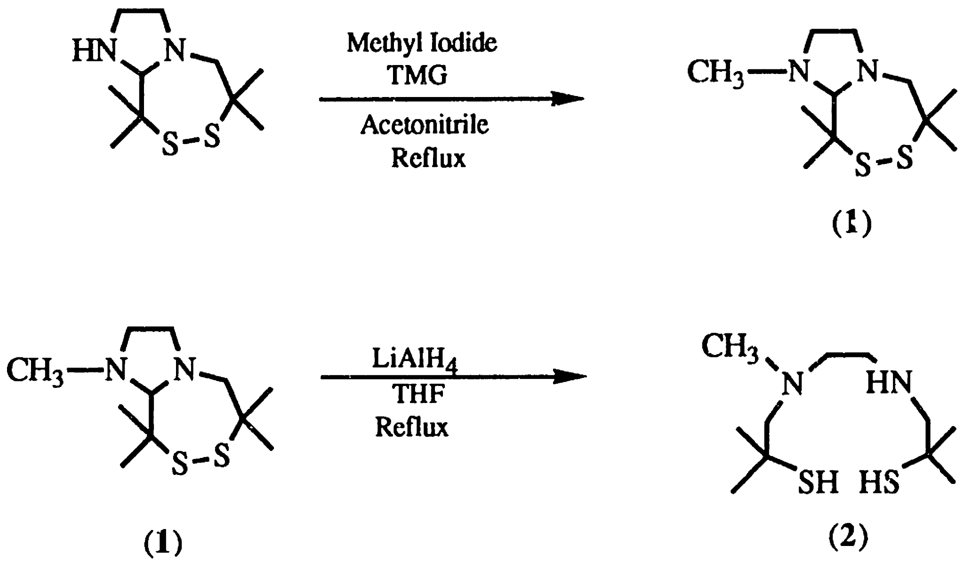
A second approach that shows more promise in long term stabilization of the DADT ligands is the formation of amine salts[18]. The hydrochloride salts are readily isolable, but are very hygroscopic and tend to form disulfides over several months. The use of an organic acid, such as oxalic or tartaric, will form a more stable compound, though there can be some resulting solubility problems. The formation of acid salts has an added advantage; while the free thiol ligands tend to be amorphous or oily, the acid salts are solids.

Ligand Synthesis

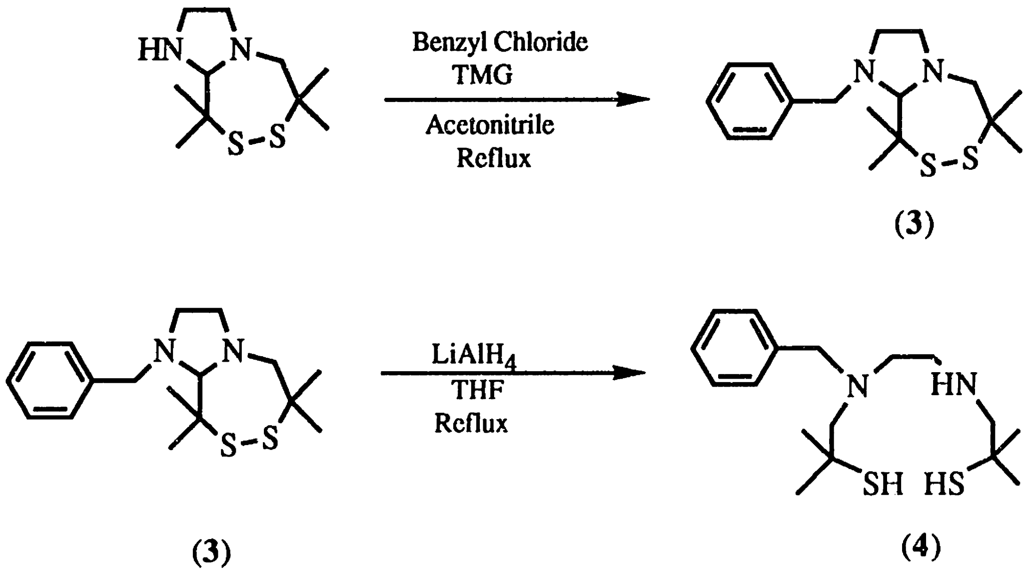
Following the procedure outlined above, compound **1** was formed by refluxing 1,1,4,4-tetramethylimidazolino[1,2-d]dithiazepine[8] (bicyclic amine), methyl iodide and tetramethylguanidine in acetonitrile. (Scheme 1.1) Subsequent lithium aluminum hydride reduction of **1** in refluxing tetrahydrofuran yielded the mono-methylated DADT ligand **2**. Purification was performed by column chromatography and the product was isolated as an amine salt. Similarly a mono-N-benzylated DADT derivative **4** was synthesized by the same procedure by replacing benzyl chloride for methyl iodide in the alkylation reaction. (Scheme 1.2) Reduction, purification and isolation procedures for **4** are similar to those employed for the synthesis of **2**. The spectroscopic characteristics of **2** and **4** are as expected.[19, 20]

Scheme 1.1 and Scheme 1.2

Scheme 1.1



Scheme 1.2



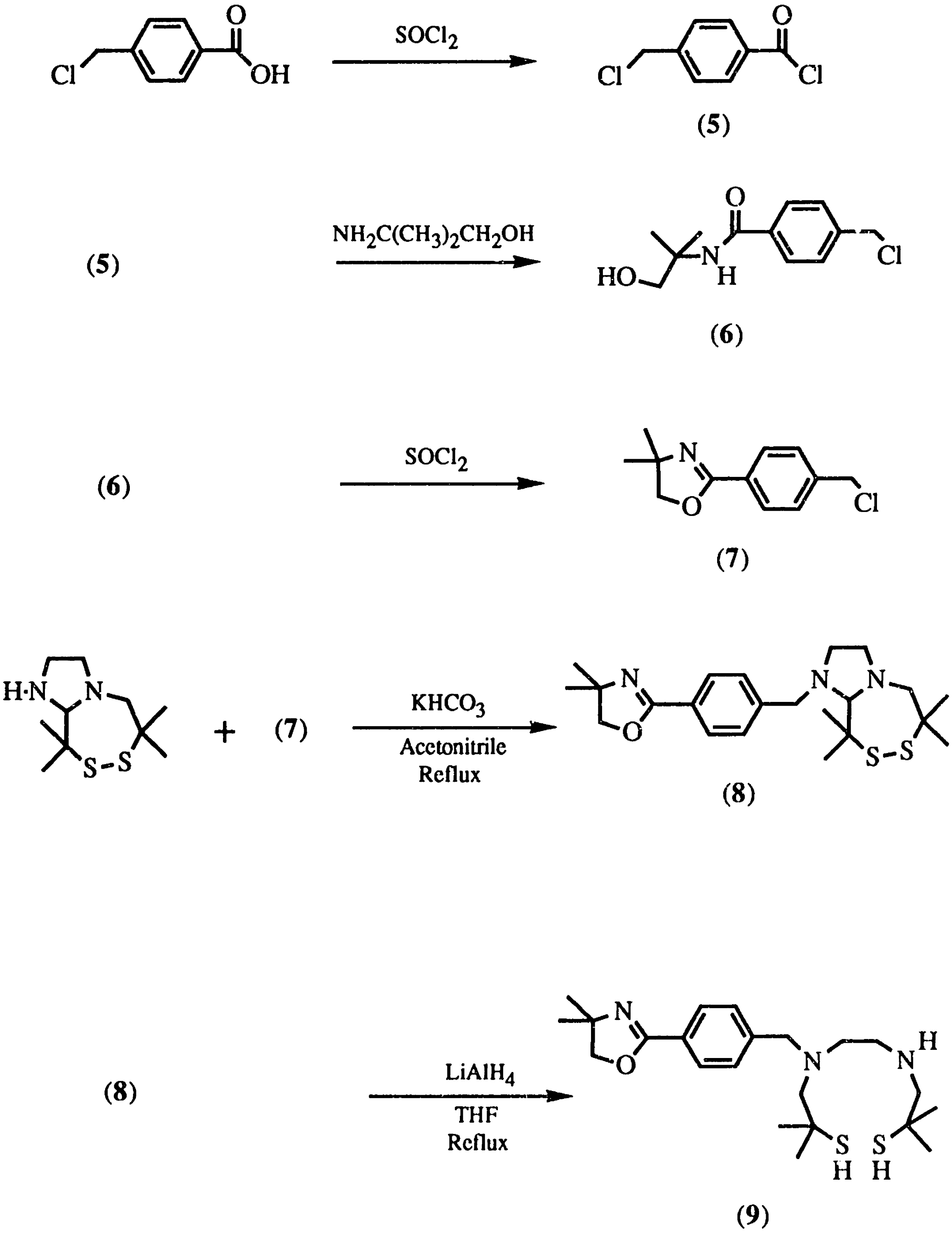
Formation of a third DADT ligand derivative (9) proceeded through the synthesis of a para-substituted benzoic acid alkylating group. (Scheme 1.3) This alkylating group was chosen for several reasons. First, a DADT ligand which was capable of forming a link to biological molecules was desired. A simple way of making such a link is by using basic peptide coupling techniques. A carboxylic acid derivatized DADT ligand can then be used to react with an amine nitrogen to form an amide bond. Second, it is desired that the linker amide bond will not be cleaved in the body. There are no natural peptides containing a benzamide moiety. Therefore no enzymatic action will break the resulting amide bond, and thus no loss of the radiolabel. Third, intramolecular interactions between carboxylic acid functionalities and the technetium atom have been observed.[21, 22] The location of the carboxylic acid at the para-position on the benzyl group makes such interactions impossible.

Unfortunately, the introduction of a carboxylic acid functionality into the DADT ligand synthesis complicates the process. Carboxylic acids react with lithium aluminum hydride to form the respective alcohol. As mentioned the basic reaction scheme for synthesis of **2** (Me-DADT) and **4** (Bzl-DADT) involves reduction with lithium aluminum hydride. Either the synthetic sequence must be changed to remove this reduction step, or a protecting group for the carboxylic acid must be employed. Greene[23] has reviewed such protecting groups and lists only one which is stable to lithium aluminum hydride reduction - 4,4-dimethyl-2-oxazoline.[24, 25]

Starting with the para-substituted benzoic acid 4-(chloromethyl)benzoic acid (Aldrich) the oxazoline-protected DADT ligand (9) was synthesized. (see Scheme 1.3) Stirring 4-(chloromethyl)benzoic acid in neat thionyl chloride overnight forms the acid chloride (5). This acid chloride is subsequently reacted with 2-amino-2-methyl-1-propanol to form the amide (6). Dehydration of this amide-alcohol with thionyl chloride cyclizes the protecting group to form the 4,4-dimethyl-2-oxazoline functionality.[24, 26] This oxazoline-protected carboxylic acid compound (7) is now useable as an alkylating agent for the bicyclic amine. Alkylation and isolation as the hydrochloride salt (8) proceeds in 55% yield. Lithium aluminum hydride reduction yields several products. The oxazoline DADT derivative (9) is isolated by column chromatography in less than 10% yield.

Scheme 1.3

Scheme 1.3



O
Cl
OH
$SOCl_2$
O
Cl
Cl
(5)
(5)
$NH_2C(CH_3)_2CH_2OH$
O
HO
N
H
Cl
(6)
(6)
$SOCl_2$
N
O
Cl
(7)
H·N
N
S
S
+
(7)
$KHCO_3$
Acetonitrile
Reflux
N
O
N
N
S
S
(8)
(8)
$LiAlH_4$
THF
Reflux
N
O
N
N
H
S
H
S
H
(9)

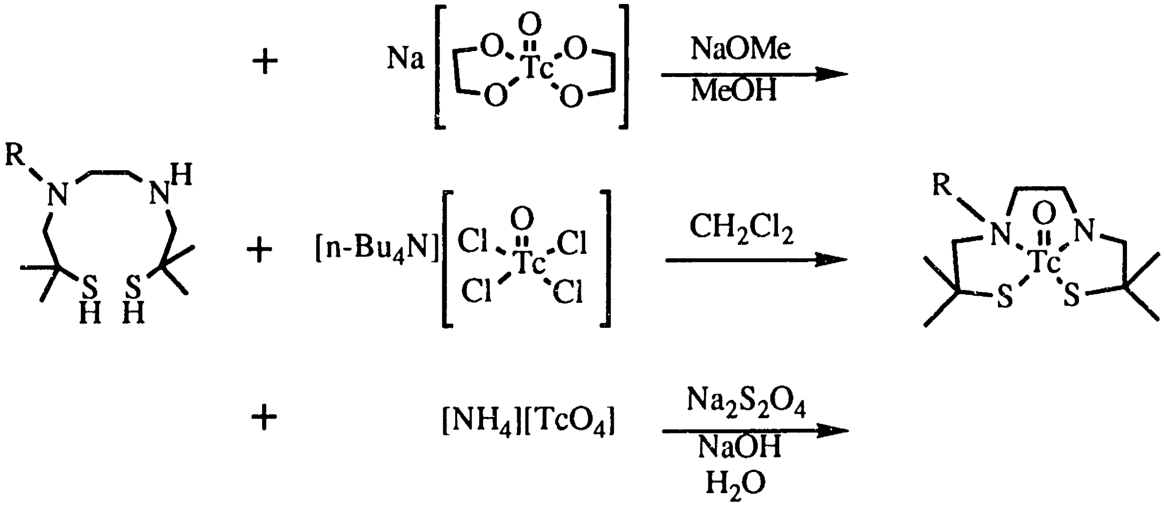
Technetium complex formation

With several DADT ligands available, the synthesis of the respective oxotechnetium DADT complex is fairly simple. Several technetium starting materials are available (see 1-3), all of which yield neutral oxotechnetium DADT complexes. Sodium oxobis(1,2-ethanediolato)technetate[12, 13] Na[TcO(eg)$_2$], a purple compound which is stable under basic conditions, rapidly exchanges ligands in alcoholic solution to yield the yellow/orange TcO(DADT) complexes.

Tetra-n-butylammonium oxotetrachlorotechnetate[14] [TBA][TcOCl$_4$] can be used for ligand exchange as well. This starting material is not stable in basic aqueous media, so either acidic or nonaqueous conditions must be used. A reaction much like that of [TcO(eg)$_2$]$^-$ occurs in methylene chloride to yield a yellow/orange TcO(DADT) complex.

Mild basic reduction of pertechnetate in the presence of the DADT ligands also yields the neutral TcODADT compounds. Addition of α-D-glucoheptonic acid, to form a stable intermediate oxotechnetium complex, increases the overall yield of product.[27]

(1-3)



Technetium complexes **10** [TcO(Me-DADT)], **11** [TcO(Bzl-DADT)], and **12** [TcO(Oxazoline-DADT)] were formed by one or more of the above techniques from the respective DADT ligands. The resulting neutral complexes were separated from starting materials by column chromatography, and the isolated products were characterized. Figure 1.1 shows the NMR spectra for both the methyl (**10**) and the benzyl derivatives (**11**).

Isomer discussion

Within the oxotechnetium DADT compounds there are four isomers which can be formed (Figure 1.2): a pair of enantiomers based on the quaternary nitrogen (R and S), and a pair of diastereomers based on the relationship of the oxo group to the alkyl group bonded to the quaternary nitrogen (syn and anti). Several research groups have recently reported the separation and quantification of the yields of the syn versus anti isomers for several derivatized DADT complexes.[9, 10, 28-30] The syn pair of diastereomers is the major product of all of these studies. Lever[9, 10, 28], working with small alkyl groups, has seen results indicating that the yield of anti derivative decreases drastically with any increase in size of the N-alkylating group. Katzenellenbogen's work[29, 30] with relatively large steroid derivatives indicates less of a dependence on the size of the N-alkyl group and more of a dependence on the concentration of reactants.

Each of the technetium complexes synthesized in this work shows an infrared absorbance between 900 and 950 cm^{-1}. These absorbances are readily assignable as the Tc=O stretching frequency. While the benzyl (**11**) and oxazoline (**12**) derivatives only show one absorbance in this range (908 and 909 cm^{-1} respectively), the methyl derivative (**10**) shows two (916 and 924 cm^{-1}). The methyl derivative also shows two separate sets of signals within its ^{1}H-NMR spectrum (Figure 1.1).

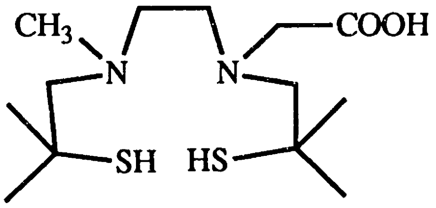
Comparison of the characterization of **10** with the compound reported by Lever[5] show that the two compounds are the same. Lever reports the isolation and structural characterization of two diastereomers. Assignment of the stretching frequencies and NMR peaks for **10** to specific diastereomers is based on Lever's results.

Upon isolation of the benzyl (**11**) and oxazoline (**12**) derivatives, no second sets of NMR signals were noted. This, along with only one oxotechnetium absorbance within their respective infrared spectra, indicates that only one set of isomers was formed. Through a partial crystal structure of **11** (see Appendix II), it has been confirmed that the isolated isomer is syn. While the isolation of only one set of diastereomers of **11** does not preclude the existence of the anti diastereomer pair, it does further support Lever's observation that an increase in size of the N-alkyl group results in a decrease in yield of anti isomers.

Oxazoline derivative

Compound **12** was readily isolated by column chromatography from the reaction mixture. This oxazoline derivative is very similar to that of the benzyl derivative (**11**). NMR and infrared spectroscopies indicate the isolation of only one set of isomers. Despite reports of removal procedures,[24,25] the removal of the oxazoline protecting group from this technetium complex was not found to proceed in any appreciable yield.

Recent synthetic alternatives



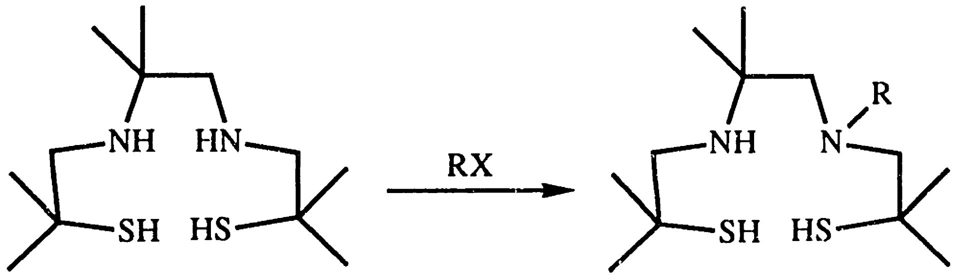
N,N'-Disubstituted DADT

Several recent publications have outlined alternative synthetic sequences to those used in this work. Work with DADT ligands should consider the variety of synthetic possibilities that these publications present.

Lever has done some recent work with acid derivatives of the DADT ligand. The first derivative is a N,N'-disubstituted derivative (see left).[5] This derivative is formed by N-methylation of the bicyclic amine, lithium aluminum hydride reduction to form **2**, and finally, a second alkylation procedure with a carboxylic acid. Upon chelation with technetium a cationic complex is formed.

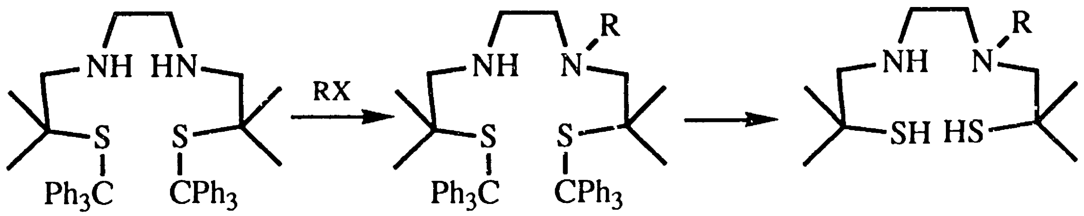
A second carboxylic acid derivative has been developed by Lever by placing gem-dimethyl groups next to one of the nitrogens for steric hindrance.[6] This sterically hindered DADT ligand preferentially forms a mono-N-alkylated derivative.(see 1-4)

(1-4)



Katzenellenbogen et al.[29, 30] have reported the alkylation of several sulfur protected DADT ligands. (see 1-5) The reduction to the free thiol is performed first. Next the sulfurs are protected with triphenylmethyl groups. Finally the compound is alkylated, and the mono-N-alkylated product is separated. This route is viable, but has several steps which lower the yield drastically. First, the sulfur protection of the DADT ligands proceeds with a poor yield. Second, the N-alkylation reaction yields more than one product. Third, the sulfur protecting groups must be removed prior to reaction with the metal.

(1-5)



The final alternative is that of Kung,[31] which is to build the DADT ligand piecemeal (see 1-6) and use mild reduction (sodium borohydride). This approach is more useful for some types of molecules than others. While a bit more complicated, N-alkyl derivatives can be developed in this manner.

(1-6)

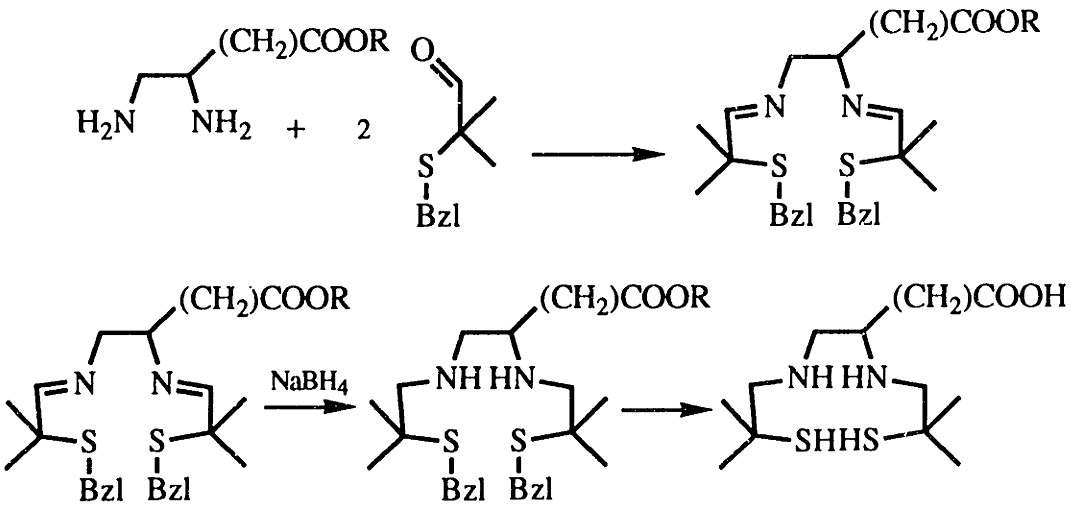


Figure 1.1. NMR spectra of [TcO(Me-DADT)] (**10**) and [TcO(Bzl-DADT)] (**11**).

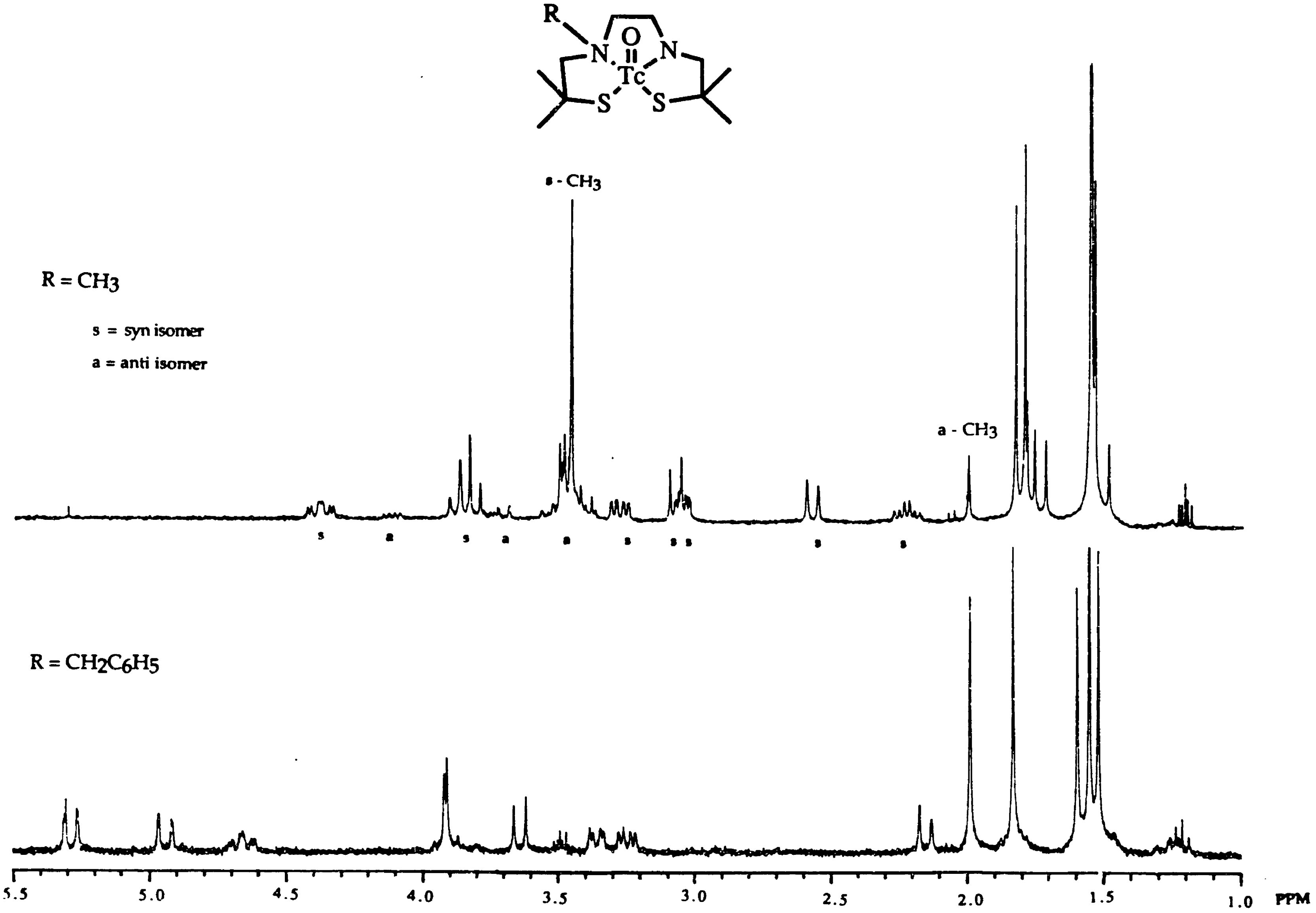
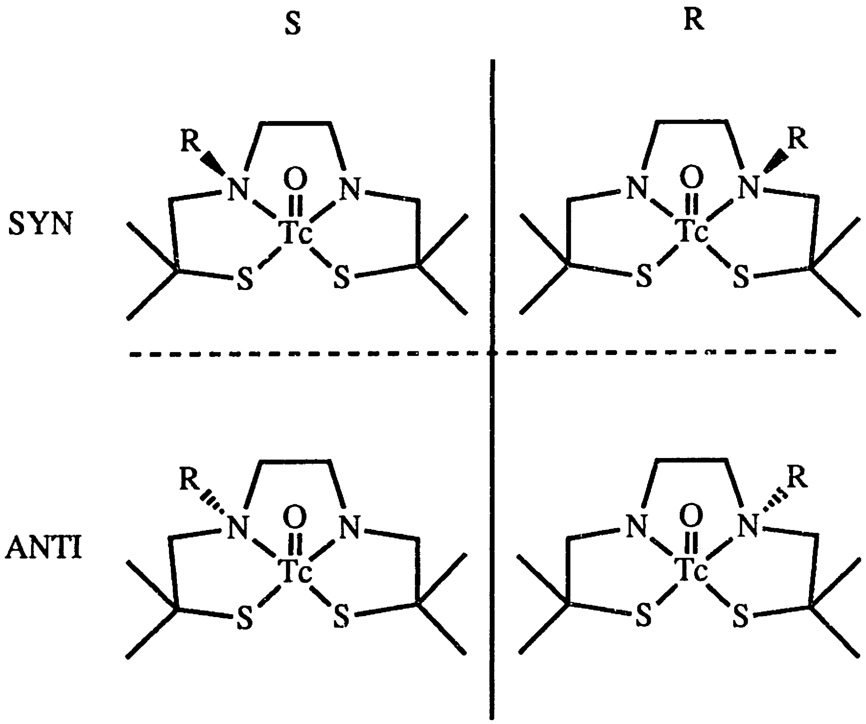

R
O
N
N
Tc
S
S
s - CH3
a - CH3
R = CH3
s = syn isomer
a = anti isomer
s
a
s
a
a
s
s s
s
s
R = CH2C6H5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
PPM

Figure 1.2. Possible isomers for TcODADT-R.


S
R
SYN
ANTI
R
N
O
Tc
S

CONCLUSION

The DADT ligand system reacts well with the oxotechnetium core. The synthesis of the organic ligands, as well as that of the technetium complex, have been well studied. Unfortunately, the procedure that has been used for ligand synthesis to date is very restrictive and allows for little modification. A problem arises with any DADT derivative which is sensitive to reduction. As is witnessed by the preceding results and discussion, carboxylic acid derivatives of DADT ligands are very difficult to prepare when strong reduction is used.

The observations that stereochemistry can be affected by the size of the alkylating group[28] and the concentration of reactants[30] are important. Further study of the variations in isomer distribution should be carried out, especially to confirm that benzyl groups yield a large majority of one set of isomers. It is known that the syn and anti isomers of $TcON_2S_2$ complexes have different biodistributions.[4, 29, 30] Preparation of one set of diastereomers preferentially over the other will have major effects upon the usefulness of the resulting radiopharmaceuticals.

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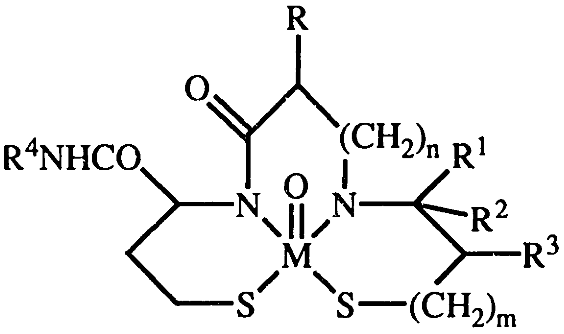
CHAPTER 2.

COMPLEXES OF AMINE-AMIDE-DITHIOL CHELATING LIGANDS

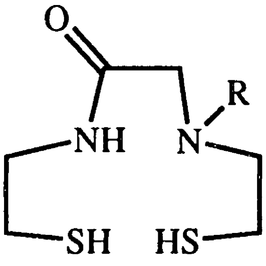
INTRODUCTION

In 1984, E. F. Byrne and G. L. Tolman[1] were issued a patent on an amine-amide-dithiol (AADT) tetradentate N_2S_2 ligand system. (see Figure) The synthetic procedure in the patent outlines the stepwise synthesis of a series of AADT ligands by the use of protecting groups and peptide coupling techniques, with subsequent reaction with an oxotechnetium core. (For a specific ligand synthesis see Scheme 2.1) Since the filing of the patent, there have been no further publications about this AADT ligand; however, some unpublished results[2] recently became public knowledge. This includes the crystal structure of an oxotechnetium compound (m=n=0, $R=R^1=R^2=R^3=$ H, and $R^4=CH_3$). Public release of this information has allowed further studies of this ligand system.



Byrne AADT Compounds[1]

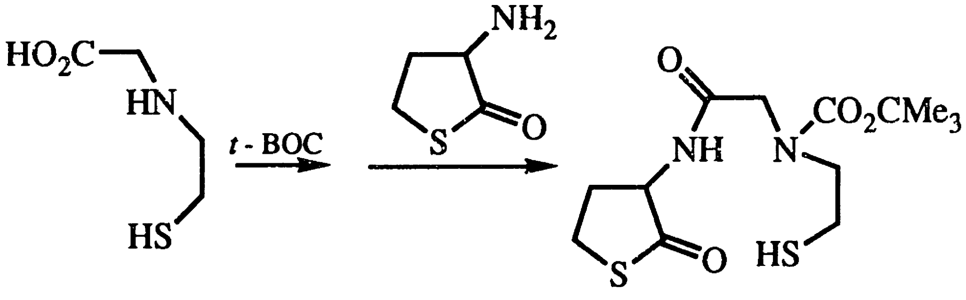
As an N_2S_2 ligand system, the amine-amide-dithiol (AADT) has several advantages over the diamine-dithiol (DADT) ligands (see chapter one). First, unlike the DADT ligands, the two nitrogens can be differentiated by their respective reactivities. The amine nitrogen is reactive under most alkylating conditions, whereas the amide nitrogen is not. Second, as will be shown in the work that follows, the sulfurs within the AADT ligand are much more easily protected from disulfide formation.

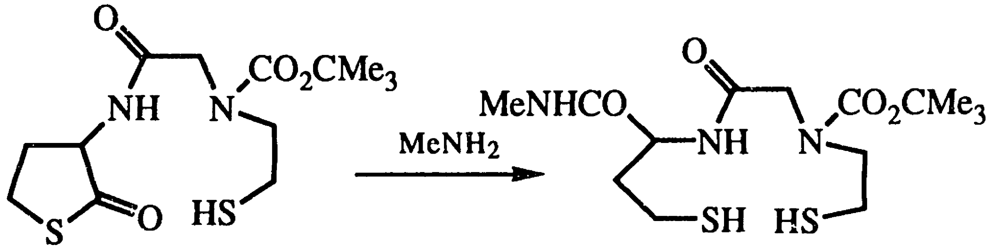


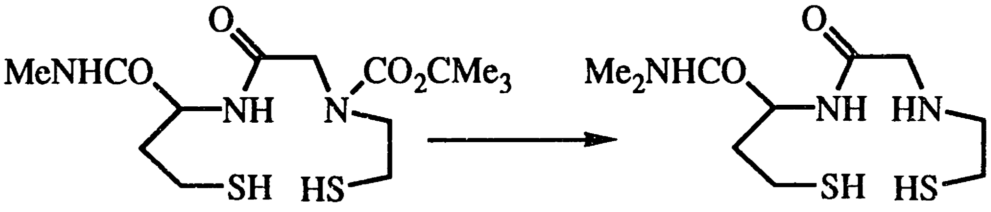
N-alkylated AADT

A series of novel amine-amide-dithiol ligands (AADT's) and their respective complexes were synthesized from a variety of starting materials. The structure of these new ligands were based upon that of the series of ligands synthesized by Byrne et al.[1, 2] The synthetic sequence used in this work is different than that used by Byrne, and whereas Byrne created some C-alkylated derivatives, the focus of this work is to develop N-alkylated derivatives.

Scheme 2.1 Byrne Ligand Synthesis[1] (m=n=0, $R=R^1=R^2=R^3=$ H, $R^4=CH_3$)


HO2C
HN
HS
t - BOC
NH2
S
O
O
NH
N
CO2CMe3
S
O
HS


O
NH
N
CO2CMe3
S
O
HS
MeNH2
MeNHCO
O
NH
N
CO2CMe3
SH
HS


MeNHCO
O
NH
N
CO2CMe3
SH
HS
Me2NHCO
O
NH
HN
SH
HS

EXPERIMENTAL

CAUTION: 99Tc is a weak β^--emitter with a half-life of 2.12×10^5 years. All manipulations involving technetium were carried out in laboratories approved for low-level radioactivity and precautions followed were detailed previously.[3, 4]

General. Ammonium pertechnetate was supplied as a gift by DuPont Biomedical Products. Flash chromatography was performed using either Kieselgel TLC grade silica or ICN Biomedical neutral alumina, as indicated. The columns were pressurized using a hand-powered blower (Fisher). Thin layer chromatography was performed using EM Science Silica Gel 60 F-254 TLC plates which were developed using 0.05% $PdCl_2$ in 0.24 M HCl to identify S-containing compounds. Preparative TLC was done on Analtech Uniplate-T Silica gel GF tapered plates. Melting points were obtained with a Mel-Temp apparatus and are uncorrected. IR spectra were measured from 4000 to 400 cm^{-1} on a Mattson Cygnus 100 FT-IR spectrometer. Potassium bromide pellets were used unless otherwise indicated. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer. UV-visible absorption spectra were recorded with a Hewlett-Packard 8451A photodiode array spectrophotometer. Fast atom bombardment mass spectra (FABMS), in positive or negative mode, were measured on a MAT 731 mass spectrometer equipped with an Ion Tech B11N FAB gun operating at an accelerating voltage of 8 keV. The FAB gun produced a beam of 6-8 keV xenon neutrals. Samples were dissolved in a p-nitrobenzylalcohol matrix (NBA) unless otherwise indicated. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

Benzamidomethanol[5], acetamidomethanol[6], 2-((triphenylmethyl)thio)ethylamine[7], sodium oxobis(1,2-ethanediolato)technetate[7, 8], tetra-n-butylammonium oxotetrachlorotechnetate[9], and oxotrichlorobis(triphenylphosphine)rhenium[10] were synthesized by literature preparations. Prior to use, distilled water was run through a Barnstead Ultrapure D8902 cartridge, followed by redistillation in a Corning AG-1 water still. All other chemicals and solvents were of reagent grade and used as received.

(1) - N-[(2-triphenylmethylthio)ethyl]-2-bromoacetamide - BrOAetTr

$C_{23}H_{22}BrNOS$ MW= 440

Bromoacetic acid (Fluka, 5.56 g, 40 mmole) and N-hydroxysuccinimide (4.166 g, 36.23 mmole) were combined in a flask containing methylene chloride. The resulting slurry was cooled in an ice bath. Dicyclohexylcarbodiimide (DCC, 7.5 g, 36.41 mmole) was dissolved in methylene chloride and slowly added to the stirring slurry. After completion of addition, the ice bath was removed and the solution was stirred for 45 minutes. A solution of 2-((triphenylmethyl)thio)ethylamine (11.25 g, 35.27 mmole) in methylene chloride was added, and the solution stirred for 2 more hours. The white precipitate (dicyclohexylurea) was removed and washed with methylene chloride. The organic layers were combined and then washed with distilled water followed by 1 M aqueous sodium bicarbonate. The organic layer was dried over anhydrous potassium carbonate. After filtration the solvent was evaporated to yield **1** as a white solid. The solid was washed with methanol and dried *in vacuo.* Yield 11.45 g (26.02 mmole, 74%).

M.P.= 130-135°C.

^{1}H-NMR ($CDCl_3$) δ 2.43 (tr, J=6.3 Hz, 2H, CH_2S), 3.11 (q, J=6.3Hz, 2H, CH_2N), 3.61 (s, 2H, $BrCH_2$), 7.2-7.4 (m, 9H, aryl), 7.4-7.5 (m, 6H, aryl).

IR vmax 3077, 1652 (CO), 1485, 1440, 752, 743, 700 cm^{-1}.

Anal. Calc. for $C_{23}H_{22}BrNOS$: C, 62.73; H, 5.03; Br, 18.14; N, 3.18; S, 7.29.
Found: C, 62.78; H, 5.08; Br, 18.08; N, 3.22; S, 7.29.

(2) - N,N'-bis[2-((triphenylmethyl)thio))ethyl]glycinamide - $Aa(aetTr)_2$

$C_{44}H_{42}N_2OS_2$ MW= 678

Potassium bicarbonate (1.742 g, 17.42 mmole) and 2-((triphenylmethyl)thio)ethylamine (5.54 g, 17.37 mmole) were combined in a flask and dissolved in acetonitrile. A benzene slurry of BrOAetTr (**1**, 7.64 g, 17.37 mmole) was slowly added to the refluxing acetonitrile solution. The mixture was refluxed for 12 hours, concentrated to a yellow oil, and partitioned between benzene and water. The organic layer was dried over anhydrous magnesium sulfate, filtered, and solvent was removed. The resulting solid was dissolved in 1% $MeOH/CH_2Cl_2$ and chromatographed (Silica gel, 1% $MeOH/CH_2Cl_2$ eluant). The major sulfur-containing fraction ($PdCl_2$ detection) was collected and dried *in vacuo* to form **2** as a white foamy solid. Yield 9.00 g (13.27 mmole, 76%).

M.P.=70-78°C.

^1H-NMR (CD_2Cl_2) δ 1.6 (br s, 2H, NH's), 2.3 (tr, J= 6 Hz, 4H, CH_2S), 2.4 (2 1/2 AB quartets, 2H, CH_2's), 2.98 (s, 2H, CH_2CO), 3.0 (2 1/2 AB quartets, 2H, CH_2's), 7.1-7.5 (m, 30H, aryl).

FABMS$^+$ m/z =1038 (M_2-(aet-Tr))H$^+$, 679 (MH)$^+$, 319 (small)(Aet-Tr)$^+$, 243 (Tr)$^+$.

IR νmax 3054, 1674 (CO), 1517, 1487, 1443, 743, 699 cm^{-1}.

Anal Calculated for $C_{44}H_{42}N_2OS_2$: C, 77.84; H, 6.23; N, 4.13; S, 9.44; O, 2.36.
Found: C, 77.08; H, 6.39; N, 4.16; S, 9.44.

(3) - N,N'-bis[2-(((benzoylamino)methyl)thio)ethyl]glycinamide - Aa(aetBzm)$_2$

$C_{22}H_{28}N_4O_3S_2$ MW= 460

To a solution of Aa(aetTr)$_2$ (**2**, 1g, 1.5 mmole) in trifluoroacetic acid (Aldrich, 10 ml) was added benzamidomethanol (0.45g, 2.98 mmole). This dark orange/brown solution was stirred for 45 minutes, at which time triethylsilane (Aldrich, 0.5 ml, 3.1 mmole) was added to precipitate triphenylmethane. Hexane (10 ml) and a drop of water were added, and the two layers were partitioned. Ether was added to the trifluoroacetic acid layer to precipitate a white solid. This solid, the trifluoroacetic acid salt of **3**, was filtered, dissolved in methylene chloride, and washed with 1 M aqueous sodium bicarbonate. The organic layer was dried over anhydrous potassium carbonate, filtered, and the solvent was removed *in vacuo*. Yield 0.2g (0.43 mmole, 29%).

(4) - N-benzylidene-2-[(triphenylmethyl)thio]ethylamine - Bzl-iet-Tr

$C_{28}H_{25}NS$ MW= 407

To a solution of benzaldehyde (Aldrich) in methanol was added an equivalent amount of 2-((triphenylmethyl)thio)ethylamine. The solution was stirred for 10 hours. The solution was filtered and **4** was isolated in quantitative yield.

M.P.= 87-88°C.

^1H-NMR ($CDCl_3$) δ 2.56 (tr, J= 7Hz, 2H), 3.51 (tr, J=7Hz, 2H), 7.2-7.3 (m, 9H, aryl), 7.4-7.5 (m, 9H, aryl), 7.6-7.8 (m, 2H, aryl), 8.13 (s, 1H, CH=N).

FABMS$^+$ m/z = 816 (M_2H_2)$^+$, 727 (M_2 - C_7H_7)H_4^+, 408 (MH)$^+$, 330 (M_2 - 2Tr)H_4^+, 244 (TrH)$^+$.

Anal Calculated for $C_{28}H_{25}NS$: C, 82.51; H, 6.18; N, 3.44; S, 7.87.
Found: C, 82.32; H, 6.22; N, 3.40; S, 7.77.

(5) - N-benzyl-2-[(triphenylmethyl)thio]ethylamine - Bzl-aet-Tr

$C_{28}H_{27}NS$ MW= 409

An ethanol solution of Bzl-iet-Tr (**4**, 2.71g, 6.66 mmole) and sodium borohydride (Alfa, 1 g , 26 mmole) was refluxed for 5 hours. The solvent was removed under reduced pressure, and the resulting solid was partitioned between benzene and water. The organic layer was dried over anhydrous magnesium sulfate, and filtered. The benzene was removed *in vacuo* to yield **5** as a white solid. Yield 2.26 g (5.52 mmole, 83%).

M.P.= 85-89°C.

^{1}H-NMR (CD_2Cl_2) δ 1.35 (br s, 1H, NH), 2.33 (tr, J=6.6 Hz, 2H), 2.53 (tr, J=6.6 Hz, 2H), 3.60 (s, 2H, $\underline{CH_2}$-C_6H_5), 7.1-7.3 (m, 12H, aryl), 7.4-7.5 (m, 8H, aryl).

FABMS$^+$ m/z = 819 $(M_2H)^+$, 411 $(MH_2)^+$, 244 $(TrH)^+$, 168 $(M\text{-}Tr)H^+$.

IR vmax 1487, 1441, 1111, 758, 736, 701, 674, 625 cm^{-1}.

Anal Calculated for $C_{28}H_{27}NS$: C, 82.11; H, 6.64; N, 3.42; S, 7.83.

Found: C, 82.01; H, 6.65; N, 3.40; S, 7.76.

(6) - N-benzyl-N-[(N'-((triphenylmethyl)thio)ethyl)acetamide]-2-((triphenylmethyl)thio)ethylamine - Bzl[aa(aetTr)$_2$]

$C_{51}H_{48}N_2OS_2$ MW= 768

Synthesis I

To a stirring solution of Aa(aetTr)$_2$ (**2**, 2.75 g, 4.05 mmole) and potassium bicarbonate (0.63 g , 6.3 mmole) in acetonitrile was added benzyl chloride (Mallinckrodt, 3 ml, 26 mmole). The acetonitrile solution was refluxed for 20 hours, the white solid was filtered, and the remaining solution concentrated under reduced pressure. The resulting oil was dissolved in methylene chloride and chromatographed (Silica gel, 1% methanol in methylene chloride as eluant). The major fractions were combined and the solvent was removed *in vacuo* to give **6** as a foamy white solid. Yield 0.87 g (1.1 mmole, 28%).

Synthesis II

A solution of Bzl-aet-Tr (**5**, 3.16 g, 7.73 mmole), BrOAetTr (**1**, 3.44 g, 7.82 mmole), and potassium bicarbonate (9 g, 9 mmole) in acetonitrile was refluxed for twelve hours. The solvent was removed, and the resulting oil partitioned between water and methylene chloride. The organic layer was dried over anhydrous potassium carbonate, and the solvent was removed under reduced pressure. The resulting solid was dissolved in methylene chloride, and chromatographed (Silica gel, 1% methanol in methylene chloride as eluant). The major sulfur containing fraction was collected and dried *in vacuo* to yield 6 as a foamy white solid. Yield 3.81g (4.98 mmole, 64%).

M.P.= 110-120°C.

^{1}H-NMR (CD_2Cl_2) δ 2.21 (q, J= 5.7 Hz, 4H, CH_2S), 2.42 (2 1/2 AB quarts, 2H, CH_2's), 2.81 (s, 2H, CH_2CO), 2.94 (2 1/2 AB quarts, 2H, CH_2's), 3.40 (s, 2H, $\underline{CH_2}$-C_6H_5), 7.1-7.3 (m, 21H, aryl), 7.3-7.5 (m, 14H, aryl).

FABMS$^+$ m/z = 769 (MH)$^+$, 525 (M-Tr)$^+$, 319 (small) (Aet-Tr)$^+$, 244 (TrH)$^+$.

IR vmax 3055, 1678 (CO), 1511, 1489, 1443, 742, 699 cm^{-1}.

Anal Calculated for $C_{51}H_{48}N_2OS_2$: C, 79.65; H, 6.29; N, 3.64; O, 2.08; S, 8.34.
Found: C, 79.29; H, 6.28; N, 3.71; S, 8.55.

(7) - N-benzyl-N-[(N'-(((benzoylamino)methyl)thio)ethyl)acetamide]-2-(((benzoylamino)methyl)thio)ethylamine - Bzl[aa(aetBzm)$_2$]

$C_{29}H_{34}N_4O_3S_2$ MW= 550

A solution of Bzl[aa(aetTr)$_2$] (6, 1.90 g, 2.47 mmole) and benzamidomethanol (0.9 g, 6 mmole) in 10 ml trifluoroacetic acid was stirred for 45 minutes. Triethylsilane (1 ml, 6.2 mmole) was added to precipitate triphenylmethane. Hexane (10 ml) and a drop of water were added to wash the trifluoroacetic acid layer. The trifluoroacetic acid layer was concentrated, and ether was added to precipitate a white oil. This precipitate was dissolved in methylene chloride, and washed with 1 M aqueous sodium bicarbonate. The organic layer was dried over anhydrous potassium carbonate, filtered, concentrated to a white foam, and chromatographed (Silica gel, 1-2% methanol in methylene chloride eluant gradient). Yield 0.38 g (0.69 mmole, 28%) of an amorphous hygroscopic solid.

^{1}H-NMR (CD_2Cl_2) δ 2.72-2.80 (m (2 tr overlaid), 4H, CH_2-$C\underline{H_2}S$), 2.87 (tr, J=6 Hz, 2H, $CH_2C\underline{H_2}NR_2$), 3.05 (s, 2H, $NR_2C\underline{H_2}C(O)$), 3.45 (q, J=6.6 Hz, 2H, $NHC\underline{H_2}CH_2$), 3.62 (s, 2H, NR_2CH_2Ph), 4.55 (d, J= 3 Hz, 2H, $SC\underline{H_2}NH$), 4.57 (d, J=2.4 Hz, 2H, $SC\underline{H_2}NH$), 7.2-7.6 (m, 13H, aryl, 2 ($C_6H_5C(O)N\underline{H}CH_2$)), 7.7-7.9 (2 d, 4H, aryl), 7.99 (broad tr, 1H, $C(O)N\underline{H}(CH_2)_2$).

FABMS$^+$ m/z = 1101 (M_2H)$^+$, 834 (M_2-2Bzm)H_2^+, 700 (M_2-3Bzm)H_2^+, 551 (MH)$^+$, 418 (M-Bzm)H_2^+, 384 (M-(S-Bzm))$^+$, 370 (M-(CH_2S-Bzm))$^+$, 285 (M-2Bzm)H_2^+, 237 ($C(O)NHCH_2CH_2SBzm$)$^+$.

(8) - N-benzyl-N-[N'-(thioethyl)acetamide]aminoethanethiol - Bzlaa(aet)$_2$

$C_{13}H_{20}N_2OS_2$ MW= 284

A solution of Bzl[aa(aetTr)$_2$] (**6**) in 10 ml trifluoroacetic acid was stirred for 45 minutes. Triethylsilane was added to precipitate triphenylmethane. Hexane (10 ml) and a drop of water were added, and the resulting layers were partitioned. Ether was added to the trifluoroacetic acid layer to precipitate a white solid/oil. The solid was filtered, redissolved in methylene chloride, washed with 1 M aqueous sodium bicarbonate, dried over anhydrous potassium carbonate, filtered, and concentrated under reduced pressure to yield **8** as an off-white oil.

FABMS$^+$ m/z = 567 $(M_2H)^+$, 477 $(M_2\text{-}C_7H_6)^+$, 285 $(MH)^+$, 251 $(M\text{-}HS)^+$, 237 $(M\text{-}CH_4S)^+$, 195 $(M\text{-}C_9H_9O_2)$.

(9)- N-[4-(carboxy)benzylidene]-2-[(triphenylmethyl)thio]ethylamine potassium salt- K Acid-iet-Tr

$C_{29}H_{24}KNO_2S$ MW= 489

To a solution of 4-carboxybenzaldehyde (Aldrich) in 0.5 N KOH/MeOH was added one equivalent of 2-((triphenylmethyl)thio)ethylamine in methanol. The solution was allowed to stir for 6 hours, at which time the white precipitate was filtered. The white solid (**9**) was washed thoroughly with acetone and dried *in vacuo*. Yield 95%.

M.P. ≈ 230 °C (decomp).

^{1}H-NMR (CD_3OD) δ 2.52 (tr, J=7.2 Hz, 2H, CH_2S), 3.47 (tr, J= 6.9Hz, 2H, CH_2N), 7.1-7.3 (m, 9H, aryl), 7.4-7.5 (m, 6H, aryl), 7.70 (1/2 'A_2B_2', J=8.7Hz, 2H, R-$C_6\underline{H}_4$-R'), 7.99 (1/2 'A_2B_2', J=8.7Hz, 2H, R-$C_6\underline{H}_4$-R'), 8.20 (s, 1H, CH=N).

FABMS$^-$ m/z = 901 $(2M\text{-}H)^-$, 756 $((M\text{-}H) + 2NBA)^-$, 603 $((M\text{-}H)+NBA)^-$, 450 $(M\text{-}H)^-$, 208 $(M\text{-}Tr)^-$.

IR vmax 1705, 1636, 1442, 1259, 1218, 1119, 767, 752, 740, 699, 673 cm^{-1}.

(10) - N-[4-(carboxy)benzylidene]-2-[(triphenylmethyl)thio]ethylamine - Acid-iet-Tr

$C_{29}H_{25}NO_2S$ MW= 451

An ethanol solution of 4-carboxybenzaldehyde (Aldrich, 5 g, 33.33 mmole) and 2-((triphenylmethyl)thio)ethylamine (10.6 g, 33.22 mmole) was stirred for 3 hours. The white solid (**10**) was filtered and washed with ethanol. Yield 14.60 g (32.02 mmole, 96%)

MP ≈ 210°C (decomp).

^{1}H-NMR (CD_3OD) δ 2.52 (tr, J=7.2 Hz, 2H, CH_2S), 3.47 (tr, J= 6.9Hz, 2H, CH_2N), 7.1-7.3 (m, 9H, aryl), 7.4-7.5 (m, 6H, aryl), 7.70 (1/2 'A_2B_2', J=8.7 Hz, 2H, R-$C_6\underline{H}_4$-R'), 7.99 (1/2 'A_2B_2', J=8.7 Hz, 2H, R-$C_6\underline{H}_4$-R'), 8.20 (s, 1H, CH=N).

FABMS$^+$ m/z = 320 (Aet-Tr)$^+$, 243 (Tr)$^+$.

FABMS$^-$ m/z = 901 (2M-H)$^-$, 756 ((M-H) + 2NBA)$^-$, 603 ((M-H)+NBA)$^-$, 450 (M-H)$^-$, 208 (M-Tr)$^-$.

IR vmax 1705, 1636, 1442, 1259, 1218, 1119, 767, 752, 740, 699, 673 cm^{-1}.

(11) - N-[4-(carboxy)benzyl]-2-[(triphenylmethyl)thio]ethylamine - Acid-aet-Tr

$C_{29}H_{27}NO_2S$ MW= 453

To a slurry of Acid-iet-Tr (**10**) in methanol was added an equivalent of KOH using 0.5 N KOH/MeOH. Sodium cyanoborohydride (Alfa) was added and the solution was stirred for several hours. Acetic acid (5%) was slowly added to precipitate **11** as a white solid. Yield 70%.

M.P.= Decomp. 205-208°C.

^{1}H-NMR (CD_3OD, KOH) δ 2.40 (triplet, J=6Hz, 2H, CH_2), 2.54 (triplet, J=6Hz, 2H, CH_2), 3.56 (singlet, 2H, $C\underline{H}_2C_6H_4$), 7.1-7.3 (m, 11H, aryl), 7.3-7.4 (m, 6H, aryl), 7.90 (1/2 'A_2B_2', J=7.6Hz, 2H, R-$C_6\underline{H}_4$-R').

FABMS$^-$ m/z = 905 (2M-H)$^-$, 605 ((M-H)+NBA)$^-$, 452 (M-H)$^-$, 210 (M-Tr)$^-$.

IR vmax 1594, 1553, 1489, 1444, 1374, 769, 752, 743, 699, 629 cm^{-1}.

(12) - N-[4-(carboxy)benzyl-N-[(N'-((triphenylmethyl)thio)ethyl)acetamide]-2-((triphenylmethyl)thio)ethylamine - Acid-aa(aetTr)$_2$

$C_{52}H_{48}N_2O_3S_2$ MW=812

To a slurry of AcidaetTr (**11**, 0.455 g, 1.0 mmole) in acetone was added tetramethylguanidine (TMG, Aldrich) until all of the solid had dissolved. To this solution was added BrOAetTr (**1**, 0.442 g, 1.0 mmole). This solution was stirred for 10 hours. The white precipitate (TMG.HBr) was filtered. The solution was concentrated under reduced pressure. The resulting oil was redissolved in methylene chloride and chromatographed (Silica gel, 1% methanol in methylene chloride eluant) Two sulfur containing fractions were isolated ($PdCl_2$ TLC detection). The first fraction was BrOAetTr (**1**), and the second fraction was the desired product (**12**). The solvent was removed *in vacuo* to yield a foamy off-white solid. Yield 0.3 g (0.37 mmole, 37%)

^{1}H-NMR (CD_2Cl_2) δ 2.35 (tr, J=5.7 Hz, 2H, CH_2-S), 2.41 (tr, J=6.6 Hz, 2H, CH_2-S), 2.53 (tr, J=6.9 Hz, 2H, CH_2-NR_2), 3.10 (quad, J=6.6 Hz, 2H, $C\underline{H}_2$-NHCO), 3.67 (s, 2H, CO-CH_2-N), 4.68 (s, 2H, CH_2-Benzyl), 6.36 (broad tr, 1H, NHCO), 7.1-7.3 (m, 20H, aryl), 7.3-7.5 (m, 12H, aryl), 7.99 (1/2 'A_2B_2', J=8.1 Hz, 2H, R-$C_6\underline{H}_4$-R').

FABMS$^-$ m/z = 965 (M+NBA)$^-$, 811 (M-H)$^-$, 569 (M-Tr)$^-$, 452 (M-($CH_2CONHCH_2CH_2STr$))$^-$, 325 (M-2Tr)$^-$, 243 (Tr$^-$), 208 ($SCH_2CH_2NCHC_6H_4CO_2$)$^-$.

(13) - N-[4-(carboxy)benzyl-N-[(N'-(((benzoylamino)methyl)thio)ethyl)acetamide]-2-(((benzoylamino)methyl)thio)ethylamine - Acid-aa(aetBzm)$_2$

$C_{30}H_{34}N_4O_5S_2$ MW= 594

A solution of Acidaa(aetTr)$_2$ (**12**) and benzamidomethanol in trifluoroacetic acid (Aldrich, 10 ml) was stirred for 45 minutes. Triethylsilane was added to precipitate triphenylmethane. Hexane (10 ml) and a drop of water were added and the solution was partitioned. The TFA layer was concentrated and ether was added to precipitate a white oil. The precipitate was redissolved in methylene chloride and washed with 1M sodium bicarbonate. The organic layer was dried over anhydrous potassium carbonate, and the solvent was removed *in vacuo* to yield **13** as a foamy oil.

^{1}H-NMR (CD_2Cl_2) δ 2.75-2.85 (m(2 tr overlaid), 4H, CH_2-S-Bzm (both sides)), 2.88 (tr, J=5.7 Hz, CH_2-NR_2), 3.58 (quad, J= 6.3 Hz, $C\underline{H}_2$-NHC(O)CH_2), 3.85 (s, 2H, C(O)CH_2NR_2), 4.54-4.60 (m (2 doub), $SC\underline{H}_2NH$), 4.78 (s, 2H, N-CH_2-Bz), 7.03 (broad tr, 1H, C(O)N$\underline{H}$(CH_2)$_2$), 7.3-7.6 (m, 10H, m-,p- protons on Bzm's, 1/2 A_2B_2 from Bzl, 2 NH's from Bzm), 7.7-7.9 (2 d, 4H, o- protons on Bzm), 8.00 (1/2 A_2B_2, 2H, Bzl).

FABMS$^-$ m/z =747 (M+NBA)$^-$, 593 (M-H)$^-$, 460 (M-Bzm)$^-$, 327 (M-2Bzm+H)$^-$;

FABMS$^+$ (NBA mw. = 154) m/z = 1189 (2M+H)$^+$, 728 (M+Bzm)$^+$, 595 (MH)$^+$, 462 (M-Bzm+2H)$^+$ or (M-benzyl acid)$^+$, 359 (462-HC(O)$NHCH_2CH_2SH$)$^+$, 329 (M-2Bzm)3H$^+$ or (M-Bzm-benzyl acid)3H$^+$, 281 (329-CH_3SH)$^+$, 194 (M-2Bzm-benzyl acid)H$^+$.

(14) - 4-(chloromethyl)benzoylchloride - Cl-Acid-Cl

$C_8H_6Cl_2O$ MW=189

A solution of 4-(chloromethyl)benzoic acid (Aldrich, 3.155 g, 18.50 mmole) in thionyl chloride (Fluka, 10 ml) was refluxed for 12 hours under a nitrogen atmosphere. The thionyl chloride was removed by repeated addition of benzene followed by removal of solvent until a white solid had precipitated. The white solid **14** was filtered and washed with benzene. Yield 2.4 g (12.7 mmole, 69%)

M.P.=165-175°C.

^{1}H-NMR ($CDCl_3$) δ 4.68(s, 2H, CH_2), 7.8 (1/2 'A_2B_2' quartet, J=9 Hz, 2H, aryl), 8.15 (1/2 'A_2B_2' quartet, J=9 Hz, 2H, aryl).

IR vmax 1780, 1744, 1680 (CO), 1290, 1206, 1175, 711 cm^{-1}.

(15) - 4-(bromomethyl)benzoylbromide - Br-Acid-Br

$C_8H_6Br_2O$ MW= 278

A solution of α-bromo-p-toluic acid (4 g, 19 mmole, Aldrich) in thionyl bromide (Aldrich) was stirred under nitrogen with mild heating for twelve hours. Addition of benzene precipitated a white solid which was filtered and washed with benzene. The solid was dried *in vacuo*. Yield 3.81 g (13.7 mmole, 72%).

M.P.= Decomp. 210-215°C.

^{1}H-NMR ($CDCl_3$) δ 4.52 (s, 2H, CH_2), 7.50 (1/2 'A_2B_2', J=8 Hz, 2H, aryl), 8.08 (1/2 'A_2B_2', J=8 Hz, 2H, aryl).

FABMS$^+$ m/z = 277 M$^+$, 273.

IR vmax 1692, 1610, 1426, 1312, 1172, 1090, 863, 701, 598 cm^{-1}.

(16) - 4-(chloromethyl)methylbenzoate - CH_3OAcidCl

$C_9H_9ClO_2$ MW= 184

A solution of Cl-Acid-Cl (**14**) in methanol was refluxed for one hour. Removal of solvent under reduced pressure yielded **16** quantitatively as a white solid.

M.P.= 32-35°C.

^{1}H-NMR (CD_2Cl_2) δ 3.89 (s, 3H, CH_3-O), 4.64 (s, 2H, CH_2-Cl), 7.48 (1/2 A_2B_2, J = 8.1 Hz, 2H, p-Benzyl), 8.02 (1/2 A_2B_2, J= 8.7 Hz, 2H, p-benzyl).

FABMS$^+$ m/z = 369 $(M_2H)^+$, 338 (M + NBA)$^+$, 185 (MH)$^+$.

IR vmax 1722, 1283, 1178, 1103, 711 cm^{-1}.

(17) - N-[4-(carboxy)benzyl]-2-[(triphenylmethyl)thio]ethylamine methyl ester- $CH_3OAcidAetTr$

$C_{30}H_{29}NO_2S$ MW= 467

A solution of $CH_3OAcidCl$ (**16**, 7.86 g , 42.0 mmole), 2-((triphenylmethyl)thio)ethylamine (14.0 g, 43.9 mmole), and potassium bicarbonate (4.35 g, 43.5 mmole) in acetonitrile was refluxed for 18 hours. The white precipitate (potassium chloride) was filtered. The remaining solvent was removed under reduced pressure to yield a brown viscous oil which was redissolved in methylene chloride and chromatographed (Alumina, 0-5% methanol in methylene chloride eluant gradient). The second sulfur-containing band ($PdCl_2$ detection) which eluted was **17**. Pure product was isolated after alumina chromatography was repeated. Yield 10.9g (23.3 mmole, 56%) of a viscous oil.

^{1}H-NMR (CD_2Cl_2) δ 1.5 (broad s, 1H, NH), 2.40 (tr, J=6.1Hz, 2H, CH_2), 2.53 (tr, J=6.0Hz, 2H, CH_2), 3.69 (s, 2H, $C\underline{H_2}C_6H_4$), 3.89 (s, 3H, CH_3), 7.1-7.3 (m, 11H, aryl), 7.4-7.5 (m, 6H, aryl), 7.97 (1/2 'A_2B_2'', J=8Hz, 2H, R-$C_6\underline{H}_4$-R').

FABMS$^+$ m/z = 936 $(M_2H)^+$, 468 $(MH)^+$, 275 (S-trityl)$^+$, 243 (trityl)$^+$, 224 (M-trityl)$^+$, 192 [M-(S-trityl)]$^+$, 178 [M-(CH_2S-trityl)]$^+$, 165 [M-(C_2H_4S-trityl)]$^+$.

(18) - N-[4-(carboxy)benzyl-N-[(N'-((triphenylmethyl)thio)ethyl)acetamide]-2-((triphenylmethyl)thio)ethylamine methyl ester- $CH_3OAcidAa(aetTr)_2$

$C_{53}H_{50}N_2O_3S_2$ MW= 826

Synthesis I

A solution of CH_3OAcid-Cl (**16**, 1 g, 5.43 mmole), $Aa(aetTr)_2$ (**2**, 4 g, 5.92 mmole), and potassium bicarbonate (0.61 g, 6.1 mmole) in acetonitrile was refluxed for 15 hours. The solvent was removed under reduced pressure to yield a foamy oil. This oil was redissolved in methylene chloride and the white solid (potassium chloride) was filtered. The remaining solution was chromatographed (Silica gel, 1% methanol in methylene chloride eluant). Two sulfur-containing fractions were collected. The first fraction yielded **18** as a white foamy solid. The second sulfur-containing band was the non-alkylated starting material ($Aa(AetTr)_2$ (**2**)). The yield of **18** was 1.16 g (1.40 mmole, 26%).

Synthesis II

A solution of CH_3OAcidAet-Tr (**17**, 5.6g, 12.0 mmole), BrOAetTr (**1**, 5.0g, 11.4 mmole), and potassium bicarbonate (1.47g, 14.7 mmole) in acetonitrile was refluxed for 22 hours. The precipitate (potassium bromide) was filtered and the remaining solution was concentrated under reduced pressure to an oil. This oil was redissolved in methylene chloride and chromatographed (Alumina, 0-1% methanol in methylene chloride eluant gradient). The second sulfur-containing band yielded **18** as a foamy white solid. Yield 4.29g (5.2 mmole, 45%).

M.P.= 110-120°C.

^{1}H-NMR (CD_2Cl_2) δ 2.3 (m, 4H), 2.4 (2 1/2 AB quarts, 2H, CH_2's), 2.83 (s, 2H, CH_2CO), 2.9 (2 1/2 AB quarts, 2H, CH_2's), 3.46 (s, 2H, CH_2-Ph), 3.88 (s, 3H, CH_3-O), 7.1-7.4 (m, 33H, aryl, 1/2 'A_2B_2', NHCO), 7.88 (1/2 'A_2B_2', J = 8.7 Hz, 2H, p-benzyl).

^{13}C-NMR ($CDCl_3$) δ29.73, 32.01, 37.78, 52.03, 53.41, 57.70, 58.39, 66.69, 66.83, 126.70, 127.89, 128.76, 129.33, 129.48, 129.80, 142.79, 144.56, 144.64, 166.74, 170.24.

FABMS$^+$ m/z = 827 (MH)$^+$, 583 (M-Trityl)$^+$, 341 (M-2Trityl)$^+$, 243 (Trityl)$^+$.

IR vmax 3055, 1721 (ester CO), 1679 (amide CO), 1488, 1443, 1278 (ester stretch), 1109 (ester stretch), 742, 700 cm^{-1}.

Anal Calculated for $C_{53}H_{50}N_2O_3S_2$: C, 76.97; H, 6.09; N, 3.39; O, 5.80; S, 7.75.
Found: C, 76.91; H, 6.12; N, 3.54.

(19) - N-[4-(carboxy)benzyl-N-[(N'-(((benzoylamino)methyl)thio)ethyl)acetamide]-2-(((benzoylamino)methyl)thio)ethylamine methyl ester -CH_3OAcidAa(aetBzm)$_2$

$C_{31}H_{36}N_4O_5S_2$ MW= 608

A trifluoroacetic acid solution of **18** (1.61g, 1.95mmole) and benzamidomethanol (1.0g, 6.62 mmole) was stirred for one hour. Triethylsilane (1 ml, 6 mmole) was added and the white precipitate was removed. The trifluoroacetic acid solution was concentrated under reduced pressure and neutralized with 1 M sodium bicarbonate. This was partitioned with methylene chloride. The organic layer was dried with anhydrous potassium carbonate and concentrated to an oil. Solvent was removed *in vacuo* to yield **19** as a clear oil.

(20) - N-[4-(carbomethoxy)benzyl]-N-[N'-(thioethyl)acetamide]aminoethanethiol - CH_3OAcidAa(aet)$_2$

$C_{15}H_{22}N_2O_3S_2$ MW= 342

A solution of **18** (0.5 g, 0.12mmole) in trifluoroacetic acid (10 ml) was stirred for thirty minutes. Triethylsilane (1 ml, 6 mmole) was added, and the white precipitate was removed by partitioning with 10 ml hexanes (one drop of water added to help separation). The trifluoroacetic acid layer was concentrated under reduced pressure and neutralized with 1M sodium bicarbonate. This was partitioned with methylene chloride. The organic layer was dried with anhydrous potassium carbonate, and solvent was removed *in vacuo* to yield **20** as a yellow oil.

FABMS$^+$ m/z = 683 $(M_2H)^+$, 535 $(M_2\text{-}C_9H_9O_2)^+$, 343 $(MH)^+$, 296 $(M\text{-}CH_4S)^+$, 195 $(M\text{-}C_9H_9O_2)^+$.

(21) - 4-(chloromethyl)-(2-(benzyloxy)phenyl)benzoate - BOP-acid-Cl

$C_{21}H_{17}ClO_3$ MW= 352.5

In a mildly exothermic reaction benzyloxyphenol (6.231 g, 31.12 mmole), 4-(dimethylamino)pyridine (DMAP, Aldrich, 4.254 g, 34.87 mmole), and Cl-Acid-Cl (**14**, 6.155 g, 32.06 mmole) were combined in methylene chloride and stirred for 18 hours. The white precipitate (DMAP.HCl) was filtered. The remaining solution was concentrated under reduced pressure to a brown oil, redissolved in methylene chloride, and chromatographed (Alumina, benzene eluant). The first sulfur-containing fraction yielded **21** as a white solid. Yield 5.677 g (16.10 mmole, 52%).

M.P.=98-100°C.

^{1}H-NMR (CD_2Cl_2) δ 4.59 (s, 2H, CH_2Cl), 5.01 (s, 2H, CH_2O), 6.9-7.0 (m, 2H, aryl), 7.1-7.3 (m, 7H, aryl), 7.46, (1/2 'A_2B_2', J=8.2 Hz, 2H, R-$C_6\underline{H}_4$-R'), 8.10 (1/2 'A_2B_2', J=8.6 Hz, 2H, R-$C_6\underline{H}_4$-R').

FABMS$^+$ m/z = 353 $(MH)^+$, 319 $(MH_2\text{-}Cl)^+$, 243 $(M\text{-}C_6H_5CH_2OH_2)^+$, 199 $(C_6H_5CH_2OC_6H_4O)^+$, 181 $(199\text{-}H_2O)^+$.

IR vmax 1734, 1500, 1288, 1268, 1244, 1190, 1175, 1109, 1071, 1018, 756, 738, 704, 696 cm^{-1}.

Anal Calculated for $C_{21}H_{17}ClO_3$: C, 71.49; H, 4.86; Cl, 10.05; O, 13.60.
Found: C, 71.90; H, 5.09; Cl, 9.70.

(22) - N-[4-(carboxy)benzyl]-2-[(triphenylmethyl)thio]ethylamine 2-(benzyloxy)phenyl ester - BOP-Acid-AetTr

$C_{42}H_{37}NO_3S$ MW= 635

A solution of BOP-acid-Cl (**21**, 1 g, 2.84 mmole), 2-((triphenylmethyl)thio)ethylamine (1 g, 3.13 mmole), and potassium bicarbonate (0.335 g, 3.35 mmole) in acetonitrile was refluxed for 20 hours. The white precipitate (potassium chloride) was filtered. The remaining solution was concentrated under reduced pressure to a brown viscous oil, redissolved in methylene chloride and chromatographed (Alumina, 0-5% methanol in methylene chloride eluant gradient). The second fraction which eluted contained **22** as a viscous oil. Yield 0.98 g (1.54 mmole, 54%). To form the hydrochloride salt, the oil was dissolved in ether and HCl (g) was bubbled through the solution to precipitate a white solid.

M.P.=85-90°C (HCl Salt).

^{1}H-NMR (CD_2Cl_2) δ1.6 (broad s, 1H, NH), 2.45 (tr, J=6.1 Hz, 2H, CH_2), 2.58 (tr, J=6.4 Hz, 2H, CH_2), 3.77 (s, 2H, $C\underline{H}_2C_6H_4$), 5.12 (s, 2H, $C\underline{H}_2C_6H_5$) 7.0-7.2 (m, 2H, aryl), 7.2-7.6 (m, 24H, aryl), 8.19 (1/2 'A_2B_2', J=8.1 Hz, 2H, R-$C_6\underline{H}_4$-R').

FABMS$^+$ m/z = 636 (MH)$^+$, 394 (M-trityl)$^+$, 347 [M-(CH_2S-trityl)]H$^+$, 333 [M-(C_2H_4S-trityl)]$^+$, 289 (S-trityl)$^+$, 243 (trityl)$^+$.

IR(HCl Salt) vmax 1740, 1497, 1452, 1444, 1282, 1260, 1180, 1110, 1072, 1019, 744, 697 cm^{-1}.

(23) - N-[4-(carboxy)benzyl-N-[(N'-((triphenylmethyl)thio)ethyl)acetamide]-2-((triphenylmethyl)thio)ethylamine 2-(benzyloxy)phenyl ester-BOP-acid-aa(aetTr)$_2$

$C_{65}H_{58}N_2O_4S_2$ MW= 994

Synthesis I

A 50% acetonitrile/benzene solution of Aa(aetTr)$_2$ (**2**, 2.65 g, 3.91 mmole), BOP-acid-Cl (**21**, 1.505g, 4.270 mmole), and potassium bicarbonate (0.4 g, 4 mmole) was refluxed for 24 hours. The white precipitate (potassium chloride) was filtered, and the remaining solution was concentrated under reduced pressure to a brown oil. This oil was redissolved in methylene chloride and chromatographed (Alumina, 0-5% methanol in methylene chloride eluant gradient). The first sulfur-containing fraction is the desired product. Chromatography was repeated using methylene chloride as an eluant to yield **23** as a foamy oil. Yield 1.01 g (1.02 mmole, 26%)

Synthesis II

A solution of BOPAcidaetTr (**22**, 1.25 g, 1.96 mmole), BrOAetTr (**1**, 0.89 g, 2.02 mmole), and potassium bicarbonate (0.25 g, 2.5 mmole) in acetonitrile was refluxed for 20 hours. The white solid (potassium bromide) was filtered, and the remaining solution was concentrated under reduced pressure to a brown oil. The oil was redissolved in methylene chloride and chromatographed (Alumina, 0-1% methanol in methylene chloride eluant gradient). The second sulfur containing band contained the desired product. Yield 0.91 g (0.92 mmole, 46%).

M.P.=50-60°C.

^{1}H-NMR (CD_2Cl_2) δ 2.31 (tr, J=5 Hz, 2H, $C\underline{H_2}S$), 2.33 (tr, J=6.4 Hz, 2H, $C\underline{H_2}S$), 2.44 (tr, J= 6.4 Hz, 2H, $R_2NC\underline{H_2}$), 2.85 (s, 2H, $NC\underline{H_2}CO$), 2.97 (q, J=6 Hz, 2H, $C(O)NHC\underline{H_2}$), 3.50 (s, 2H, $PhC\underline{H_2}N$), 5.11 (s, 2H, $PhC\underline{H_2}O$), 7.0-7.5 (m, 41H, aryl protons), 8.05 (1/2 'A_2B_2', J=8 Hz, 2H, $OC(O)C_6\underline{H_4}CH_2$).

FABMS$^+$ m/z =995 $(MH)^+$, 751 $(MH\text{-}Ph_3CH)^+$, 719 $(MH\text{-}Ph_3CSH)^+$, 705 $(MH\text{-}Ph_3CSCH_2)^+$, 509 $(MH\text{-}2Ph_3C)^+$, 475 $(509\text{-}H_2S)^+$, 447 $(509\text{-}2S)^+$, 433 $(447\text{-}CH_2)^+$, 419 $(447\text{-}2CH_2)^+$, 391 $(419\text{-}2CH_2)^+$, 243 $(Ph_3C)^+$.

IR vmax 1739, 1676, 1497, 1444, 1281, 1259, 743, 699 cm^{-1}.

Anal Calculated for $C_{65}H_{58}N_2O_4S_2$: C, 78.44; H, 5.87; N, 2.81; S, 6.43; O, 6.44.
Found: C, 78.12; H, 5.84; N, 2.72; S, 6.23

(24) - N-[4-(carboxy)benzyl-N-[(N'-(((acetylamino)methyl)thio)ethyl)acetamide]-2-(((acetylamino)methyl)thio)ethylamine 2-(benzyloxy)phenyl ester - BOPacidaa(aetAcm)$_2$

$C_{33}H_{40}N_4O_6S_2$ MW= 652

To a trifluoroacetic acid solution of BOPOAcidAA(AetTr)$_2$ (**23**, 0.844 g, 0.849 mmole) was added acetamidomethanol (0.3 g, 3 mmole). The orange solution was stirred for one hour, at which time triethylsilane (0.5 ml, 3 mmole) was added. Addition of hexanes and a drop of water allowed for the removal of the resulting white solid. The two layers were partitioned and the trifluoroacetic acid layer was concentrated *in vacuo*. Methylene chloride was added, followed by 1M sodium bicarbonate to neutralize the remaining acid. Upon neutralization the organic layer was removed and dried with anhydrous potassium carbonate. The solution was filtered and dried *in vacuo* to form a yellow oil, which was chromatographed (Alumina, 1-20% methanol in methylene chloride eluant gradient). The sulfur containing fractions were combined and concentrated *in vacuo* to yield **24** as a clear oil. Yield 40 mg (0.0613 mmole, 8%)

^{1}H-NMR (CD_2Cl_2) δ 1.87 (s, 6H, CH_3's), 3.0-3.3 (m, 10H, 8 CH_2S's, R_2NCH_2), 3.02 (s, 2H, $CH_2C(O)$), 3.38 (q, J=6.45 Hz, $C(O)NHC\underline{H}_2$), 3.67 (s, 2H, $PhCH_2N$), 5.01 (s, 2H, $PhCH_2O$), 6.0 (broad tr, 1H, amide proton), 6.5 (broad tr, 1H, amide proton), 6.9-7.3 (m, 9H, aryl), 7.43 (1/2 'A_2B_2', J=8.0 Hz, 2H, $O(O)CC_6\underline{H}_4CH_2$), 7.7 (broad tr, 1H, amide proton), 8.06 (1/2 'A_2B_2', J=8.5 Hz, 2H, $O(O)CC_6\underline{H}_4CH_2$).

(25) - Tetraphenylarsonium oxo[N, N'-bis(2-thioethyl)glycinamido]technetate (V) - Ph_4As [TcOaa(aet)$_2$]

Anion - $C_6H_{10}N_2O_2S_2Tc$ MW= 305

An aqueous solution of ammonium pertechnetate (0.106 mmole) was placed in a vial. To this was added a solution of α-D-glucoheptonic acid sodium salt (Sigma, 40 mg, 0.16 mmole) and a methanolic solution of **2** (60 mg, 0.13 mmole). After addition of sodium dithionite (2ml of a 0.12M solution in 0.5M sodium hydroxide), the solution was refluxed for 20 minutes to yield a yellow/orange solution. Tetraphenylarsonium chloride hydrate (45 mg, 0.11 mmole) was added as counterion. The solution was concentrated and dried *in vacuo*. The resulting solid was redissolved in methylene chloride, filtered, and chromatographed (Silica gel, 1-5% methanol in methylene chloride eluant gradient). The resulting yellow/orange band was collected and dried *in vacuo* to yield **25** as a yellow/orange solid. Yield 16 mg (0.023 mmole, 22%).

^{1}H-NMR (CD_2Cl_2) (anion only) δ 1.96 (m, 1H, CH_2), 3.35 (m, 2H, CH_2), 3.57 (m, 2H, CH_2), 3.72 (1/2 AB, J=17Hz, CH_2CO), 3.80 (m, 1H, CH_2), 3.95 (m, 1H, CH_2), 4.53 (m, 1H, CH_2), 4.71 (1/2 AB, J=17Hz, CH_2CO).

FABMS$^-$ (Tetraethylammonium hydroxide mw. = 297) m/z = 305 $(M)^-$.

(26) - Oxo[N-benzyl-N-(N'-(2-thioethyl)acetamido)aminoethanethiolato] technetium (V) - [TcOBzlaa(aet)$_2$]

$C_{13}H_{17}N_2O_2S_2Tc$ MW=396

Sodium oxobis(1,2-ethanediolato)technetate (25 mg, 0.1 mmole) was dissolved in sodium methoxide/methanol (25% w/w). To this solution was added BzlAA(aetBzm)$_2$ (**7**, 57 mg, 0.103 mmole). The purple solution was refluxed for 30 minutes. The resulting yellow solution was dried *in vacuo* and redissolved in benzene and chromatographed (Silica gel, 70% benzene; 25% methylene chloride; 5% acetonitrile eluant). This yielded a broad yellow band which was collected and dried *in vacuo*. Yield 26 mg (0.066 mmole, 66%).

MP = 208-210° C.

^{1}H-NMR (syn isomer) (CDCl$_3$) δ 1.54 (1/4 ABCD (triplet of doublets), J= 4.5 Hz, J= 12.6 Hz, 1H, CH$_2$C$\underline{H_2}$NBzl), 2.99 (1/4 ABCD (doublet of doublets), J= 4.5 Hz, J=13.5 Hz,1H, CH$_2$C$\underline{H_2}$S (amine side)), 3.16 (1/4 ABCD (doublet of doublets), J= 3.6Hz, J= 12.6 Hz, 1H, CH$_2$C$\underline{H_2}$S (amine side)), 3.31 (1/2 AB, J= 15.6 Hz, 1H, C$\underline{H_2}$CO), 3.42 (1/2 ABC$_2$ (multiplet), J=, 2H, CH$_2$C$\underline{H_2}$S (amide side)), 3.83 (1/4 ABCD, J=3.6 Hz, J=13.5 Hz, 1H, CH$_2$C$\underline{H_2}$NBzl), 3.92 (1/4 ABC$_2$ (multiplet), J=6.3 Hz, 1H, C$\underline{H_2}$NCO), 4.44 (1/4 ABC$_2$ (multiplet), J=6.3 Hz, 1H, C$\underline{H_2}$NCO), 4.76 (1/2 AB, J=15 Hz, 1H, C$\underline{H_2}$Ph), 4.81 (1/2AB, J=15.6 Hz, 1H, C$\underline{H_2}$CO), 5.16 (1/2AB, J=15 Hz, 1H, C$\underline{H_2}$Ph), 7.57 (singlet, 5H, aryl).

^{13}C{^{1}H}-NMR (CDCl$_3$) δ 33.91(CH$_2$S), 42.07(CH$_2$S), 59.29(CH$_2$N), 60.29(CH$_2$N), 65.81(CH$_2$N), 65.95(CH$_2$N), 129.43, 130.24, 130.31, 131.55, 154.70(aryl), 181.49(CO).

FABMS$^+$ m/z = 793 (M$_2$H)$^+$, 703 (M$_2$H - C$_7$H$_6$)$^+$, 613 (M$_2$H - C$_{14}$H$_{12}$)$^+$, 550 (M + NBA)$^+$, 397 (MH)$^+$, 307 (MH - C$_7$H$_6$)$^+$.

IR νmax 1653, 1636, 1317, 947, 932, 706 cm^{-1}.

Anal Calculated for $C_{13}H_{17}N_2O_2S_2Tc$:

C, 39.39; H, 4.32; N, 7.07; O, 8.07; S, 16.18; Tc, 24.97.

Found: C, 38.73; H, 4.34; N, 6.97 (May contain 1/6 CH$_2$Cl$_2$).

C, 38.52; H, 4.26; N, 6.82 (Calculated with 1/6 CH$_2$Cl$_2$).

(27) - Oxo[N-benzyl-N-(N'-(2-thioethyl)acetamido)aminoethanethiolato] rhenium (V) - [ReOBzlaa(aet)$_2$]

$C_{13}H_{17}N_2O_2S_2Re$ MW=483

To a methylene chloride solution of oxotrichlorobis(triphenylphosphine)rhenium (68 mg, 0.082 mmole) was added a methanolic solution of BzlAA(aetH)$_2$ (8, 26 mg, 0.092 mmole). The resulting solution was refluxed under a nitrogen atmosphere for three hours. The resulting purple/grey solution was concentrated *in vacuo* , redissolved in benzene and chromatographed (Alumina, 70% benzene, 25% methylene chloride, 5% acetonitrile eluant). A broad, faint purple band was eluted (caution: at low concentrations this band can be very difficult to see), collected, and solvent was removed *in vacuo* to give a red/purple solid. Yield 18 mg (0.037mmole, 46%).

MP = 220-224°C.

^{1}H-NMR (CD_2Cl_2) (syn isomer) δ 1.52 (1/4 ABCD (triplet of doublets), J=4.5 Hz, J=13 Hz, 1H, $C\underline{H}_2$NBzl), 2.93 (1/4 ABCD (doublet of doublets), J=4.5 Hz, J=12 Hz, 1H, $C\underline{H}_2$S (amine side)), 3.10 (1/4 ABCD, (doublet of doublets), J=4.5 Hz, J=13.5 Hz, 1H, $C\underline{H}_2$S (amine side)), 3.2 (1/2 ABC_2 (multiplet), 2H, $C\underline{H}_2$S (amide side)), 3.75 (1/4ABCD (triplet of doublets), J=4.5 Hz, J=13.4 Hz, 1H, $C\underline{H}_2$NBzl), 3.82 (1/2 AB, J=16.5 Hz, 1H, $C\underline{H}_2$CO), 4.1 (1/4 ABC_2 (multiplet), 1H, $C\underline{H}_2$NCO), 4.6 (1/4 ABC_2 (multiplet), 1H, $C\underline{H}_2$NCO), 4.70 (1/2AB, J=13.5 Hz, 1H, $C\underline{H}_2$Ph), 5.06 (1/2 AB, J=16.5 Hz, 1H, $C\underline{H}_2$CO), 5.12 (1/2AB, J=14 Hz, 1H, $C\underline{H}_2$Ph), 7.5 (singlet, 5H, aryl).

FABMS$^+$ m/z = 485 $(MH)^+$, 393 (MH-tropylium)$^+$, 329 (393- H_2O-SCH_2)H^+.

IR vmax 1653, 1646, 1316, 961, 955, 706 cm^{-1}.

(28) - Oxo[N-(4-carboxybenzyl)-N-(N'-(2-thioethyl)acetamido)aminoethanethiolato] technetium (V) - [TcOAcidaa(aet)$_2$]

$C_{14}H_{17}N_2O_4S_2Tc$ MW= 440

To an aqueous solution of ammonium pertechnetate (0.1 mmole) and α-D-glucoheptonic acid sodium salt (Sigma, 50 mg, 0.18 mmole) was added an ethanolic solution of AcidAA(aetBzm)$_2$ (**13**, 60 mg, 0.101 mmole). Addition of sodium dithionite (2 ml of a 0.12M solution in 0.5M sodium hydroxide) yielded a purple solution, which was refluxed for thirty minutes. The resulting yellow/orange solution was concentrated *in vacuo* and partitioned between distilled water and ethyl acetate. The ethyl acetate portion was dried with potassium carbonate, and the solvent was removed *in vacuo* to give an orange/brown solid. Yield 13 mg (0.030 mmole, 30%)

MP = > 260°C.

FABMS$^-$ m/z =439 $(M-H)^-$.

(29) - Oxo[N-(4-carboxybenzyl)-N-(N'-(2-thioethyl)acetamido)aminoethanethiolato] technetium (V) methyl ester - [TcOCH$_3$OAcidaa(aet)$_2$]

$C_{15}H_{19}N_2O_4S_2Tc$ MW= 454

Sodium oxobis(1,2-ethanediolato)technetate (25 mg, 0.096 mmole) was dissolved in methanol and 0.5M NaOH. A methylene chloride solution of CH_3OAcidAA(aetBzm)$_2$ (**19**, 62 mg, 0.102 mmole) was added, and the resulting solution was refluxed for 30 minutes. The resulting yellow/orange solution was concentrated under reduced pressure, redissolved in methylene chloride, and chromatographed (Alumina, 0.25% methanol; 0.25% glacial acetic acid in methylene chloride eluant). The yellow/orange fraction was collected and dried *in vacuo*. Yield 23 mg (0.051 mmole, 53%).

MP = > 260°C.

^{1}H-NMR (CD_2Cl_2) δ 1.5 (1/4ABCD(hidden under water peak), 1H, $CH_2C\underline{H}_2N(CH_2)_2$), 3.09 (1/4ABCD, J=4.3 Hz, J=11.3 Hz, 1H, $C\underline{H}_2S$ (amine side)), 3.19(1/4ABCD, J=3.4 Hz, J=12.4 Hz, 1H, $C\underline{H}_2S$ (amine side)), 3.42 (1/2AB, J=15.8 Hz, 1H, $C\underline{H}_2CO$), 3.52 (1/2 ABC_2, 2H, $C\underline{H}_2S$ (amide side)), 3.89 (1/4ABCD (partially hidden beneath 3.94 ppm peak), J=3.4 Hz, J=13.5 Hz, 1H, $CH_2C\underline{H}_2N(CH_2)_2$), 3.94 (singlet, 3H, CH_3O), 4.03 (1/4ABC_2, 1H, $C\underline{H}_2NCO$), 4.54 (1/4 ABC_2, 1H, $C\underline{H}_2NCO$), 4.89 (1/2AB, J=15.8Hz, 1H, $C\underline{H}_2CO$), 4.91 (1/2AB, J=13.5 Hz, 1H, $C_2H_4C\underline{H}_2N$), 5.3 (1/2 AB, J=13.5 Hz, 1H, $C_2H_4C\underline{H}_2N$), 7.60 (1/2 'A_2B_2', J=7 Hz, 2H, R-$C_6\underline{H}_4$-R'), 8.05 (1/2 'A_2B_2', J= 7Hz, 2H, R-$C_6\underline{H}_4$-R').

^{1}H-NMR ($CDCl_3$) δ 1.5 (1/4ABCD(triplet of doublets)(hidden under water peak), J=, 1H, $CH_2C\underline{H}_2N$ (amine side)), 3.07 (1/4ABCD (doublet of doublets), J=4.2 Hz, J=13.2 Hz, 1H, $CH_2C\underline{H}_2S$ (amine side)), 3.17 (1/4ABCD (doublet of doublets), J=3 Hz, J=13.2 Hz, 1H, $CH_2C\underline{H}_2S$ (amine side)), 3.41 (1/2AB, J=16.2 Hz, 1H, $C\underline{H}_2CO$), 3.56 (1/2 ABC_2 (multiplet), J=7.8 Hz, J=13.2 Hz, 2H, $CH_2C\underline{H}_2S$ (amide side)), 3.86 (1/4ABCD, J=3.6 Hz, J=13.5 Hz, 1H, $CH_2C\underline{H}_2N$ (amine side)), 3.95 (singlet, 3H, CH_3O), 4.06 (1/4ABC_2 (multiplet, J=6.9 Hz, J=13.2 Hz, 1H, $C\underline{H}_2NCO$), 4.56 (1/4ABC_2 (multiplet), J=6.9 Hz, 1H, $C\underline{H}_2NCO$), 4.84 (1/2AB, J=15.9 Hz, 1H, $C\underline{H}_2C_6H_4$), 4.89 (1/2AB, J=12.3 Hz, 1H, $C\underline{H}_2CO$), 5.3 (1/2AB, J=14.4 Hz, 1H, $C\underline{H}_2C_6H_4$), 7.54 (1/2 A_2B_2, J=8.1 Hz, 2H, C_6H_4), 8.15 (1/2A_2B_2, J=8.7 Hz, 2H, C_6H_4).

FABMS$^+$ (NBA mw. = 154) m/z = 454 (M^+), 220 $(M-CH_2)^{2+}$.

IR νmax 1719 (ester CO), 1710 (ester CO), 1652 (amide CO), 1642 (amide CO), 1285 (CC(O)O stretch), 1113 (CCO stretch), 948 (TcO), 935 (TcO)cm^{-1}.

(30) - Oxo[N-(4-carboxybenzyl)-N-(N'-(2-thioethyl)acetamido)aminoethanethiolato] rhenium (V) methyl ester - [ReOCH_3OAcidaa(aet)$_2$]

$C_{15}H_{19}N_2O_4ReS_2$ MW= 541

To a methylene chloride solution of oxotrichlorobis(triphenylphosphine)rhenium (68 mg, 0.08 mmole) was added a methanol solution of **20** (MeOAcidAA(aetH)$_2$) (27 mg, 0.08 mmole). This solution was refluxed under nitrogen for three hours. The resulting purple/grey solution was concentrated under reduced pressure, redissolved in methylene chloride, and chromatographed (alumina, 0.5% methanol in methylene chloride eluant). A faint purple band eluted, was collected, and was dried *in vacuo* to give a red/purple solid. Yield 18 mg (0.033 mmole, 42%).

^{1}H-NMR (CD_2Cl_2) (syn isomer) δ 1.52 (1/4 ABCD (triplet of doublets), J=4.5 Hz, J=13 Hz, 1H, $C\underline{H}_2NBzl$), 2.93 (1/4 ABCD (doublet of doublets), J=4.5 Hz, J=12 Hz, 1H, $C\underline{H}_2S$ (amine side)), 3.02 (1/4 ABCD, (doublet of doublets), J=4.5 Hz, J=13.5 Hz, 1H, $C\underline{H}_2S$ (amine side)), 3.2 (1/2 ABC_2 (multiplet), 2H, $C\underline{H}_2S$ (amide side)), 3.72 (1/4ABCD (triplet of doublets), J=4.5 Hz, J=13.4 Hz, 1H, $C\underline{H}_2NBzl$), 3.82 (1/2 AB, J=15 Hz, 1H, $C\underline{H}_2CO$), 3.93 (s, 3H, CH_3), 4.1 (1/4 ABC_2 (multiplet), 1H, $C\underline{H}_2NCO$), 4.6 (1/4 ABC_2 (multiplet), 1H, $C\underline{H}_2NCO$), 4.73 (1/2AB, J=13.5 Hz, 1H, $C\underline{H}_2Ph$), 5.02 (1/2 AB, J=15 Hz, 1H, $C\underline{H}_2CO$), 5.15 (1/2AB, J=13.5 Hz, 1H, $C\underline{H}_2Ph$), 7.60 (1/2 'A_2B_2', J=8.5 Hz, 2H, aryl), 8.15 (1/2 'A_2B_2', J=8.5 Hz, 2H, aryl);

^{13}C-NMR ($CDCl_3$) δ 20.55(CH_3), 31.38(CH_2S), 36.56(CH_2S), 59.23(CH_2N), 60.48(CH_2N), 63.14(CH_2N), 66.32(CH_2N), 130.69, 132.63, 133.81, 139.88, 153.15(aryl), 162.63(C(O)O), 190.40(CO).

(31) - Oxo[N-(4-carboxybenzyl)-N-(N'-(2-thioethyl)acetamido)aminoethanethiolato] technetium (V) 2-(benzyloxy)phenyl ester - [TcOBOPAcidaa(aet)$_2$]

$C_{27}H_{27}N_4O_5S_2Tc$ MW= 622

To a solution of sodium oxobis(1,2-ethanediolato)technetate (20 mg, 0.078 mmole) in methanol was added sodium hydroxide (1 ml of a 0.5M aqueous solution) and BOPOAcidAA(aetAcm)$_2$ (**24**, 52 mg, 0.080 mmole). The solution was refluxed for one hour, concentrated under reduced pressure, and chromatographed (Preparative TLC, 5% methanol in methylene chloride eluant). The yellow/orange band at the bottom of the plate was removed, and **31** was separated from the silica by repeated washings with methanol. The resulting solution was dried to a yellow solid *in vacuo*. Yield 18 mg (0.029 mmole, 37%).

^{1}H-NMR (CD_2Cl_2) δ 1.5 (1/4ABCD(triplet of doublets)(hidden under water peak), J=, 1H, $CH_2C\underline{H}_2N$ (amine side)), 3.07 (1/4ABCD (doublet of doublets), J=4 Hz, J=13 Hz, 1H, $CH_2C\underline{H}_2S$ (amine side)), 3.17 (1/4ABCD (doublet of doublets), J=3 Hz, J=13 Hz, 1H, $CH_2C\underline{H}_2S$ (amine side)), 3.41 (1/2AB, J=17 Hz, 1H, $C\underline{H}_2CO$), 3.56 (1/2 ABC_2 (multiplet), J=8 Hz, J=13 Hz, 2H, $CH_2C\underline{H}_2S$ (amide side)), 3.86 (1/4ABCD, J=4 Hz, J=13 Hz, 1H, $CH_2C\underline{H}_2N$ (amine side)), 4.06 (1/4ABC_2 (multiplet, J=7 Hz, J=13 Hz, 1H, $C\underline{H}_2NCO$), 4.56 (1/4ABC_2 (multiplet), J=7 Hz, 1H, $C\underline{H}_2NCO$), 4.83 (1/2AB, J=17 Hz, 1H, C$\underline{H}_2C_6H_4$), 4.86 (1/2AB, J=14 Hz, 1H, C$\underline{H}_2$CO), 5.03 (s, 2H, OC$\underline{H}_2C_6H_5$), 5.3 (1/2AB, J=14 Hz, 1H, NC$\underline{H}_2C_6H_4$), 6.9-7.3 (m, 5H, aryl), 7.4-7.5 (m, 2H, aryl), 7.54 (1/2 'A_2B_2', J=8 Hz, 2H, R-$C_6\underline{H}_4$-R'), 7.6-7.7 (m, 2H, aryl), 8.15 (1/2 'A_2B_2', J=8 Hz, 2H, R-$C_6\underline{H}_4$-R').

FABMS$^-$ m/z = 621 (M-H)$^-$.

Partial X-Ray Structure of [TcO(Bzlaa(aet)$_2$)] (26).[11] A brown parallelepiped crystal was grown by hexanes diffusion into a methylene chloride solution of (**26**). X-ray data were collected at room temperature on an Enraf-Nonius CAD4F-11 κ-geometry diffractometer using graphite monochromated Mo Kα radiation (λ=0.71073 Å). The structure was solved by direct methods.[12] The non-hydrogen atoms were refined anisotropically. Upon refinement there was a significant amount of electron density in the difference Fourier map besides that of the model compound. This extra electron density lay very close to a three-fold axis. Elemental analysis of the crystals was consistent with 1/6 of a methylene chloride molecule per molecule of (**26**). It was impossible to manufacture a model of this moiety. Crystal data of the partial structure are in Table 2.I and atomic coordinates are in Table 2.II.

Partial X-Ray Structure of [ReO(Bzlaa(aet)$_2$)] (27).[11] A red prismatic crystal was grown by hexanes diffusion into a methylene chloride solution of (**27**). X-ray data were collected at room temperature on an Enraf-Nonius CAD4F-11 κ-geometry diffractometer using graphite monochromated Mo Kα radiation (λ=0.71073 Å). The structure was solved by direct methods.[12] The non-hydrogen atoms were refined anisotropically. Upon refinement there was a significant amount of electron density in the difference Fourier map besides that of the model compound. The electron density lay very close to a three-fold axis. This structure suffers much the same problem as that of **26**. Analysis of the crystals has not been completed, and no model of the electron density has been successful. Crystal data of the partial structure are in Table 2.III and atomic coordinates are in Table 2.IV.

Table 2.I. Crystal data for structure determination for $[\mathrm{TcO(BzlAa(aet)_2)}]$ **(26)**.

Empirical formula	$C_{13}H_{17}N_2O_2S_2Tc$
Formula weight	394.41
Crystal color, habit	brown, parallelepiped
Crystal dimensions, mm	0.200 X 0.240 X 0.180
Crystal system	rhombohedral (hexagonal axes)
a, Å	26.012 (6)
c, Å	12.412 (2)
V, $Å^3$	7273 (4)
Space group	$R\bar{3}$(h)
Z	18
D (calcd), g/cm^3	1.621
F_{000}	3600
μ, cm^{-1}	11.03
Diffractometer	Enraf-Nonius CAD4F-11
Radiation (λ, Å)	Mo K_α (0.71069)
Temperature, °C	23
Scan mode	ω
Scan width, deg	$(0.80 + 0.35 \tan\theta)$
Scan rate, deg/min	0.9 - 8.0 (in ω)
Max 2θ, deg	55.0
No. of reflcns measured	
total	2069
unique	2060
Corrections	Lorentz-polarization
Structure solution	Direct Methods[12]
Refinement	full-matrix least-squares[13]
Function minimized	$\Sigma w(\lvert Fo\rvert - \lvert Fc\rvert)^2$
Least-squares weights	$4Fo^2/\sigma^2(Fo)^2$
p-factor	0.03
Anomalous dispersion	All non-hydrogen atoms
No. observations	$I>3.00\sigma(I)$, 1396
No. variables	181
R, R_w	0.057, 0.076
goodness of fit	2.19
Max shift/error in final cycle	0.22
Max. peak in final diff. map, $eÅ^{-3}$	2.04
Min. peak in final diff. map, $eÅ^{-3}$	-0.50

Table 2.II. Atomic positional parameters for [TcO(Bzlaa(aet)$_2$)] (**26**).

atom	x	y	z
Tc	0.56105(5)	0.05334(5)	0.80851(9)
S(1)	0.5793(2)	-0.0200(2)	0.8559(3)
S(2)	0.5445(2)	0.0153(2)	0.6399(3)
O(1)	0.4975(4)	0.0461(4)	0.8533(8)
O(2)	0.6946(5)	0.2207(4)	0.7438(9)
N(1)	0.6230(4)	0.1036(4)	0.9385(8)
N(2)	0.6163(5)	0.1266(5)	0.7326(8)
C(1)	0.6257(6)	0.0103(6)	0.976(1)
C(2)	0.6625(6)	0.0777(6)	0.963(1)
C(3)	0.6577(5)	0.1662(6)	0.905(1)
C(4)	0.6580(6)	0.1733(6)	0.786(1)
C(5)	0.6167(6)	0.1319(7)	0.613(1)
C(6)	0.5611(7)	0.0812(7)	0.566(1)
C(7)	0.5843(5)	0.0994(6)	1.037(1)
C(8)	0.6196(6)	0.1303(7)	1.135(1)
C(9)	0.6402(7)	0.1880(8)	1.150(1)
C(10)	0.673(1)	0.218(1)	1.238(2)
C(11)	0.683(1)	0.185(1)	1.314(2)
C(12)	0.661(1)	0.127(1)	1.302(1)
C(13)	0.6280(8)	0.0977(8)	1.214(1)

Table 2.III. Crystal data for structure determination for [ReO(BzlAa(aet)$_2$)] (**27**).

Empirical formula	$C_{13}H_{17}N_2O_2S_2Re$
Formula weight	484.62
Crystal color, habit	red, prismatic
Crystal dimensions, mm	0.120 x 0.120 x 0.120
Crystal system	rhombohedral (hexagonal axes)
a, Å	26.038 (3)
c, Å	12.418 (4)
V, $Å^3$	7291 (3)
Space group	R $\overline{3}$ (h)
Z	18
D (calcd), g/cm^3	1.986
F_{000}	4194
μ, cm^{-1}	78.50
Diffractometer	Enraf-Nonius CAD4F-11
Radiation (λ, Å)	Mo K_{α} (0.71069)
Temperature, °C	23
Scan mode	ω
Scan width, deg	$(0.80 + 0.35 \tan\theta)$
Scan rate, deg/min	1.9 - 16.0 (in ω)
Max 2θ, deg	54.9
No. of reflcns measured	
total	3959
unique	3798
Corrections	Lorentz-polarization
Structure solution	Direct Methods[12]
Refinement	full-matrix least-squares[13]
Function minimized	$\Sigma w(\lvert Fo\rvert - \lvert Fc\rvert)^2$
Least-squares weights	$4Fo^2/\sigma^2(Fo)^2$
p-factor	0.03
Anomalous dispersion	All non-hydrogen atoms
No. observations	$I>3.00\sigma(I)$, 2322
No. variables	182
R, R_W	0.052, 0.053
goodness of fit	1.37
Max shift/error in final cycle	2.15
Max. peak in final diff. map, $eÅ^{-3}$	3.14
Min. peak in final diff. map, $eÅ^{-3}$	-2.01

Table 2.IV. Atomic positional parameters for [ReO(Bzlaa(aet)$_2$)] (**27**).

atom	x	y	z
Re	0.22774(2)	0.84145(3)	0.64147(4)
S(1)	0.2456(2)	0.9329(2)	0.6905(3)
S(2)	0.2099(2)	0.8612(2)	0.4722(3)
O(1)	0.1639(4)	0.7844(4)	0.6892(8)
O(2)	0.3632(4)	0.8098(5)	0.5774(8)
N(1)	0.2827(5)	0.8231(5)	0.5647(8)
N(2)	0.2886(5)	0.8531(5)	0.7717(9)
C(1)	0.2923(6)	0.9493(6)	0.810(1)
C(2)	0.3280(6)	0.9190(6)	0.798(1)
C(3)	0.2298(8)	0.8117(8)	0.399(1)
C(4)	0.2858(7)	0.8192(7)	0.446(1)
C(5)	0.3262(7)	0.8186(6)	0.620(1)
C(6)	0.3251(6)	0.8250(6)	0.741(1)
C(7)	0.2507(6)	0.8192(6)	0.870(1)
C(8)	0.2869(6)	0.8238(6)	0.969(1)
C(9)	0.3077(8)	0.7866(8)	0.984(1)
C(10)	0.2955(7)	0.8654(7)	1.046(1)
C(11)	0.340(1)	0.792(1)	1.076(2)
C(12)	0.328(1)	0.869(1)	1.138(1)
C(13)	0.351(1)	0.835(1)	1.151(2)

RESULTS AND DISCUSSION

Two procedures have been developed to form N-alkylated analogs of Byrne's amine-amide-dithiol ligands. Scheme 2.3 shows an example of these two procedures towards the formation of a benzyl-AADT compound. The first procedure involves a series of amine-alkylation procedures. This procedure leads to very simple formation of the desired ligands, but the overall yields are relatively low. The second procedure involves reductive alkylation[14] with subsequent N-alkylation. This reductive alkylation procedure has a higher yield of product, but is dependent on the availability of specific aldehydes. Another disadvantage of this second procedure is that sodium borohydride reduction is used, which restricts the incorporation of some functionalities.

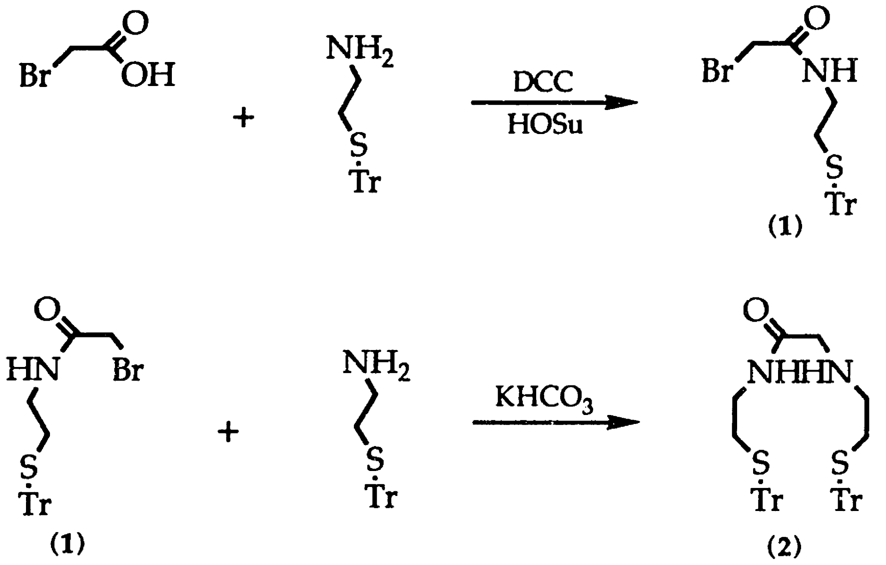
Ligand chemistry

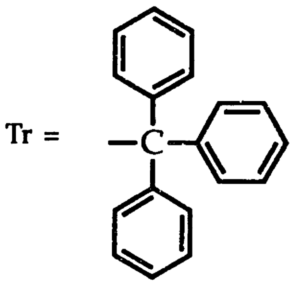
Compound **1** (N-[(2-triphenylmethylthio)ethyl]-2-bromoacetamide) is a bromoacetamide derivative which was formed by peptide coupling techniques involving bromoacetic acid and 2-((triphenylmethyl)thio)ethylamine[7]. The reaction of **1** with a second equivalent of 2-((triphenylmethyl)thio)ethylamine yields a basic S-protected amine-amide-dithiol ligand backbone (**2**, N,N'-bis[2-((triphenylmethyl)thio))ethyl]glycinamide) by simple N-alkylation. (see Scheme 2.2)

Direct alkylation of **2** with benzyl chloride (Scheme 2.3) yields compound **6** (N-benzyl-N-[(N'-((triphenylmethyl)thio)ethyl)acetamide]-2-((triphenylmethyl)thio)ethylamine) in approximately 30% yield. Purification of the compound yields the product **6** and the starting material **2**. This isolation of starting material indicates that the reaction proceeds in low yield due to the slow reactivity of the amine with the benzyl chloride. A reductive alkylation procedure for compound **6** was developed to improve the yield.

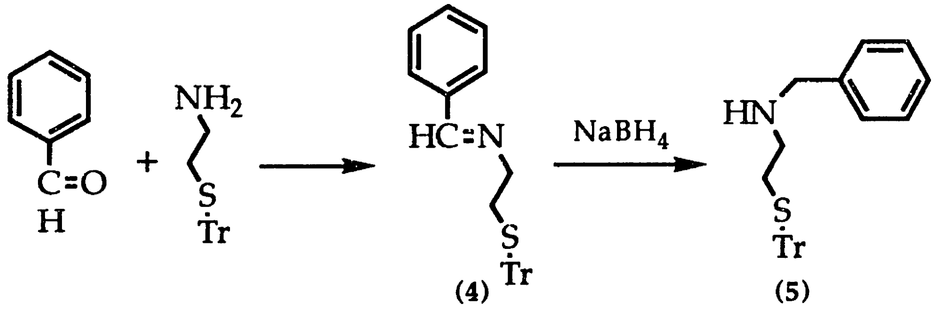
Compound **4** (N-benzylidene-2-[(triphenylmethyl)thio]ethylamine) was formed by a Schiff's base reaction between benzaldehyde and 2-((triphenylmethyl)thio)ethylamine (see Scheme 2.3). Reduction of **4** with sodium borohydride completed the reductive alkylation [14] to form the N-benzyl amine **5** (N-benzyl-2-[(triphenylmethyl)thio]ethylamine). Mono-N-alkylation of **5** with **1** yields the N-benzyl amine-amide-dithiol ligand **6**. (Scheme 2.3)

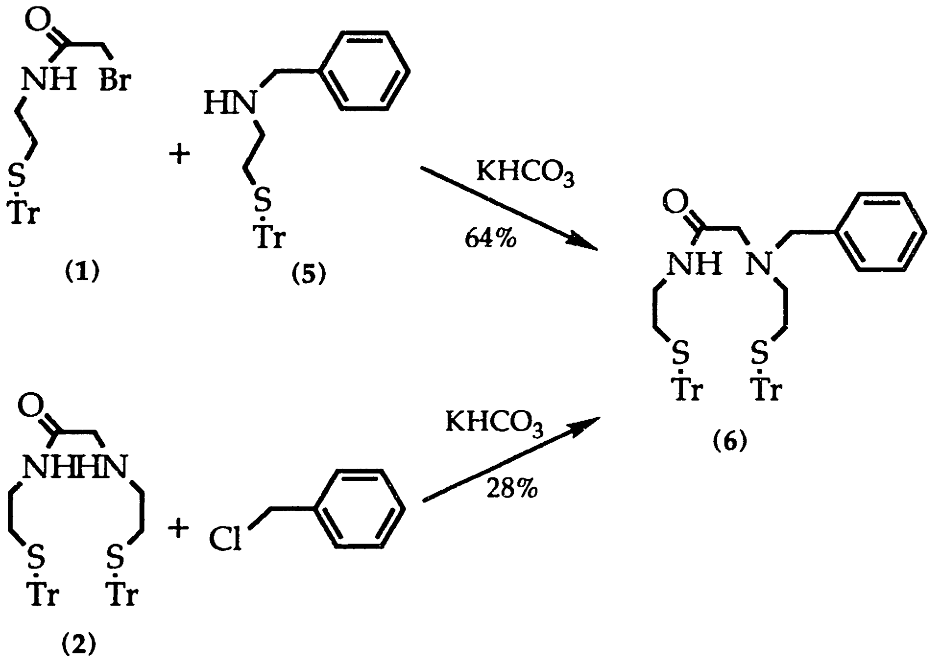
Scheme 2.2

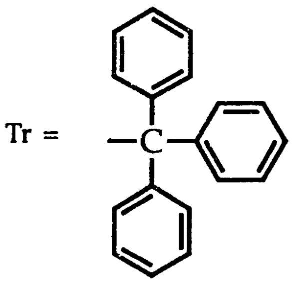

Br
OH
O
+
NH2
S
Tr
DCC
HOSu
Br
NH
O
S
Tr
(1)
O
HN
Br
S
Tr
(1)
+
NH2
S
Tr
KHCO3
O
NHHN
S
Tr
S
Tr
(2)


Tr =
C

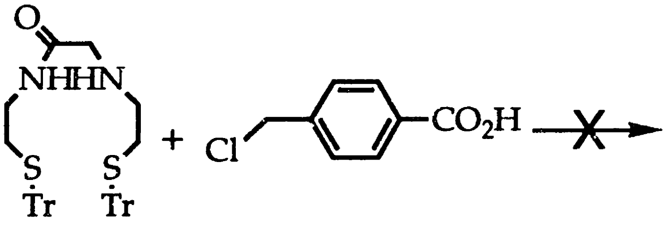
Scheme 2.3


NH2
C=O
H
+
S
Tr
HC=N
S
Tr
(4)
NaBH4
HN
S
Tr
(5)


O
NH
Br
S
Tr
(1)
+
HN
S
Tr
(5)
KHCO3
64%
O
NH
N
S
Tr
S
Tr
(6)
O
NHHN
S
Tr
S
Tr
(2)
+
Cl
KHCO3
28%


Tr =
C

(2-1)



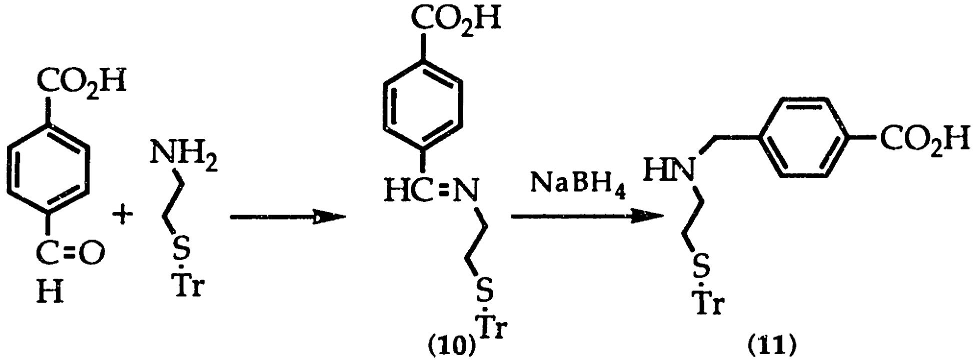
(2)

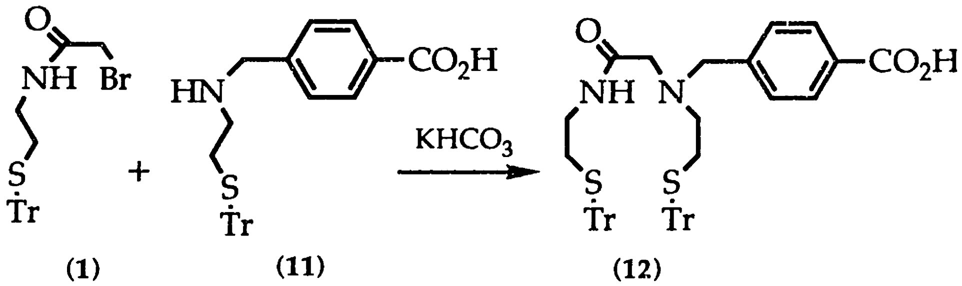
Reaction of **2** with 4-(chloromethyl)-benzoic acid in an analogous formation to the first synthetic procedure for **6** yielded no mono-N-alkylated amine-amide-dithiol (see 2-1). Formation of the carboxylic acid functionalized AADT ligand was achieved through the use of reductive alkylation. (Scheme 2.4) Reaction of 4-carboxybenzaldehyde with the S-protected amine-thiol forms the 4-carboxybenzylidene **10**. Compound **10** is insoluble in most solvents; however, formation of **9** (the potassium salt of **10**) with 0.5 N potassium hydroxide/methanol allows sodium borohydride reduction to occur. After reduction the product (**11**, N-[carboxy(benzyl]-2-[(triphenylmethyl)thio]ethylamine), along with some starting material (**10**), is precipitated with acetic acid. Formation of **12** (N-[4-(carboxy)benzyl-N-[(N′-((triphenylmethyl)thio)ethyl)acetamide]-2-((triphenylmethyl)thio)ethylamine) proceeds by an N-alkylation reaction between **11** and **1**, but proceeds in low yield due to solubility problems and the impure starting material.

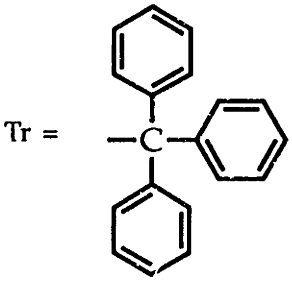
Carboxylic acid esters

The solubility and yield problems of the carboxylic derivatives **11** and **12** were circumvented through the use of carboxylic acid esters of the para-substituted benzoic acid. (Scheme 2.5) Development of alkylating agents for the AADT ligand proceeded through manipulation of 4-(chloromethyl)benzoic acid (Aldrich). Reacting the functionalized benzoic acid with neat thionyl chloride yielded 4-(chloromethyl)benzoyl chloride (**14**). Similarly the bromo derivative, 4-(bromomethyl)benzoyl bromide (**15**) could be formed by stirring α-bromo-p-toluic acid (Aldrich) in neat thionyl bromide.

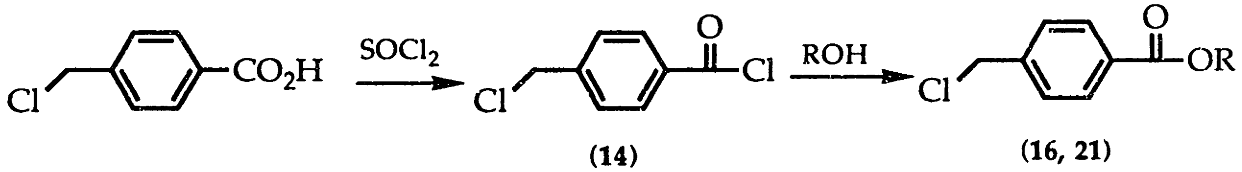
Scheme 2.4

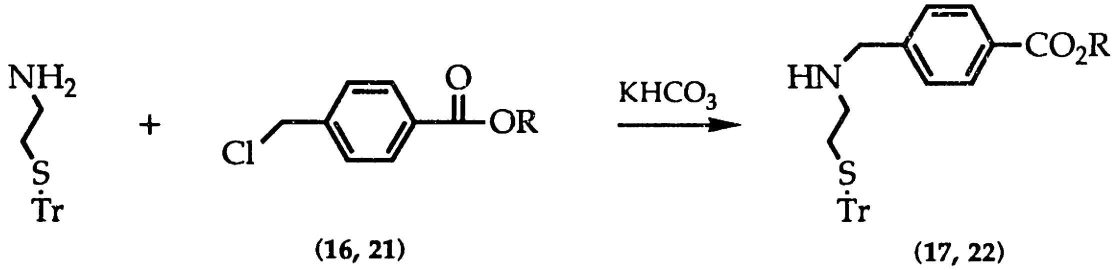

CO₂H
NH₂
C=O
H
S
Tr
+
CO₂H
HC=N
S
Tr
(10)
NaBH₄
HN
CO₂H
S
Tr
(11)

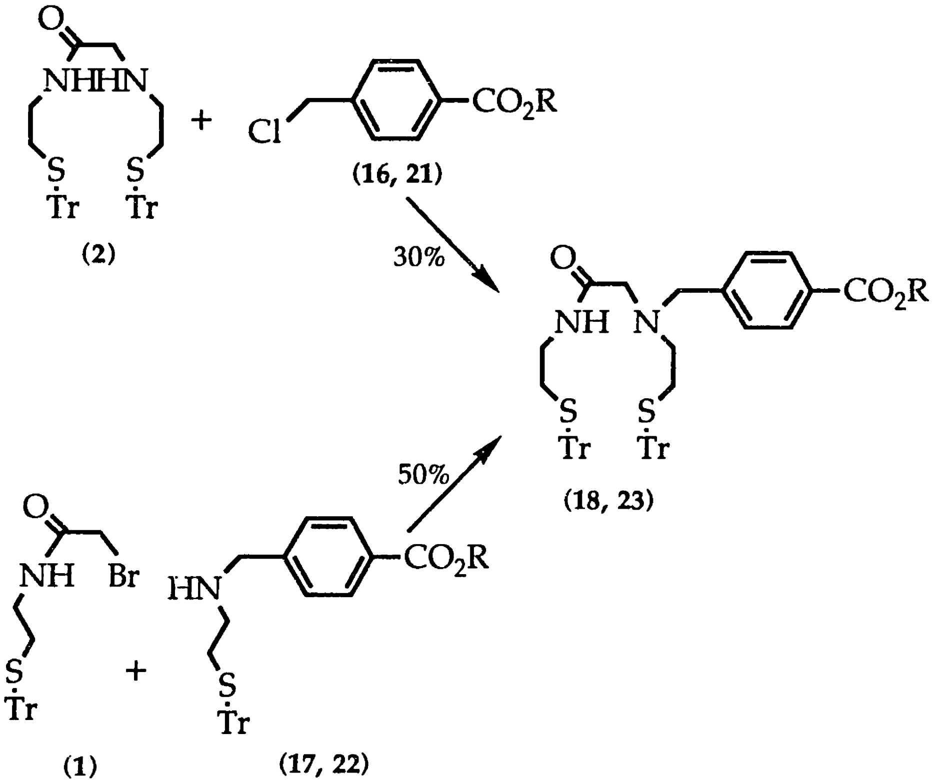

O
NH
Br
S
Tr
(1)
+
HN
CO₂H
S
Tr
(11)
KHCO₃
O
NH
N
CO₂H
S
Tr
S
Tr
(12)

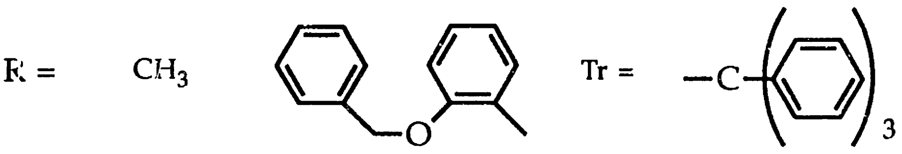

Tr =
C

Scheme 2.5


CO2H
SOCl2
Cl
(14)
ROH
OR
(16, 21)


NH2
S
Tr
+
(16, 21)
KHCO3
HN
CO2R
(17, 22)


NHHN
(2)
(16, 21)
30%
50%
(18, 23)
NH
Br
(1)
(17, 22)
CO2R


R =
CH3
O
Tr =
—C
3

Subsequent reaction of the acid chloride (**14**) with methanol yielded the benzoic acid ester **16**, 4-(chloromethyl)methylbenzoate. (Scheme 2.5, R= CH_3) Alkylation of the AADT ligand (**2**) with **16** yielded the mono-N-alkylated DADT ligand **18** (N-[4-(carboxy)benzyl-N-[(N'((triphenylmethyl)thio)ethyl)acetamide]-2-((triphenylmethyl)thio)ethylamine methyl ester) in 25% yield. Alternately, the reaction of **16** 2-((triphenylmethyl)thio)ethylamine produced a secondary amine **17** (N-[4-carboxy)benzyl]-2-[(triphenylmethyl)thio]ethylamine methyl ester) in 55% yield. Subsequent reaction of **17** with the bromoacetamide derivative **1** yielded the mono-N-alkylated derivative **18** in 50% yield.

Synthetically, the carboxylic ester is much easier to use. The ester functionality circumvents the solubility problems which were encountered with the carboxylic acid derivatives **11** and **12**. The reductive alkylation procedure was not used for ester preparation due to a lack of availability of the appropriate aldehyde starting material.

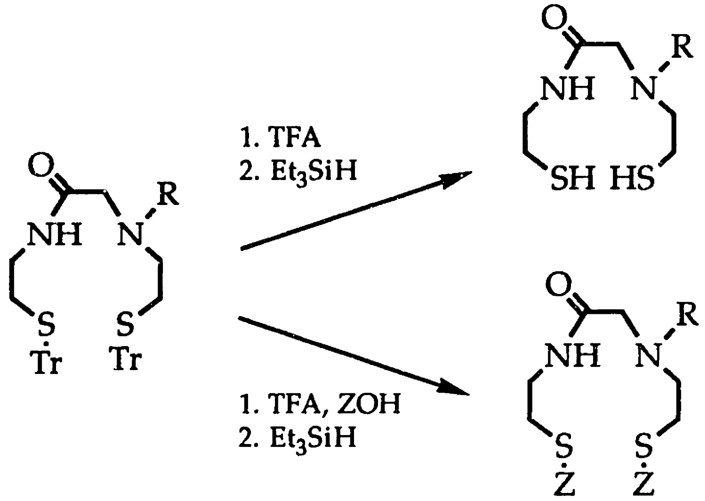
A second set of esters were formed (Scheme 2.5, R=$C_6H_5CH_2OC_6H_4$) by incorporation of the benzyloxyphenyl dual functional group.[15, 16] This group was incorporated for its carboxylic acid protecting qualities and its second characteristic of readily forming an activated ester upon acidolysis. Synthesis of 4-(chloromethyl)-(2-(benzyloxy)phenyl)benzoate (**21**) was performed by reacting 2-(benzyloxy)phenol with compound **14**. Subsequent synthesis of compounds **22** and **23** were performed by procedures analogous to those described for compounds **17** and **18** by using compound **21** in place of **16**.

Sulfur-Protection

The stepwise synthesis of the AADT ligands has a strong dependence on the use of sulfur protecting groups. Without these protecting groups, disulfide formation will occur and thus lead to the need for strong reducing agents. With the triphenylmethyl protecting group (trityl), the problem of disulfide formation is avoided. The trityl group is very unreactive to many reaction conditions[17] which makes it very useful for ligand synthesis; however, this creates a problem during metal complex formation. The trityl group can be removed in trifluoroacetic acid upon the addition of triethylsilane to precipitate triphenylmethane (see Scheme 2.6).

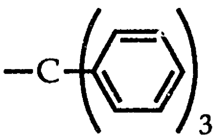
Removal of the trityl protecting group from **6** results in the isolation of the dithiol **8** (Bzlaa(aet)$_2$). Likewise, the removal of the trityl groups from **18**

Scheme 2.6

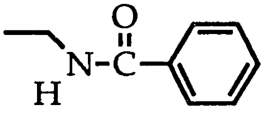


R	Z	Compound
H	Bzm	**3**
$C_6H_5CH_2$	Bzm	**7**
	H	**8**
$HO_2CC_6H_5CH_2$	Bzm	**13**
$CH_3O_2CC_6H_5CH_2$	Bzm	**19**
	H	**20**
$C_6H_5CH_2OC_6H_4O_2CC_6H_5CH_2$	Acm	**24**

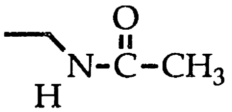
Tr =



Bzm =



Acm =



results in the isolation of compound **20** (MeOAcidaa(aet)$_2$). Unfortunately, the removal of the trityl groups to form the dithiol allows for the formation of disulfides under oxidative conditions. Other sulfur-protecting groups must be employed to prevent disulfide formation, while maintaining the ability to complex metals.

The Davison group has studied a variety of sulfur-protecting groups for N_2S_2 ligands[18, 19, 20] in relation to technetium complex formation. From these studies it has been found that the benzamidomethyl[5] and acetamidomethyl[6] groups are of great use.

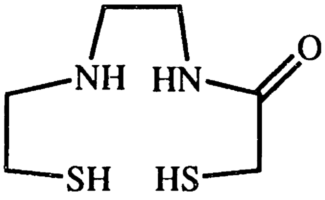
Formation of benzamidomethyl- and acetamidomethyl-protected ligands proceeds through the same reaction conditions used for the removal of the trityl group. (see Scheme 2.6) Introduction of the appropriate alcohol (benzamidomethanol[5] or acetamidomethanol[6]) to the orange trifluoroacetic acid solution results in an equilibrium between the protecting groups. Addition of triethylsilane precipitates the trityl cation and shifts the equilibrium to the amidomethyl-protected ligands. Following this procedure and using benzamidomethanol to form the benzamidomethyl protecting group, compounds **3** (Haa(aetBzm)$_2$), **7** (Bzlaa(aetBzm)$_2$), **13** (Acidaa(aetBzm)$_2$), and **19** (MeOAcidaa(aetBzm)$_2$) were made and isolated. One acetamidomethyl-protected ligand **24** (BOPOAcidaa(aetAcm)$_2$) was synthesized.

Complex Formation (see Scheme 2.7)

The technetium complexes **25** [Ph$_4$As][TcOaa(aet)$_2$] and **28** [TcOAcidaa(aet)$_2$] were synthesized by the reduction of pertechnetate (TcO_4^-) by sodium dithionite in the presence of the appropriate ligand and α-D-glucoheptonic acid. Heating for 15-30 minutes under mildly basic conditions was required for the reaction to go to completion. The addition of α-D-glucoheptonic acid was required for the formation of a stable oxobis(glucoheptonate)technetate (V) intermediate. Without the intermediate, the pertechnetate would be reduced to TcO_2, which is very stable and will not react with the ligand.

Complexes **26** [TcOBzlaa(aet)$_2$], **29** [TcOCH$_3$OAcidaa(aet)$_2$], and **31** [TcOBOPOAcidaa(aet)$_2$] were formed by the reaction of the respective ligand with sodium oxobis(1,2-ethanediolato)technetate[7, 8] in a sodium methoxide/methanol solution. The oxobis(1,2-ethanediolato)technetate anion is similar in structure to the bis(glucoheptonate) intermediate, but can be readily formed and isolated as a starting material. As with the pertechnetate reduction reactions, heat and base were required for the reaction to go to completion.

Compounds **27** [ReOBzlaa(aet)$_2$] and **30** [ReOCH$_3$OAcidaa(aet)$_2$] were synthesized by the use of a rhenium (V) starting material - oxotrichlorobis(triphenylphosphine)rhenium.[10] This complex readily reacts with deprotected ligand in methylene chloride with heating to yield the desired product. Direct reduction of perrhenate by stannous chloride and acid in the presence of an AADT ligand works as well.

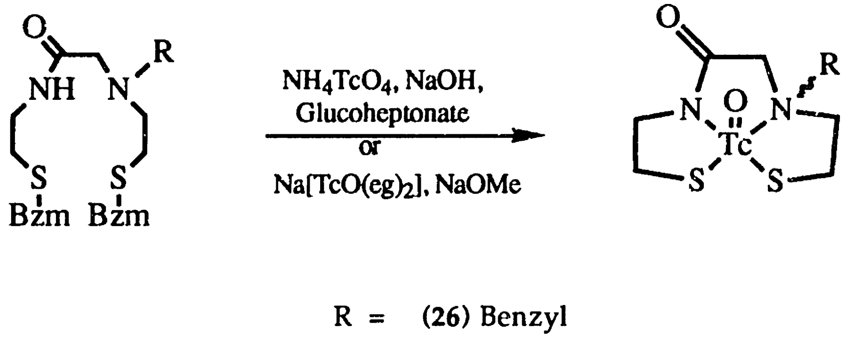


MAMA ligand

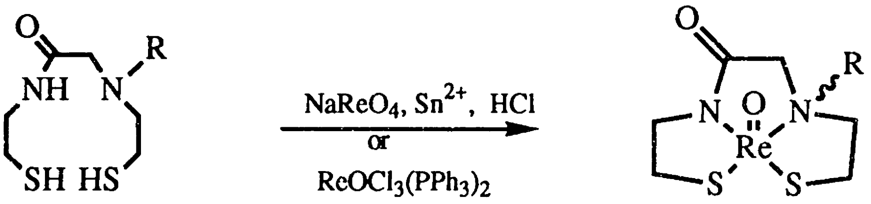
While the DADT ligands from chapter 1 formed the respective oxotechnetium complexes at room temperature, it was found that the AADT ligands required heating to at least 60°C for 15-30 minutes for reasonable yields of complex to form. This phenomenon has previously been reported by Fritzberg et al.[21], who reported some kinetic studies on a similar N_2S_2 ligand system (MAMA). No kinetic studies have been performed with the AADT ligands, but the initial results have been similar to those reported for MAMA.

While technetium is readily reduced by mild reducing agents, rhenium requires stronger reductants.[22] Sodium dithionite in base, a mild reducing agent used with technetium, does not work with rhenium. Stannous chloride in acidic media is used for the reduction of rhenium. The use of acidic medium conflicts with the use of the benzamidomethyl and acetamidomethyl protecting groups, which require nucleophilic quenching to be removed. For the case of the rhenium compounds, the deprotected AADT ligands are required for the synthetic procedures. Unfortunately, as has been mentioned previously, these deprotected ligands are readily susceptible to oxidation.

Scheme 2.7.



R = **(26)** Benzyl
(28) 4-carboxybenzyl
(29) 4-carboxybenzyl methyl ester
(31) 4-carboxybenzyl 2-(benzyloxy)phenyl ester



R = **(27)** Benzyl
(30) 4-carboxybenzyl methyl ester

Complex characterization

Table 2.V summarizes some of the important characterizational information about complexes **25 - 31**. The fast atom bombardment mass spectrometry data are indicative of the complexes as formulated. The N-benzyl compounds **26** and **27** show strong parent molecular ions and decomposition products based on loss of tropylium ion. The carboxylic acid and ester compounds show weak parent molecular ions and few decomposition products in either the positive or negative modes.

Each of the AADT complexes has infrared stretches in the 930-970 cm^{-1} range, which is indicative of a metal-oxo double bond. The rhenium-oxo stretch is 10-20 cm^{-1} higher than those seen for the technetium-oxo stretches. This higher stretching frequency has been found with other oxorhenium N_2S_2 complexes[22] and is indicative of a slightly stonger metal to oxygen bond.

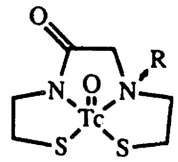
Each of the oxometal AADT complexes has two infrared absorbances within the range of the metal oxo stretch. With the DADT ligands (Chapter 1), this was due to the presence of two diastereomers. While this may be true of the AADT complexes as well, other analyses have not been conclusive (See isomer discussion).

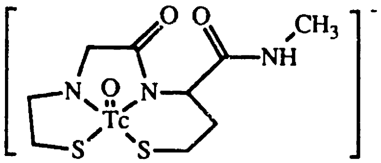
The amide carbonyl stretches of both the technetium and rhenium complexes (1640-1650 cm^{-1}) are found at lower stretching frequencies than those found with the free ligands. This shift of 20-40 cm^{-1} is indicative that the amide nitrogen is deprotonated and coordinated to the metal oxo core. No shift of the carboxylic acid or ester carbonyl stretching frequencies (1720 cm^{-1}) from those of the free ligands is noted, indicating that this functionality is not bound to the metal.

The coordination of the AADT ligands to a metal oxo core makes the methylene protons inequivalent. The location of these methylene proton resonances vary only slightly between the AADT complexes of a specific metal. Typical ^{1}H-NMR's of the methylene region for both an oxotechnetium (**26**) and an oxorhenium (**27**) AADT complex are shown in Figure 2.1.

The ^{1}H-NMR of compound **26** [TcOBzlaa(aet)$_2$] contains two AB quartets as well as 2 ABCD splitting patterns. The first AB quartet ($C\underline{H_2}CO$) is centered at 4.0 ppm (Δ(AB)=1.5 ppm, J(AB)=16 Hz). The AB quartet for the benzyl methylene protons ($C\underline{H_2}C_6H_5$) is farther downfield at 5.0 ppm (Δ(AB)=0.4ppm, J(AB)=15 Hz). The two ethylene units consisted of the more complicated splitting patterns. The

Table 2.V. Infrared and Mass Spectral Data for Compounds **25-31**.





(Patent Compound^2)

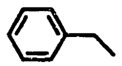
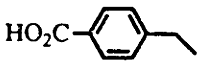
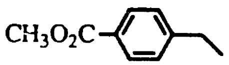
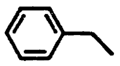
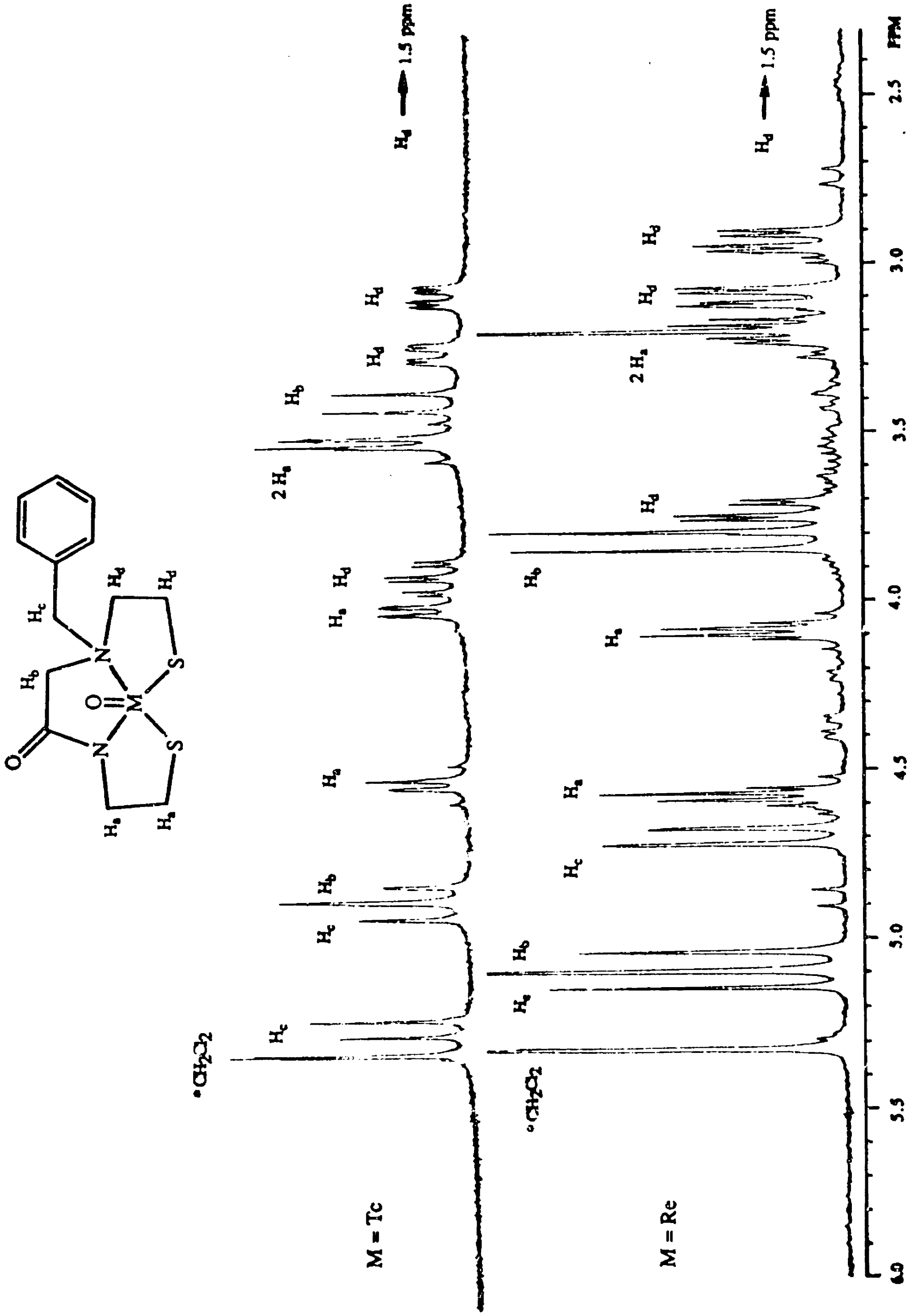
M	R	M.W.	FABMS (m/z)	IR (cm^{-1})	
Tc	Patent Compound^2	363 (anion)		ν(C=O) ν(Tc=O)	1650, 1620 920
Tc	-	305 (anion)	305 $(M)^-$		
		396 (neutral)	793 $(M_2H)^+$ 397 $(MH)^+$	ν(C=O) ν(Tc=O)	1650 (amide) 947, 932
		440 (neutral)	439 $(M-H)^-$		
		454 (neutral)	454 $(M)^+$ (minor) 220 $[(M-CH_3)H_2]^{2+}$	ν(C=O) ν(Tc=O)	1715 (ester), 1650 (amide) 948, 935
Re		484 (neutral)	485 $(MH)^+$	ν(C=O) ν(Re=O)	1650 (amide) 961, 955

Figure 2.1. ^{1}H-NMR of Compounds **26** and **27** (2.5 - 6.0 ppm).



O
N
M
S
Ha
Hb
Hc
Hd
M = Tc
M = Re
*CH2Cl2
Hc
Hb
Ha
Hd
2 Ha
Hd → 1.5 ppm
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
PPM

first ABCD pattern at 3.4 (two overlapping resonances), 3.9, and 4.9 ppm's has been assigned to the ethylene unit on the amide side of the complex (H_a's). The second ABCD pattern at 1.5, 3.0, 3.2, and 3.8 ppm's has been assigned to the remaining ethylene protons on the amine side of the ligand (H_d's).

For compound **27** [ReOBzlaa(aet)$_2$] the methylene protons show the same splitting patterns, though the chemical shifts are slightly shifted due to the differences between the two metals. The two AB quartets are at 4.4 ppm ($C\underline{H_2}C(O)$, Δ(AB)=1.2 ppm, J(AB)=16 Hz) and 4.9 ppm ($C\underline{H_2}C_6H_5$, Δ(AB)=0.4 ppm, J(AB)=14 Hz). The first ABCD resonances ($C(O)NC\underline{H_2}C\underline{H_2}S$) are at 3.2, 4.1, and 4.6 ppm's, and the second ABCD resonances ($(CH_2)_2NC\underline{H_2}C\underline{H_2}S$) are at 1.5, 2.9, 3.1, and 3.8 ppm's.

The remaining protons in each of the complexes are unaffected by the change from technetium to rhenium. The aromatic and ester resonances are in the expected ranges established for these protons. The p-substituted phenyl rings give a distinctive splitting pattern (A_2B_2) with doublets at 7.6 and 8.0 ppm.

The two ABCD patterns in each of these complexes are of the most interest. The difference in the two splitting patterns may be due to a difference in the out-of-plane bending of the two ethylene units.[23] The first ABCD pattern (with overlapping resonances) indicates a more planar environment where two of the four protons are equivalent, or similar in environments. The second ABCD pattern is indicative of a large out-of-plane bending resulting in four inequivalent protons. This difference in the ethylene units is confirmed by the crystal structures which follow. Assignment of the resonances to the specific ethylene groups was made using this structural information, and ^{1}H-NMR data from structurally related rhenium compounds reported by Katzenellenbogen.[24]

Partial Crystal Structure of Compound 26 - [TcOBzlaa(aet)$_2$].

Compound **26** [TcOBzlaa(aet)$_2$] was crystallized by diffusion of hexanes into a solution of the complex in methylene chloride. Solution of the diffraction pattern resulted in the expected electron densities assignable to the atoms in the complex, as well as some extra electron density situated on a three-fold axis. By elemental analysis it has been concluded that the excess electron density is due to a partial molecule of methylene chloride. A model of this moiety could not be designed. A PLUTO[25] drawing of compound **26** is shown in Figure 2.2, and selected bond angles and distances of this incomplete structure are shown in Table 2.VI. The $OTcN_2S_2$ core was distorted from a perfect square pyramid. The technetium atom was found to be 0.74 Å above the plane delineated by the two nitrogens and two sulfurs. The benzyl group was found syn in relation to the technetium-oxygen bond.

The Tc-N(1) (amine nitrogen) bond length of 2.19 Å is within the range normally seen for technetium-nitrogen bond lengths.[26] The Tc-N(2) bond length 1.96 Å is slightly shorter than this range, but this shorter bond length has been seen previously reported for technetium to amide nitrogen bonds.[19] The Tc-S bond lengths of 2.26 Å is also typical for technetium N_2S_2 compounds. The Tc-O(1) bond length of 1.66 Å is within the normal range and is consistent with an infrared stretch of 940 cm^{-1}. Finally, the C(3)-N(1)-C(7) bond angle of 108° is typical for sp^3 hybridization, whereas the C(4)-N(2)-C(5) bond angle of 117° is typical for sp^2 hybridization. All other bond lengths and angles are unexceptional.

Partial Crystal Structure of Compound 27 - [ReOBzlaa(aet)$_2$].

Compound **27** [ReOBzlaa(aet)$_2$] was crystallized by diffusion of hexanes into a solution of the complex in methylene chloride. Solution of the resulting diffraction pattern yielded the expected electron densities for the complex as well as some extra electron density situated on a three-fold axis. No model of this excess electron density has been developed. It is possible that this electron density is the same as that found in the crystals of compound **26**, and that no model for the moiety can be developed. A PLUTO[25] drawing of compound **27** is shown in Figure 2.3, and selected bond angles and lengths are shown in Table 2.VII. The $OReN_2S_2$ core was distorted from a perfect square pyramid. The rhenium atom was found to be 0.72 Å above the plane delineated by the two nitrogens and two sulfurs. The benzyl group was found syn in relation to the rhenium-oxygen bond.

Very few differences are found between this structure and that of compound **26**. Since the size of the rhenium atom is only slightly different from the technetium atom due to the lanthanide contraction, these results are not surprising.[22] The rhenium-oxygen bond length (1.69 Å) is found to be slightly longer than the technetium-oxygen bond length of compound **26**. This is consistent with previously reported structures.[22] All other bond lengths and angles are unexceptional.

Figure 2. 2. PLUTO drawing of [TcO(Bzlaa(aet)$_2$)] (**26**).

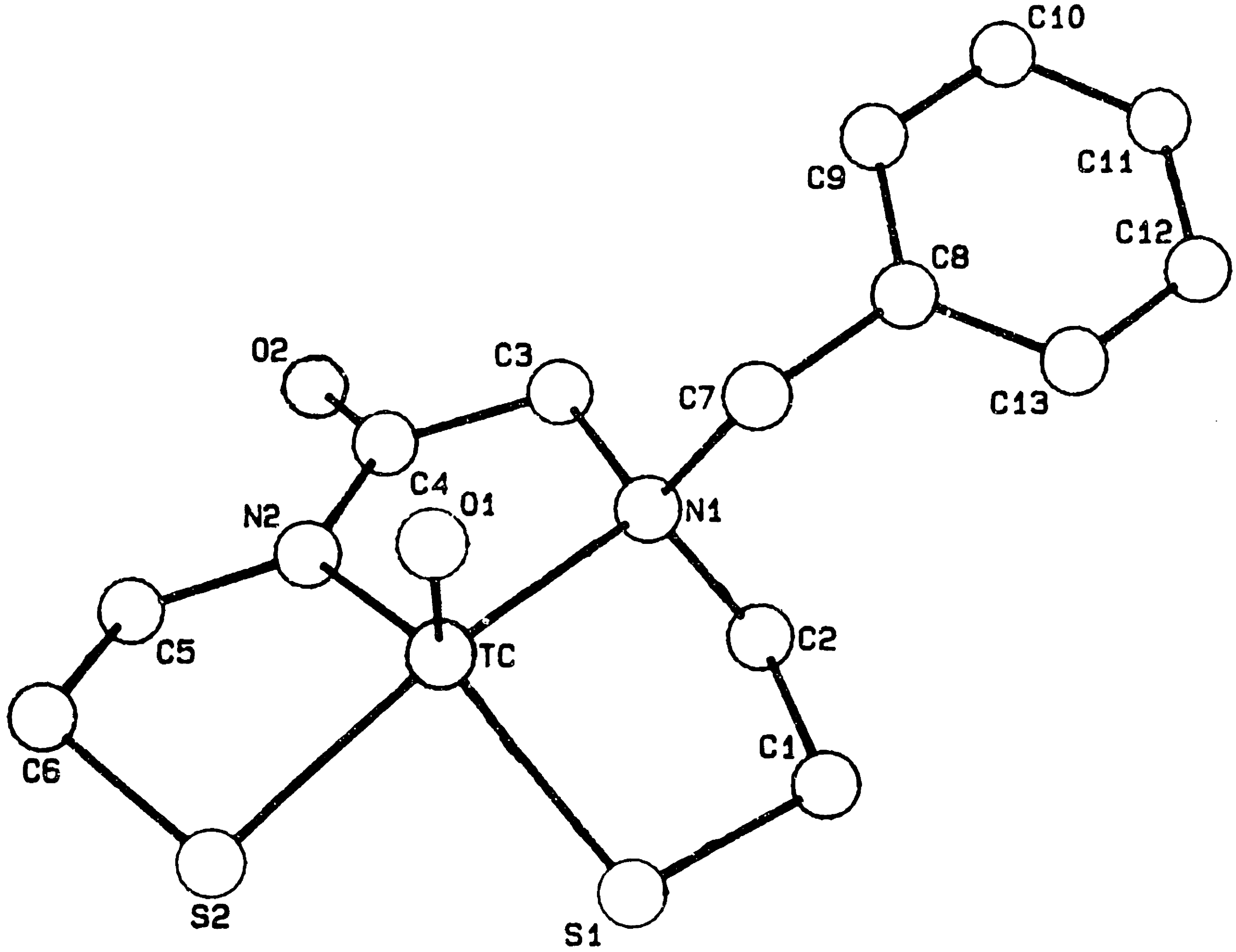

C10
C9
C11
C12
C8
O2
C3
C7
C13
C4
O1
N2
N1
C5
TC
C2
C6
C1
S2
S1

Table 2.VI. Selected bond lengths and angles for (**26**).

Bond Lengths (Å)		Bond Angles (deg)	
Tc-N(1)	2.19(1)	O(1)-Tc-S(1)	115.7(3)
Tc-N(2)	1.96(1)	O(1)-Tc-S(2)	107.4(3)
Tc-O(1)	1.663(8)	O(1)-Tc-N(1)	102.4(4)
Tc-S(1)	2.263(4)	O(1)-Tc-N(2)	118.3(5)
Tc-S(2)	2.263(4)	S(1)-Tc-S(2)	86.9(2)
N(1)-C(2)	1.51(1)	S(1)-Tc-N(1)	84.8(3)
N(1)-C(7)	1.56(1)	S(1)-Tc-N(2)	125.7(3)
N(2)-C(4)	1.33(2)	Tc-N(1)-C(3)	108.3(7)
N(2)-C(5)	1.50(2)	Tc-N(1)-C(7)	106.3(7)
		C(3)-N(1)-C(7)	108(1)
		N(1)-C(7)-C(8)	114(1)
		C(4)-N(2)-C(5)	117(1)

Estimated standard deviations in the least significant figure are given in parentheses.

Figure 2.3. PLUTO drawing of [ReO(Bzlaa(aet)$_2$)] (**27**).

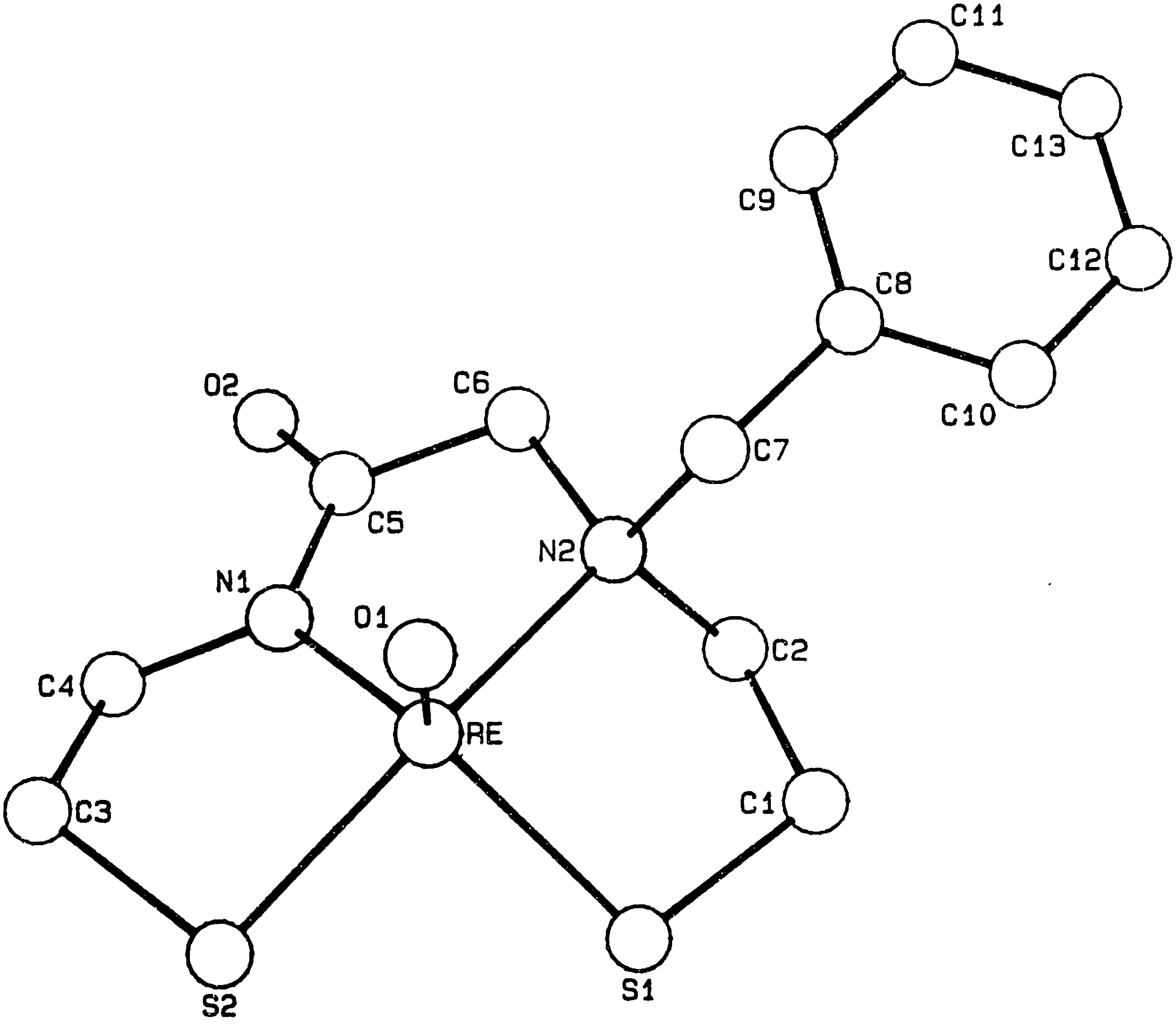

C11
C13
C9
C12
C8
O2
C6
C10
C7
C5
N2
N1
O1
C2
C4
RE
C3
C1
S2
S1

Table 2.VII. Selected bond lengths and angles for (**27**).

Bond Lengths (Å)		Bond Angles (deg)	
Re-N(1)	1.97(1)	O(1)-Re-S(1)	115.1(3)
Re-N(2)	2.18(1)	O(1)-Re-S(2)	107.5(3)
Re-O(1)	1.688(9)	O(1)-Re-N(1)	118.2(4)
Re-S(1)	2.269(4)	O(1)-Re-N(2)	100.9(4)
Re-S(2)	2.266(4)	S(1)-Re-S(2)	88.2(2)
N(1)-C(4)	1.49(1)	S(1)-Re-N(1)	126.3(3)
N(1)-C(5)	1.38(1)	S(1)-Re-N(2)	84.3(3)
N(2)-C(2)	1.53(2)	Re-N(2)-C(6)	109.7(8)
N(2)-C(7)	1.54(2)	Re-N(2)-C(7)	107.2(7)
		C(6)-N(2)-C(7)	107(1)
		N(2)-C(7)-C(8)	114(1)

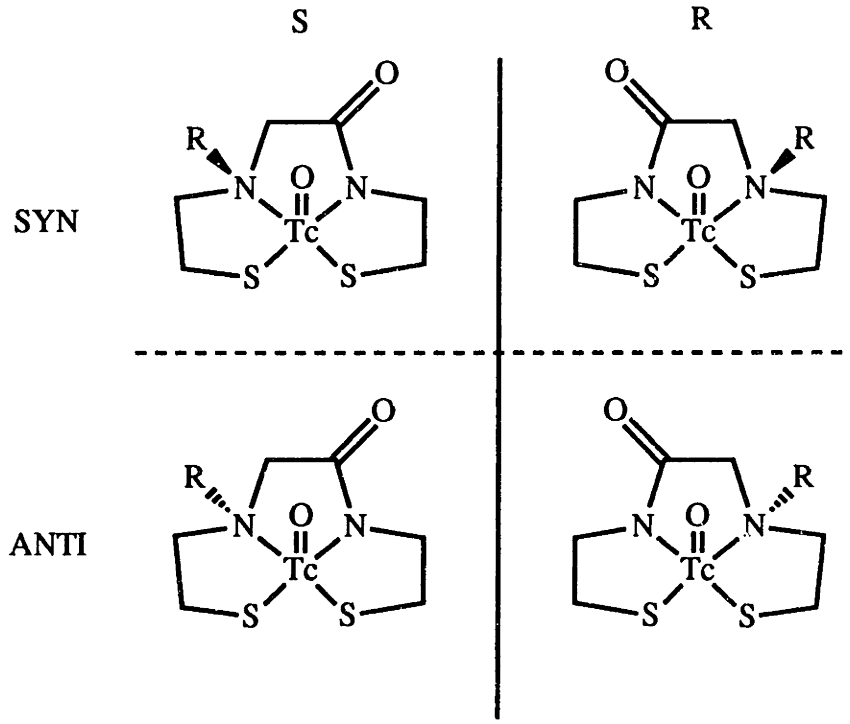
Estimated standard deviations in the least significant figure are given in parentheses.

Isomer Discussion

Within the oxo-metal AADT complexes there are four isomers which can be formed (See Figure 2.4). Two enantiomers (R and S) are formed from the quaternary amine nitrogen, and two sets of diastereomers (syn and anti) are formed by the orientation of the N-alkyl group in relation to the metal-oxygen bond. Lever[27-29] and Katzenellenbogen[24, 30] have published several articles in which they discuss the isomer distributions for oxotechnetium and oxorhenium N-alkylated diamine-dithiol (DADT) compounds. Both research groups have found that the syn set of diastereomers has a much higher yield than that of the anti set. Lever et al.[27-29], by use of a series of small alkyl groups, has found that with an increase in size of the N-alkyl group the relative yield of anti isomer decreases. The work by Katzenellenbogen et al.[24, 30] has involved the labeling of steroids with DADT complexes and the results have shown isomer distributions dependent upon the concentration of reactants.

In this work a large N-alkyl group is used. Only one set of the diastereomers (syn) of both the technetium and rhenium compounds is isolated. The infrared data in Table 2.V indicate that the anti isomers may be present for both technetium and rhenium. However, HPLC and other chromatography of compound **26** [TcOBzlaa(aet)$_2$] do not indicate that a second diastereomer is formed in any appreciable yield. The ^{1}H-NMR spectrum of the technetium complex shows no indication of a second isomer. The rhenium complex (**27**) ^{1}H-NMR spectrum (see Figure 2.1) shows what may be a second low-intensity spectrum attributable to anti isomers. Partial crystal structures show that the isolated isomers are syn.

Figure 2.4. Possible Isomers for Oxo-metal AADT Complexes


S
R
SYN
ANTI
O
R
N
N
Tc
S
S

CONCLUSION

A series of novel N-alkylated amine-amide-dithiol (AADT) ligands have been synthesized. The respective neutral oxotechnetium and oxorhenium complexes of these ligands have been synthesized and isolated.

Compared to the diamine-dithiol (DADT) ligands discussed in Chapter 1, a greater synthetic flexibility is achievable for the AADT ligands. Overall, the oxo-metal complex formation for the AADT ligands is slower than that for the DADT ligands. Heat is also required for the AADT reactions to go to completion. Though no kinetic studies were done, the results are similar to those recently reported for a different monoamine-monoamide (MAMA) ligand.[21] While the syn diastereomers of both the oxotechnetium and oxorhenium AADT complexes have been isolated and characterized, the existence of an anti diastereomer has not been ruled out.

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13. Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where: $w = 4Fo / \sigma^2(Fo^2)$

$\sigma^2(Fo^2) = [S^2 (C+R^2B) + (pFo^2)^2]/Lp^2$

S = scan rate

C = Total Integrated Peak Count

R = Ratio of Scan Time to background counting time.

B = Total Background Count

Lp = Lorentz-polarization factor

p = p-factor.

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CHAPTER 3.

NITRIDOTECHNETIUM COMPLEXES OF BIS(AMIDE)-THIOL-THIOETHER CHELATING LIGANDS

INTRODUCTION

In 1981 the first nitridotechnetium compound was reported by Baldas.[1] Since then, Baldas and others have isolated a variety of nitridotechnetium compounds.[2] With the availability of readily isolable nitridotechnetium compounds has come much speculation of the applicability of this relatively new core to radiopharmaceutical development.[3-5] Dichloronitridobis(triphenylphosphine)technetium[6] [$TcNCl_2(PPh_3)_2$], and the tetrachloronitridotechnetate anion[7] [$TcNCl_4$]$^-$ are of particular interest as starting materials due to their simple synthesis from pertechnetate.

The nitridotechnetium(V) core is isoelectronic with the oxotechnetium(V) core, but the two cores differ in overall charge. Whereas the 2- oxo ligand forms a 3+ technetium (V) core, the 3- nitrido ligand forms a 2+ technetium (V) core. This difference in charge can have an important effect upon a resulting radiopharmaceutical. Whereas some neutral compounds have been found to readily cross the blood-brain barrier, certain monocationic compounds will localize in heart tissue, and many anionic compounds localize in the kidneys.[8] By changing from an oxo- to a nitrido-technetium(V) core, the overall charge of the complex can be changed. As a result a different biodistribution can be effected while keeping similar substituents.

This work sets out to repeat some of the known oxotechnetium N_2S_2 chemistry using one of the nitrido technetium starting materials. Experiments involving mono-S-substituted N,N'-ethylenebis(mercaptoacetamide) derivatives,[9] and N,N'-ethylenebis(salicylideneimine)[10] have yielded new nitridotechnetium complexes which show similarities to their oxotechnetium analogs.

EXPERIMENTAL

CAUTION: ^{99}Tc is a weak β^{-}-emitting isotope with a half-life of 2.12 x 10^5 years. All manipulations involving technetium were carried out in laboratories approved for low-level radioactivity and the precautions followed were detailed previously[11, 12].

General. Ammonium pertechnetate was supplied as a gift by DuPont Biomedical Products. Flash chromatography was performed using either Kieselgel TLC grade silica or ICN Biomedical neutral alumina, as indicated. The column was pressurized using a hand-powered blower (Fisher). Melting points were obtained with a Mel-Temp apparatus and are uncorrected. IR spectra were measured from 4000 to 400 cm^{-1} on a Mattson Cygnus 100 FT-IR spectrometer. Potassium bromide pellets were used unless otherwise indicated. Resonance Raman spectra were recorded using a Spex double monochromator equipped with a cooled RCA 31034 photomultiplier tube and photon counting electronics. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian XL-300 spectrometer. Fast atom bombardment mass spectra (FABMS), in positive or negative mode, were measured on a MAT 731 mass spectrometer equipped with an Ion Tech B11N FAB gun operating at an accelerating voltage of 8keV. The FAB gun produced a beam of 6-8 keV xenon neutrals. Samples were dissolved in a p-nitrobenzylalcohol matrix unless indicated as triethylamine (TEA).

Literature procedures were followed for the synthesis of the following compounds: Tetraphenylarsonium nitridotetrachlorotechnetate ($Ph_4As[TcNCl_4]$),[7] N-[2-((2-(((benzoylamino)methyl)thio)acetyl)amino)-ethyl]-2-(benzylthio)acetamide,[9] N-[2-((2-thioacetyl)amino)ethyl]-2-methylthio)-acetamide,[9] N,N'-Ethylenebis(salicylideneimine).[10] Prior to use, distilled water was run through a Barnstead Ultrapure D8902 cartridge, followed by redistillation in a Corning AG-1 water still. All other chemicals were of reagent grade and used as received.

(1) - Tetraphenylarsonium nitrido[N-(2-(benzylthio)acetamido)-2-((2-thioacetylamino)-ethyl)]technetate(V) - $Ph_4As[TcN(ema(Bzl))]$

$[C_{24}H_{20}As][C_{13}H_{15}N_3O_2S_2Tc]$ MW= 383(cation) 408(anion)

To a methanol solution of tetraphenylarsonium nitridotetrachlorotechnetate (68.5 mg, 0.107 mmole) was added N-[2-((2-(benzoylthio)acetyl)amino)ethyl]-2-(benzylthio)acetamide (43.5 mg, 0.108mmole), and 0.75 ml of 25% (w/w) sodium methoxide in methanol. This solution was stirred for six hours, concentrated to a yellow oil under reduced pressure, and chromatographed (Alumina, 1-10% methanol in methylene chloride eluant gradient). A yellow band eluted which was isolated and dried *in vacuo* to yield **1** as a yellow solid. Yield 57 mg (.072 mmole, 67.3%). The product was found to be unstable in chlorinated solvents over a period of several days.

MP = slow decomposition above 200°C.

^{1}H-NMR (CD_3CN): δ 2.99 (ABCD, J^1=7Hz, 1H, $NC\underline{H_2}CH_2N$), 3.20 (AB, J(AB)= 16.3 Hz, 1H), 3.26 (AB, J(AB)=16.2 Hz, 1H,), 3.2-3.5 (overlapping multiplets, 4H, CH_2's), 3.54 (AB, J(AB)=13.6 Hz, 1H, $C\underline{H_2}C_6H_5$), 4.03 (AB, J(AB)=13.5 Hz, 1H, $C\underline{H_2}C_6H_5$), 4.32 (ABCD, J^1=6.4 Hz, J^2=2.1 Hz, 1H, $NC\underline{H_2}CH_2N$), 7.33 (m, 5H, $CH_2C_6\underline{H_5}$), 7.6-7.8 (m, 16H, $(C_6\underline{H_5})_4As$), 7.8-7.9 (m, 4H, $(C_6\underline{H_5})_4As$).

^{13}C-NMR (CD_3CN): δ 38.98 (CH_2S), 41.76 (CH_2S), 43.87 (CH_2S), 52.61 ($N\underline{C}H_2\underline{C}H_2N$), 129.07 ($CH_2\underline{C_6}H_5$), 129.69 ($CH_2\underline{C_6}H_5$), 130.71 ($CH_2\underline{C_6}H_5$), 131.91 ($(\underline{C_6}H_5)_4As$), 134.30 ($(\underline{C_6}H_5)_4As$), 135.51 ($(\underline{C_6}H_5)_4As$), 178.67 (NC=O), 179.69 (NC=O)

IR νmax 1653, 1560, 1437, 1384, 1081, 1051(Tc≡N), 754, 741, 688 cm^{-1}.

Raman ($CHCl_3$): ν(Tc≡N)=1056 cm^{-1}.

FABMS$^+$: m/z 383 $(Ph_4As)^+$.

FABMS$^-$ (TEA): m/z 408 $[TcN(ema(Bzl))]^-$ (M), 317 $(M - C_7H_7)^-$.

(2) - Tetraphenylarsonium nitrido[N-(2-(methylthio)acetamido)-2-((2-thioacetylamino)-ethyl)]technetate(V) - $Ph_4As[TcN(ema(Me))]$

$[C_{24}H_{20}As][C_7H_{11}N_3O_2S_2Tc]$ MW= 383(cation) 332(anion)

This complex was prepared by the same procedure as for (**1**), substituting N-[2-((2-thioacetyl)amino)ethyl]-2-methylthio)acetamide as the ligand. The yield was 70% of crude yellow solid.

MP = slow decomposition above 200°C.

^{1}H-NMR (CD_3CN): δ 1.64 (s, 3H, CH_3), 2.98 (ABCD, 1H, $NC\underline{H_2}CH_2N$), 3.1-3.4 (overlapping multiplets, 4H, CH_2's), 3.41 (ABCD, 1H, J^1=1.9 Hz, J^2=6.8 Hz,

$NC\underline{H}_2CH_2N$), 3.68 (AB, J=16.7 Hz, 1H, CH_2), 4.27 (ABCD, J^1=2.4 Hz, J^2=7 Hz, 1H, $NC\underline{H}_2CH_2N$), 7.6-7.8 (m, 16H, $(C_6H_5)_4As$), 7.8-7.9 (m, 4H, $(C_6H_5)_4As$).

^{13}C-NMR (CD_3CN): δ 23.5 (CH_3), 38.9 (CH_2S), 41.0 (CH_2S), 52.6 (NCH_2CH_2N), 131.9 ($(C_6H_5)_4As$), 134.3 ($(C_6H_5)_4As$), 135.5 ($(C_6H_5)_4As$), 178.7 (CO), 179.7 (CO).

IR νmax 1648, 1559, 1437, 1384, 1080, 1051(Tc≡N), 997, 740, 688 cm^{-1}.

FABMS$^+$: m/z 383 $(Ph_4As)^+$.

FABMS$^-$ (TEA): m/z 332 $[TcN(ema(Me))]^-$.

(3) - Reaction of Tetrachloronitridotechnetate(VI) with N,N'-ethylenebis(salicylideneimine) - TcN(sal_2en)

The procedure for (1) was repeated using N,N'-Ethylenebis(salicylideneimine) (sal_2en) as the ligand. The reaction produced a grey green solid in 20% unrecrystallized yield. The product was recrystallized from a methylene chloride, methanol, and ethyl ether mixture to give a black/green solid.

^{1}H-NMR (CD_2Cl_2): δ 4.8 (s, 4H, N-CH_2-CH_2-N), 6.76 (m, 2H, aromatic), 7.23 (m, 2H, aromatic), 7.32 (m, 2H, aromatic), 7.44 (m, 2H, aromatic), 8.36 (s, 2H, H-C=N).

IR νmax 1618 (C=N), 1599, 1535, 1440, 1292 (C-O), 1151, 1077 (Tc≡N), 753 cm^{-1}.

FABMS$^+$: m/z 391, 379 (major peak)$(TcN(salen))^+$, 268, 225, 219 $(TcC_7H_6NO)^+$.

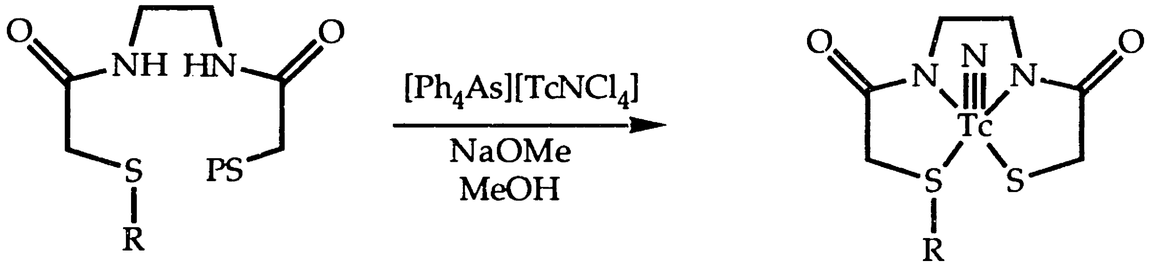
FABMS$^-$ (TEA): m/z 539 $(391 + TEA)^-$, 527 $(379 + TEA)^-$, 391, 379 $(TcN(salen))^-$, 277, 219 $(TcC_7H_6NO)^-$.

The yield of this reaction was poor. Mass spectrometry (FABMS) indicated that a second complex was formed. Further analysis was not completed due to a lack of pure products.

RESULTS AND DISCUSSION

The reaction of [Ph_4As][$TcNCl_4$] in basic methanol with N-[2-((2-(benzoylthio)acetyl)amino)ethyl]-2-(benzylthio)acetamide[9] - [(Bzl)(Bz)ema] - results in a yellow compound (**1**) which can be isolated by alumina column chromatography. The infrared spectrum shows a moderate absorbance at 1051 cm^{-1} which can be assigned as a Tc≡N stretching frequency.[13] This assignment is confirmed by a Raman resonance absorbance at the same frequency. Mass spectrometry indicates that the complex is anionic with a counterion of tetraphenylarsonium. Proton-NMR shows that the thioether moiety (a benzyl group) has not been lost during the reaction, though the benzoyl protecting group is gone. Based on this data, the compound can be formulated as a nitridotechnetium complex of a diamide-thiol-thioether ligand [Ph_4As][TcN(Bzl)ema] (see 3-1). This formulation indicates that a one electron reduction from technetium(VI) to technetium(V) occurs during the reaction.

(3-1)



1	$R = CH_2C_6H_5$	$P = COC_6H_5$
2	$R = CH_3$	$P = H$

Repeating the above reaction but replacing the ligand with N-[2-((2-thioacetyl)amino)ethyl]-2-methylthio)acetamide[9] - [(Me)(H)ema] - yields another yellow anionic complex (**2**) - [Ph_4As][TcN(Me)ema] (see 3-1). Compound **2** shows few spectroscopic differences from compound **1**. The major differences occur in the NMR and mass spectral results.

When these nitridotechnetium complexes are compared with the analogous oxotechnetium work done by Bryson,[9] few major differences can be noted. Both reactions give products with technetium in the +5 oxidation state; thus, while the oxo complexes are neutral, the nitrido complexes are monoanionic. A comparison of spectroscopic data can be seen in Table 3.I.

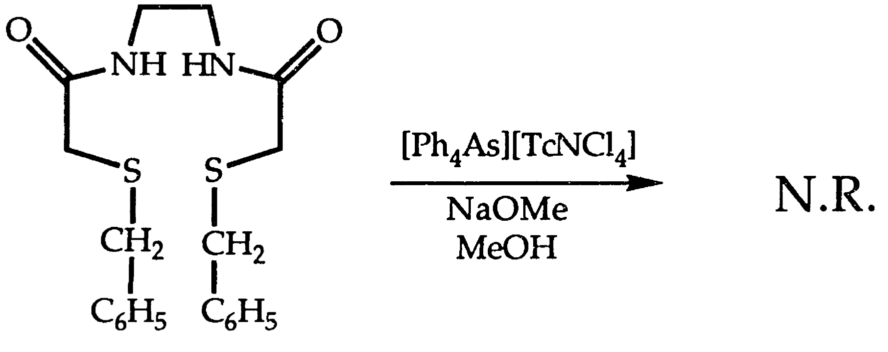
However, the chemistry of the nitrido compounds is not as simple as it would seem. First, the formation reactions are strongly dependent upon the stoichiometry of the reaction mixture. With either an excess or a deficiency of the ligand, a lowered yield of product was seen. Second, decomposition of the nitridotechnetium N_2S_2 compounds occurred under a variety of conditions. The use of silica, rather than alumina, during flash chromatography led to partial decomposition of the products. Decomposition was also noted during long-term exposure of the complexes to methylene chloride or acidic media.

Neutral complexes

The mono-functionalized EMA compounds used to form compounds **1** and **2** are trinegative when deprotonated, thus yielding an anionic complex with the nitridotechnetium (+2) core. The use of a dinegative chelating ligand should yield a neutral nitridotechnetium complex. There has been much interest in neutral complexes of technetium due to their possible applications in radiopharmaceutical development.[14]

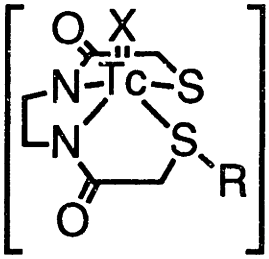
The reaction of 1,2-ethylenebis[(benzylthio)acetamide], a possible dinegative ligand, with $[Ph_4As][TcNCl_4]$ was tried (see 3-2). The expected product was the neutral nitridotechnetium bis(benzylthioether) complex $[TcN(Bzl)_2ema]$. Using reaction conditions analogous to those used for **1** and **2**, only starting materials were isolated.

(3-2)



A second reaction with a dinegative ligand was tried. Reaction of the Schiff's base compound ethylenebis(salicylideneimine)[10] (sal_2en) with $[Ph_4As][TcNCl_4]$

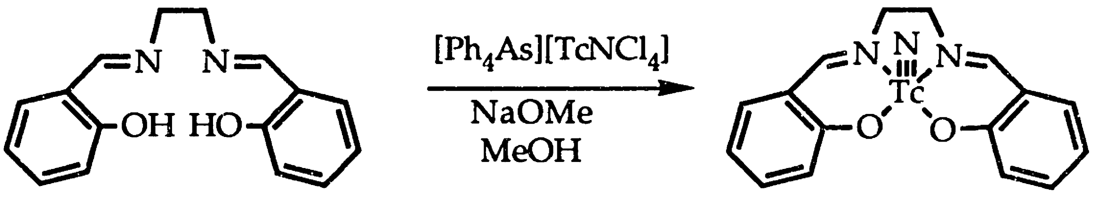
Table 3.I. Spectroscopic Data for Technetium (ema-R) Complexes



R	X	IR (cm^{-1}) (KBr)	Raman (cm^{-1}) ($CHCl_3$)	Positive FAB MS	Negative FAB MS
Methyl[9]	O	958 (vTc=O) 1631 (vC=O)		335 MH^+	
Methyl	N	1051 (vTc≡N) 1648 (vC=O)		383 Ph_4As^+	332 M^-
Benzyl[9]	O	949 (vTc=O) 1651 (vC=O)		411 MH^+ 321 $[TcO(ema)]H_2^+$ 319 $[TcO(ema)]^+$	
Benzyl	N	1051 (vTc≡N) 1653 (vC=O)	1056 (vTc≡N)	383 Ph_4As^+	408 M^- 317 $[TcN(ema)]^-$

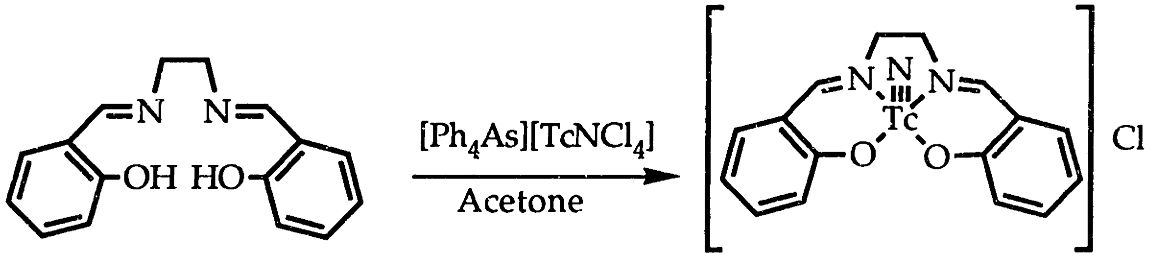
yields a black/green solid in less than 10% yield. (see 3-3) An infrared absorbance at 1077 cm^{-1} can be assigned to the Tc≡N stretch. An appropriate NMR spectrum of the complex was obtained, and mass spectral results show a parent ion peak for [TcN(sal$_2$en)]. However, there are several unassignable peaks within the mass spectrum.

(3-3)



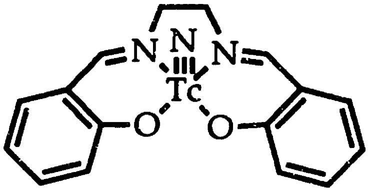
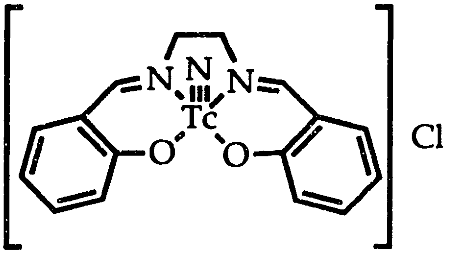
Pietzsch[15] has reported the synthesis of a different nitridotechnetium complex of sal$_2$en. Pietszch reacts $Bu_4N[TcNCl_4]$ and sal$_2$en in acetone with stirring (see 3-4) to yield a bright green complex which has been characterized as [TcNsal$_2$en]Cl by elemental analysis, ultraviolet and infrared spectroscopies, and EPR (T=130 K).

(3-4)



A comparison of (3) with [TcNsal$_2$en]Cl (see Table 3.II) indicates that the two compounds are not the same. There is no infrared absorption at 1037 cm^{-1} for (3). Also [TcNsal$_2$en]Cl does not yield an NMR spectrum while (3) does. The colors of the two compounds, while both being described as green, are quite different.

Table 3.II. Comparison between **3** and the compound reported by Pietszch[15].

	 Compound **3**	 Pietszch's Compound[15]
Color	Dark green	Bright Green
Infrared (KBr, cm^{-1})	1618 (νC=N) 1077 (νTc$\equiv$N)	1610 (νC=N) 1037 (νTc$\equiv$N)
NMR	Yes	No
EPR	No	Yes

Reduction

Within reactions **1** and **2** there is a one electron reduction from the technetium (VI) starting material to the technetium (V) products. This reduction-substitution route has been noted by other researchers working with the nitridotechnetium core.[3,18] There are three important aspects of this reduction which should considered in relation to the work presented here. First the yields of the N_2S_2 reactions (**1** and **2**) are highly dependent on the ligand to technetium stoichiometry. Second, the Schiff base reaction (**3**) proceeds in much lower yield than **1** or **2**, even though reaction conditions are the same. Third, the reaction of a bis(amide)bis(thioether) compound (N,N'-ethylenebis[(benzylthio)acetamide])[9] (see 3-2) under the same reaction conditions yields starting materials and decomposition products. These three observations can be taken as an indication that the majority of the one electron reduction proceeds through the oxidation of N_2S_2 ligand to disulfides. Thus reactions **1** and **2** proceed in 50-60% yields. The reaction of the bis(thioether) (see 3-2), which does not contain any free thiols, proceeds poorly since the technetium cannot be reduced by formation of disulfides. Finally, the reaction of the Schiff's (3-3) base proceeds poorly for similar reasons, though it has also been found to form a more stable compound in a different oxidation state.

Decomposition

Decomposition of the resulting N_2S_2 nitrido complexes in acidic media and chlorinated solvents has been noted. Previously Bryson[9] reported problems due to loss of the thioether moiety with the oxo complexes. Reports of thioether cleavage[16] in the presence of free radicals can possibly explain the stability problems in methylene chloride. Instabilities of nitrido technetium compounds in varying pH's have also been reported.[17]

CONCLUSION

While there has been some previous work involving nitrido technetium complexes in relation to radiopharmaceuticals,[3-5,7] the current research indicates that the tetradentate ligands used in this work (ema(R) and salen) are not providing practical radiopharmaceuticals. First, while the yields of (**1**) and (**2**) are good, the reactions are highly dependent upon stoichiometry. The yield of (**3**) is very small, seemingly due to its stability at a higher oxidation state and lack of reductant to reduce the nitridotechnetium core. Second, the instabilities of all of these nitridotechnetium complexes to pH changes and radical cleavage conditions are undesirable for biological uses. While a variety of stable nitridotechnetium complexes have been reported, the tetradentate N_2S_2 ligands seem to be a poor choice for chelation with this metal core (see also Tisato[18]). However, reports of other possible technetium starting materials[19, 20] warrant the study of N_2S_2 ligands with these new cores.

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APPENDIX I.

PEPTIDE COUPLING REACTIONS OF AADT COMPLEXES

INTRODUCTION

It has long been a goal of technetium chemists to develop a simple procedure for radiolabeling biological molecules. Since the early 1960's many attempts have been made with few successes[1]. Two types of approaches towards radiolabeling of molecules with technetium have developed from this work.

The first approach has been classified as direct labeling[2]. In direct labeling pertechnetate (TcO_4^-) is reduced in the presence of a peptide to yield a radiolabeled moiety. Unfortunately, the technetium is usually in a variety of oxidation states and binding sites. Subsequent *in vivo* biodistribution studies are inconclusive since a variety of biodistributions (including that of unbound technetium) are usually seen.

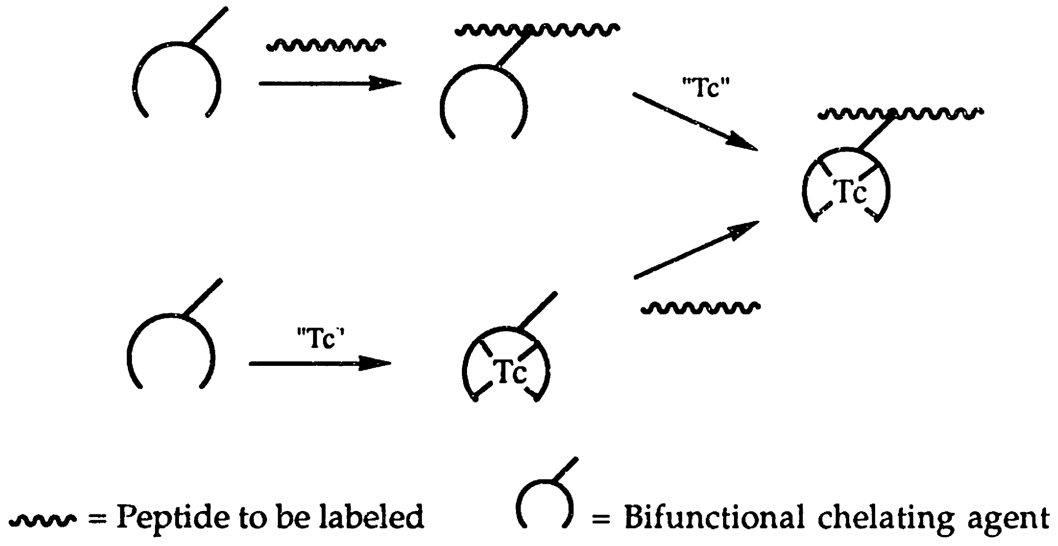
The second labeling technique has been classified as indirect labeling.[2] In this procedure a specific chelation site for the technetium is designed and employed in a known way on the biological molecule. This procedure is usually employed through the use of a bifunctional chelating agent (BCA).[3, 4] A BCA is an organic molecule containing two functionalities: the first is a stable metal chelation site, the second is a site capable of binding to a biological molecule. The use of such an agent should limit the technetium to one oxidation state and one binding site on the molecule.

Fritzberg[2, 5] has compared the efficacy of two different indirect labeling procedures (see A1-1). In the first study the BCA was first bound to the biological molecule, and then reacted with technetium. While this procedure yielded better results than the direct labeling procedure, there was still some non-specific binding and subsequent loss of radiolabel *in vivo*. Fritzberg's second study[5] involved the chelation of technetium with the BCA followed by binding to the biological molecule. Subsequent purification was relatively simple, and useful *in vivo* studies were performed.

There are, however, many other concerns besides binding site that must be considered when developing new radiolabeling procedures.[6] The overall charge of the chelation complex used for radiolabeling can be important due to its effect on biodistribution. Many technetium BCA complexes which have been developed to date have yielded charged complexes[5, 7, 8]. Development of neutral BCA's, such as Lever's[9, 10], is thought to be better in order to limit any such effects[6].

The formation of complex isomers is always a concern in radiopharmaceutical development. Recent studies[11, 12] have shown that two types of diastereomers (syn and anti) which can form from complexation have different

(A1-1)



biodistributions. The C-alkylated N_2S_2's such as those used by Fritzberg give a 50:50 yield of syn vs anti isomers.[13] Lever, however, has shown that the implementation of N-alkyl groups dramatically increases the yield of the syn isomer.[14, 15]

Intramolecular attack at the sixth coordination site (trans to the oxo group) has been shown to be a viable possibility. Structures of a bis(penicillaminato) oxotechnetium compound have shown that carboxylic acids will interact with the technetium core under the right steric conditions.[16, 17] Sterically hindered groups may be required to prohibit such interactions.

Finally there is the question of enzymatic cleavage in the body. Loss of radiolabel can proceed through biological cleavage of the linker employed, as well as the loss of non-specific radiolabel. The use of a linker which does not occur in nature should avoid this problem.

The use of the para-substituted benzoic acid linker on a bifunctional chelating agent solves many of the problems listed. The steric bulk of the benzyl group presumably prohibits any intramolecular interaction. The benzyl group also seems to limit the yield of anti isomers in a manner similar to that seen by Lever[14, 15]. The N-alkyl N_2S_2's yield neutral complexes. The benzamide linker which results from peptide coupling does not occur in nature, and thus should not be susceptible to biological cleavage.

The benzoic acid and benzoic acid ester derivatives of the AADT ligands and resulting complexes from Chapter 2 were used in a series of peptide coupling reactions in order to synthesize benzamide derivatives.

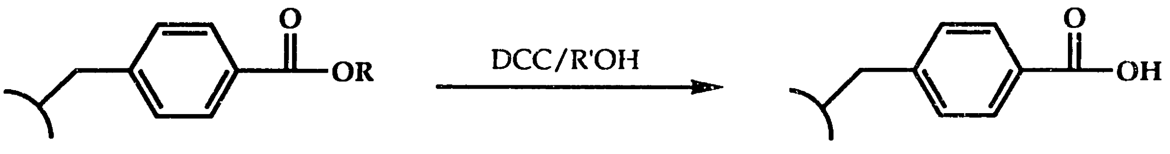
RESULTS AND DISCUSSION

The para-substituted benzoic acid functionality was first developed in Chapter 1 with the diamine-dithiol (DADT) N_2S_2's. Unfortunately, the synthetic conditions required for the development of the DADT ligands were not favorable for the incorporation of a carboxylic acid functionality. Protection of the carboxylic acid as a 4,4-dimethyloxazoline lead to the desired precursor, but the protecting group was not found to be removable from either the ligand, or the technetium complex, by the procedures described by Meyers et al.[18, 19] These results led to the development of an amine-amide-dithiol ligand (AADT) system

Similar para-substituted benzoic acid functionalities were developed with this more synthetically flexible AADT system. Syntheses of the desired ligands, as well as the respective oxotechnetium complexes, are described in Chapter 2. Heating was required for the formation of the complexes, and only the syn isomers have been isolated.

Esterification and transesterification of the acid and methyl ester derivatives of both the free ligands and the technetium complexes were attempted. A variety of peptide coupling reagents and amines have been tried in the formation of benzamide derivatives. Dicyclohexylcarbodiimide couplings aided by N-hydroxysuccinimide, 2-hydroxypyridine, or pentafluorophenol were attempted. Use of 4-(dimethylamino)pyridine as a coupling agent was also attempted. Coupling reactions were tried with both the para-substituted benzoic acid ligand and the technetium complex to no avail. Transesterification reactions with the methyl esters yielded relatively insoluble products and/or starting materials. The majority of isolable product from most of these reactions was the respective para-substituted benzoic acid (see A-2).

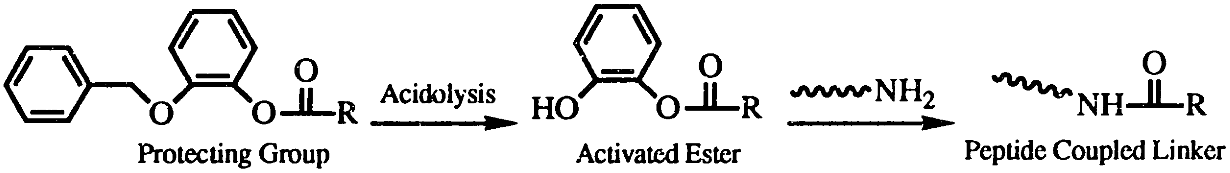
(A1-2)



R = H, CH_3 R' = Activating group

A second carboxylic ester (2-(benzyloxy)phenyl)was developed. The 2-(benzyloxy)phenyl ester has been found to be useful as a dual functional group [20- 22]. By this it is meant that the 2-(benzyloxy)phenyl group can be used as both a carboxylic acid protecting group, and an activating ester. As the 2-(benzyloxy)phenyl ester it is very stable to many reaction conditions. Subsequent acidolysis will remove the benzyl group and leave a 2-hydroxyphenyl (catechol) ester which acts as an activating group (see A-3).

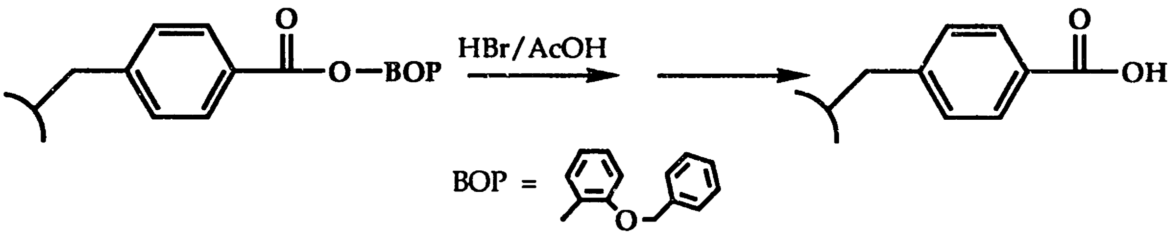
(A1-3)



Acidolysis of the 2-(benzyloxy)phenyl ester AADT ligand in hydrobromic acid/acetic acid with subsequent reaction with amines did not yield any of the desired benzamide products. Reactions with oxotechnetium compounds yielded insoluble products. By chromatographic and other techniques it is concluded that the ester functionalities have been lost to form the respective para-substituted benzoic acid and some unknown products.

The activated intermediate, the 2-hydroxyphenyl ester, was never isolated. While it is probably formed, reaction conditions seem to result in its loss to form the benzoic acid (see A1-4).

(A1-4)



CONCLUSION

Synthesis of the desired starting materials was outlined in Chapter 2. Subsequent attempts at activation and peptide coupling reactions of several para-substituted benzoic acid and acid ester derivatives of AADT ligands and TcOAADT complexes failed. No indications of benzamide formation were found.

A 2-(benzyloxy)phenyl ester was synthesized to make use of its dual functionality.[22] Loss of the benzyl protecting group to form the activated catechol ester yielded insoluble products which included the respective carboxylic acid.

It is concluded from the attempted reactions that the para-substituted benzoic acids are not reactive enough for the use of peptide coupling techniques. The acid esters seem to deesterify readily, and the formation of esters from the carboxylic acid does not proceed.

Overall the benzylic-AADT ligands solve many of the problems outlined in the introduction. Unfortunately the peptide coupling chemistry does not work. Future work with the AADT system should involve the study of other possible linkers. By the work summarized here, it is best to avoid aromatic carboxylic acids.

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APPENDIX II.

PARTIAL X-RAY CRYSTAL STRUCTURE OF [TcO(BZL-DADT)].

INTRODUCTION

An attempt was made to perform a single crystal x-ray structure determination of [TcO(BzlDADT)]. Due to disorder in the structure the data set would not refine; however, there is enough structural information available to determine which isomer was isolated.

EXPERIMENTAL

CAUTION: ^{99}Tc is a weak β-emitting isotope with a half-life of 2.12×10^5 years. All manipulations involving technetium were carried out in laboratories approved for low-level radioactivity and the precautions followed were detailed previously[1, 2].

Single crystal X-ray structure determination of [TcO(BzlDADT)][3].

Red/brown needles were formed by diffusion of hexanes into a methylene chloride solution of [TcO(Bzl-DADT)]. The crystal was monoclinic with space group I2/a. (crystal data a = 24.586 (2)Å, b = 7.045 (5)Å, β = 111.46°, V = 3821 Å^3, Z = 8) X-ray data was collected at room temperature on an Enraf-Nonius CAD4F-11 κ-geometry diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically.

RESULTS AND DISCUSSION

Upon refinement a large amount of disorder was found with the benzyl carbons. The structure is of poor quality and can only be used to indicate the location of the benzyl group in relation to the oxygen to technetium bond. PLUTO diagrams of the structure are shown in Figures A2.1 and A2.2. The benzyl group is syn in relation to the oxygen to technetium bond.

Figure A2.1. PLUTO drawing of [TcO(Bzl-DADT)].

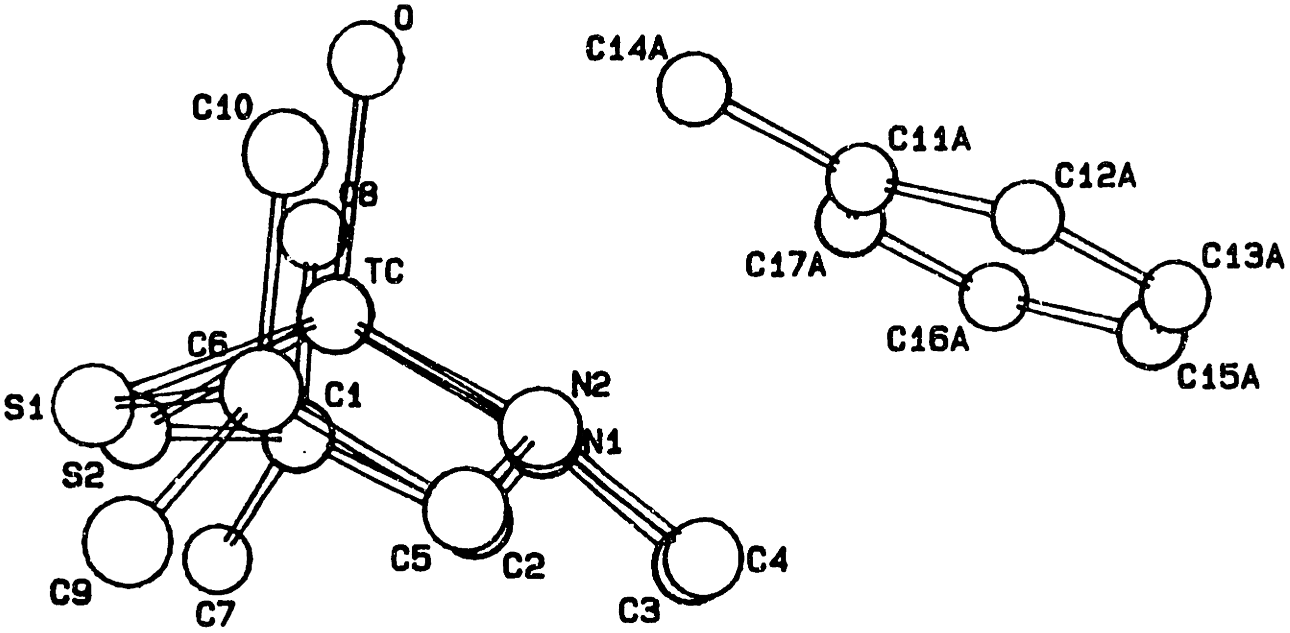
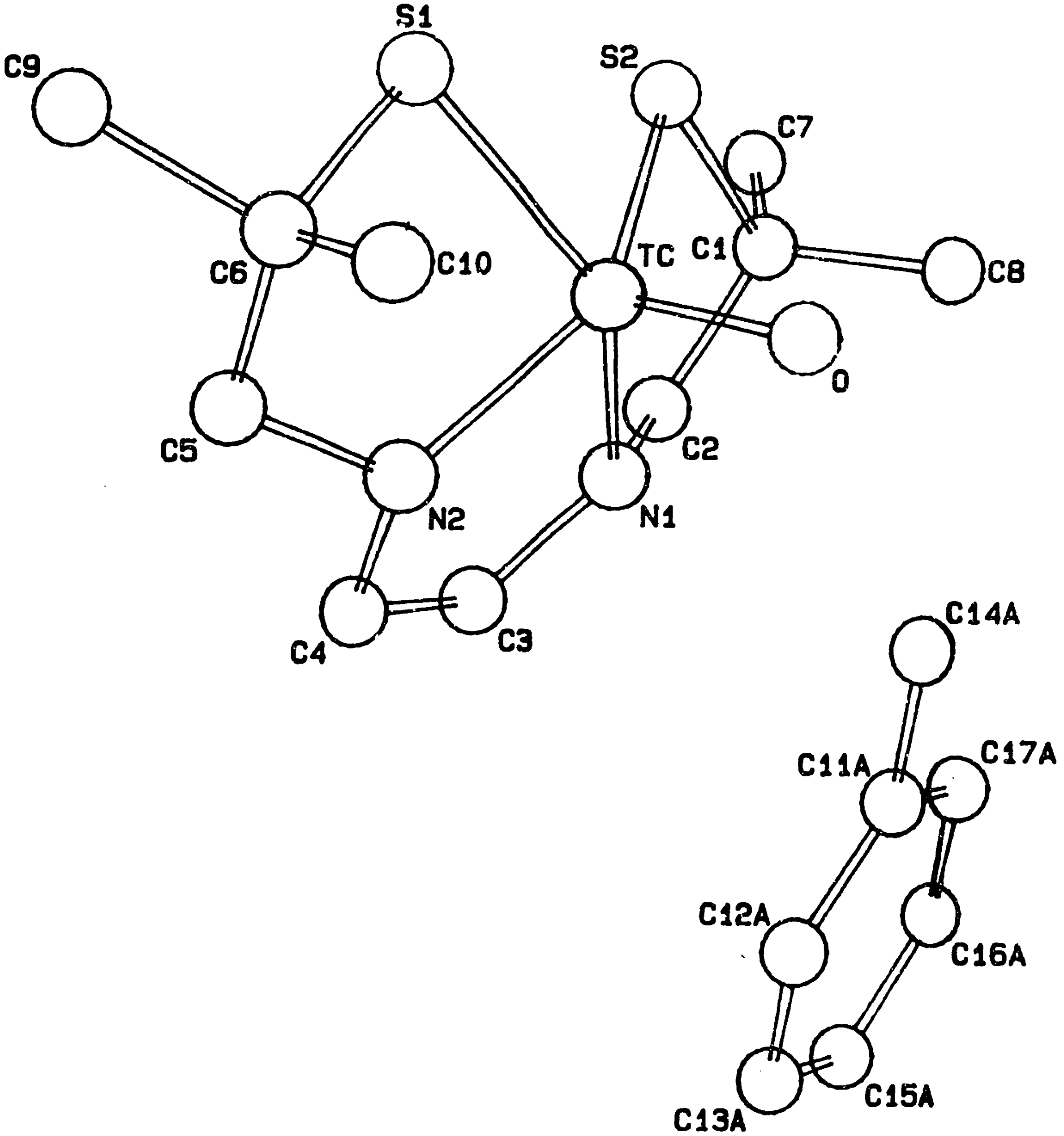

O
C14A
C10
C11A
C12A
C8
C17A
TC
C13A
C16A
C6
C15A
S1
C1
N2
N1
S2
C5
C2
C4
C9
C7
C3

Figure A2.2. PLUTO drawing of [Tco(Bzl-DADT)].


S1
C9
S2
C7
TC
C1
C6
C10
C8
O
C5
C2
N2
N1
C4
C3
C14A
C11A
C17A
C12A
C16A
C15A
C13A

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3. The synthesis of [TcO(BzlDADT)] is described in Chapter 1.

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Thanks go to Bill Davis for the crystallographic work, and for trying to teach me to solve crystal structures. Cathy Costello and Chen-hui Zeng supplied the mass spectra which helped characterize many of the compounds. Many thanks to the Spectroscopy Lab for keeping the instruments running, and solving many technical problems.

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I owe a great debt to my parents and brothers for helping make me what I am today. I hope that this is what they were expecting. Finally I would like to thank Penny for her support through thick and thin, for our many phone conversations, and for introducing me to coffee.

BIOGRAPHICAL NOTE

The author was born on July 29, 1965 in Somerville, New Jersey. He spent his early years growing up in Basking Ridge, New Jersey. At age 10 he and his family moved to Lancaster, Pennsylvania, where he graduated from Manheim Township High School in 1983. He did undergraduate research under the supervision of Professor Charles Kraihanzel at Lehigh University and graduated with a Bachelor of Science in chemistry with honors in 1987. He immediately went on to MIT and did his graduate thesis under the supervision of Professor Alan Davison, completing a Doctor of Philosophy in inorganic chemistry in 1991. On November 2, 1991 he will marry his fiancée of three years Penny Lynn Shultz, whom he met in high school. The author has accepted a Customer Support position with Cambridge Scientific Computing, and plans to stay in the Boston area.