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Rhenium and Technetium Complexes with Pentadentate Thiocarbamoylbenzamidines: Steps toward Bioconjugation

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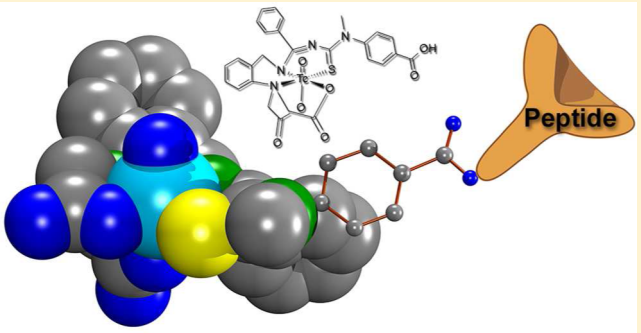
Supporting Information

ABSTRACT: Thiocarbamoylbenzimidoyl chlorides, PhC(Cl)=N−(C=S)−NR^1R^2, react with 2-(iminodiacetic acid)-benzylamine under formation of the potentially pentadentate ligands H_3L (R^1, R^2 = Et) and H_3L−COOEt (R^1 = Me, R^2 = C_6H_4-4-COOEt) in high yields. Hydrolysis of H_3L−COOEt in NaOH/MeOH gives quantitatively another benzamidine ligand H_3L−COOH. The novel ligands readily react with $(NBu_4)[MOCl_4]$ (M = Re, Tc) under formation of stable complexes with the general composition [MO(L)], in which they are triply deprotonated and fully occupy the remaining five coordination positions of the $\{MO\}^{3+}$ cores. In a "proof-of-principle" reaction for possible bioconjugations, the complex [ReO(L−COOH)] has been labeled with triglycine ethyl ester in high yields.



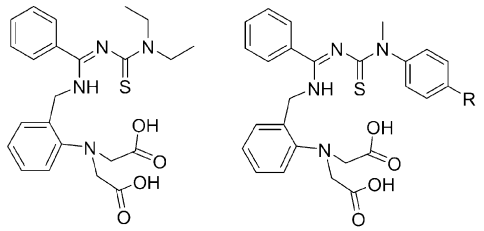
INTRODUCTION

Technetium and rhenium are important in the field of nuclear medicine due to the availability of radioisotopes suitable for diagnostic radiopharmaceuticals (^{99m}Tc: γ-emitter, Eγ = 140 keV, $t_{1/2}$ = 6.0 h),[1,2] or potential therapeutic agents for various forms of cancer or arthritis (^{186}Re and ^{188}Re: both β^--emitters with $t_{1/2}$ of 89.3 and 17.0 h, respectively).[3] Thus, thermodynamically stable and/or kinetically inert technetium and rhenium complexes, which do not undergo easy ligand exchange reactions in the plasma, are of constant interest for the development of new radiopharmaceuticals.[4] In this scene, pentadentate ligand systems would be perfectly suitable for the complexation of the common $\{Re^VO\}^{3+}$ and $\{Tc^VO\}^{3+}$ cores, which can easily be obtained by the reduction of $[MO_4]^-$ ions available from the commercial generator systems. Surprisingly, only a few examples of oxidotechnetium(V) or -rhenium(V) complexes with pentadentate ligands are hitherto structurally well characterized.[5−9] This may be understood by the facts that the syntheses of pentadentate ligands are frequently time-consuming procedures and the targeted oxido cores request systems with preferably oxygen donors for coordination in *trans* position of the normally *trans*-labilizing O^{2-} ligands.

Recently, we have reported a series of multidentate benzamidine ligands, which are formed in relatively simple reactions between benzimidoyl chlorides and functionalized primary amines.[10,11] Thus, the synthesis of pentadentate systems via reactions of benzimidoyl chlorides and potentially tetradentate ligands having a terminal primary amine group could be a very facile approach. Additionally, our interests in this type of ligand are due to the flexibility of modifications in their periphery.[12,13] This fact may play a role when the obtained technetium and rhenium complexes shall be used as chelating sites in conjugates with biologically targeting molecules, which rapidly and efficiently transport the radionuclides to the biological target.

In the present work, we describe the syntheses of novel pentadentate dialkylamino(thiocarbonyl)benzamidine ligands (Chart 1) and some of their rhenium and technetium complexes. The modification of the ligand sphere with an additional carboxylic group and the examination of a coupling reaction of the rhenium complex using triglycine ethyl ester are also demonstrated.

Chart 1. Ligands Used in This Work



H_3L

H_3L-COOEt : R = COOEt
H_3L-COOH : R = COOH

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EXPERIMENTAL SECTION

Materials. All chemicals used in this study were reagent grade and used without further purification. Solvents were dried and used freshly distilled unless otherwise stated. $(NBu_4)[ReOCl_4]$ and $(NBu_4)[TcOCl_4]$ were prepared by standard procedures.[14,15] The synthesis of the *N,N*-[(diethylamino)(thiocarbonyl)]benzimidoyl chloride was performed by the standard procedure of Beyer et al.[16] *N*-(*tert*-Butoxycarbonyl)-2-aminobenzylamine (**1**) was synthesized following the literature procedure,[17] except that the purification was carried out by recrystallization from CH_2Cl_2/*n*-hexane.

Radiation Precautions. ^{99}Tc is a weak β^--emitter. All manipulations with this isotope were performed in a laboratory approved for the handling of radioactive materials. Normal glassware provides adequate protection against the low-energy beta emission of the technetium compounds. Secondary X-rays (bremsstrahlung) play an important role only when larger amounts of ^{99}Tc are used.

Physical Measurements. Infrared spectra were measured as KBr pellets on a Shimadzu FTIR spectrometer between 400 and 4000 cm^{-1}. NMR spectra were taken with JEOL 400 MHz and Bruker 500 MHz multinuclear spectrometers. ESI mass spectra were measured with Agilent 6210 ESI-TOF (Agilent Technology) and LTQ Orbitrap XL (Thermo Scientific) mass spectrometers. All MS results are given in the form: *m*/*z*, assignment. Elemental analyses of carbon, hydrogen, nitrogen, and sulfur were determined using a Heraeus vario EL elemental analyzer. The ^{99}Tc values were determined by standard liquid scintillation counting.

Syntheses of the Ligands. *N-(tert-Butoxycarbonyl)-2-(aminodiacetic acid diethyl ester)benzylamine (**2**).* *N*-(*tert*-Butoxycarbonyl)-2-aminobenzylamine (**1**) (8.891 g, 40 mmol), ethyl bromoacetate (13.8 mL, 125 mmol), *i*-Pr_2EtN (27.8 mL, 160 mmol), and finely powdered KI (1 g) in toluene (150 mL) were heated under reflux for 48 h. After being cooled to room temperature, water (50 mL) was added. The two layers were separated. The aqueous phase was extracted with toluene (50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual was heated at ca. 80 °C under a pressure of 20 mmHg for 4 h to remove the remaining ethyl bromoacetate. The obtained yellow oil, which contained mainly the diester **2** and traces of ethyl bromoacetate, was used in the next step without further purification. Yield is about 95% (14.989 g).

Anal. Calcd for $C_{20}H_{30}N_2O_6$: C, 60.9; H, 7.7; N, 7.1. Found: C, 61.5; H, 7.7; N, 7.0. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 1.13 (t, *J* = 7.1 Hz, 6H, $OCH_2\underline{CH_3}$), 1.36 (s, 9H, CH_3), 3.90 (s, 4H, NCH_2CO), 4.05 (q, *J* = 7.1 Hz, 4H, $O\underline{CH_2}CH_3$), 4.31 (d, *J* = 5.9 Hz, 2H, $\underline{CH_2}NH$) 6.12 (s, br, 1H, NHCO), 7.01 (t, *J* = 7.5 Hz, 1H, C_6H_4), 7.14 (t, *J* = 7.7 Hz, 1H, C_6H_4), 7.22 (d, *J* = 7.7 Hz, 1H, C_6H_4), 7.25 (d, *J* = 8.0 Hz, 1H, C_6H_4).

*N-(tert-Butoxycarbonyl)-2-(aminodiacetic acid)benzylamine (**3**).* Compound **2** (7.889 g, 20 mmol) and NaOH (2.400 g, 60 mmol) in 50 mL of MeOH were stirred at room temperature for 24 h, and then the reaction mixture was evaporated to dryness in vacuum. The remaining solid was dissolved in 50 mL of cold brine solution, and cold HCl (6 M) was slowly added. The temperature was kept at 5−10 °C during this procedure until a pH of 6 was obtained. The product was extracted with THF (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated in vacuo to dryness. The obtained residue was recrystallized from $CHCl_3$ to give the pure product as a colorless solid. Yield 70% (4.737 g).

Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.8; H, 6.5; N, 8.3. Found: C, 56.2; H, 6.5; N, 8.1. IR (KBr, cm^{-1}): 3394 (s), 3124 (br, s), 1755 (vs), 1705 (vs), 1662 (vs), 1523 (s), 1488 (m), 1454 (m), 1392 (m), 1369 (m), 1303 (m), 1253 (s), 1212 (s), 1184 (s), 1049 (m), 972 (m), 856 (m), 779 (m), 682 (m), 590 (m). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 0.900 (s, 9H, CH_3), 3.41 (s, 4H, NCH_2CO), 3.80 (s, 2H, $\underline{CH_2}NH$), 6.20 (s, br, 1H, NHCO), 6.52 (t, *J* = 7.4 Hz, 1H, C_6H_4), 6.66 (t, *J* = 7.6 Hz, 1H, C_6H_4), 6.73 (d, *J* = 7.6 Hz, 1H, C_6H_4), 6.80 (d, *J* = 7.9 Hz, 1H, C_6H_4). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): 28.76 ($C(\underline{C}H_3)_3$), 40.45 ($N\underline{C}H_2Ph$), 55.01 ($N\underline{C}H_2CO$), 78.19 ($\underline{C}(CH_3)_3$), 123.32 (C_{aryl}), 124.32 (C_{aryl}), 127.55 (C_{aryl}), 128.43 (C_{aryl}), 135.25 (C_{aryl}), 148.73 (C_{aryl}−N), 156.41 ($\underline{C}ONH$), 172.65 ($NCH_2\underline{C}O$). ESI^+ MS (*m*/*z*): 339.0, 50%, $[M + H]^+$; 361.1, 70%, $[M + Na]^+$; 377.1, 20%, $[M + K]^+$. ESI^- MS (*m*/*z*): 337.3, 100%, $[M - H]^-$.

*2-(Aminodiacetic acid)benzylammonium Bis-trifluoroacetate Salt (**4**).* Compound **3** (4.737 g) and CF_3COOH (15 mL) were stirred in dry CH_2Cl_2 (15 mL) at room temperature for 2 h. The organic solvents were removed under vacuum to give quantitatively compound **4** as a colorless powder.

Anal. Calcd for $C_{15}H_{16}F_6N_2O_8$: C, 38.6; H, 3.5; N, 6.0. Found: C, 38.2; H, 3.4; N, 6.1. IR (KBr, cm^{-1}): 3144 (br, s), 1782 (vs), 1720 (vs), 1608 (s), 1492 (m), 1458 (m), 1404 (w), 1250 (s), 1218 (s), 1196 (s), 1168 (s), 1068 (w), 968 (w), 786 (w), 721 (w), 698 (w), 605 (w). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 3.92 (s, 4H, $N\underline{C}H_2CO$), 4.10 (d, *J* = 5.1 Hz, 2H, $\underline{CH_2}NH$), 7.16 (t, *J* = 7.3 Hz, 1H, C_6H_4), 7.35 (m, 2H, C_6H_4), 7.44 (d, 1H, 7.4 Hz, C_6H_4), 8.27 (s, br, 4H, OH). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): 41.13 ($N\underline{C}H_2Ph$), 55.12 ($N\underline{C}H_2CO$), 116.39 (*q*, J_{CF} = 290.0 Hz, CF_3), 124.11 (C_{aryl}), 124.59 (C_{aryl}), 130.11 (C_{aryl}), 130.42 (C_{aryl}), 131.53 (C_{aryl}), 149.48 (C_{aryl}−N), 159.00 (*q*, J_{CF} = 35.0 Hz, $CF_3\underline{C}O$), 173.27 ($NCH_2\underline{C}O$). ESI^+ MS (*m*/*z*): 239.1, 100%, $[M + H]^+$; 261.0, 10%, $[M + Na]^+$. ESI^- MS (*m*/*z*): 237.3, 100%, $[M - H]^-$, 113.1, 80%, $[CF_3COO^-]$.

*4-(N-Methylamino)benzoic Acid Ethylester (**5**).* Compound **5** was prepared by the method of Kadin.[18] A solution of ethyl 4-aminobenzoate (16.52 g), succinimide (11.90 g), and 9.1 mL of 37% aqueous formaldehyde in 100 mL of ethanol was heated on reflux for 3 h. After cooling to room temperature, the formed colorless precipitate of ethyl 4-(aminomethylsuccinimide)benzoate was collected by suction filtration. It was dissolved in 50 mL of DMSO, and $NaBH_4$ (3.33 g) was added in small portions over a period of 15 min. After being heated to 80 °C for 15 min, the reaction mixture was poured into cold water. The resulting mixture was extracted three times with ether. The combined ether extracts were dried, and the solvent was removed in vacuum. The remaining solid was recrystallized from CH_2Cl_2/MeOH, which gave colorless crystals of **5**. Yield: 62.0% (11.10 g).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8. Found: C, 67.2; H, 7.2; N, 7.8. IR (KBr, cm^{-1}): 3385 (s), 2975 (w), 2935 (w), 2900 (w), 1685 (s), 1605 (vs), 1535 (s), 1475 (m), 1370 (m), 1310 (w), 1275 (s), 1175 (s), 1105 (m), 770 (m). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 1.29 (t, *J* = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 2.82 (s, 3H, NCH_3), 4.12 (s, 1H, NH), 4.24 (q, *J* = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 6.48 (d, *J* = 6.8 Hz, 2H, Ph), 7.82 (d, *J* = 6.8 Hz, 2H, Ph).

*N-(4-Ethoxycarbonylphenyl)-N-(methyl)-N′-benzoylthiourea (**6**).* The synthesis of **6** was performed by the standard procedure using **5** as starting material.[19] Benzoyl chloride (7.00 g, 50 mmol) in 5 mL of dry acetone was added dropwise to a solution of NH_4SCN (3.80 g, 50 mmol) in 10 mL of dry acetone. After the addition was completed, the mixture was kept at 40 °C for 1 h and the formed precipitate of NH_4Cl was filtered off. Compound **5** (8.96 g, 50 mmol) in 5 mL of dry acetone was slowly added to the resulting yellow solution, which then was stirred at room temperature for 3 h. After the volume of the solvent was reduced to about 10 mL, the mixture was kept at 0 °C and the formed precipitate was filtered off, washed with cold MeOH and diethyl ether, and dried in vacuum. Yield: 73.0% (12.50 g).

Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.1; H, 5.3; N, 8.2; S, 9.4. Found: C, 62.9; H, 5.1; N, 8.3; S, 9.3. IR (KBr, cm^{-1}): 3225 (m), 3190 (w), 3060 (w), 2985 (w), 2940 (w), 2905 (w), 1710 (s), 1690 (s), 1605 (m), 1510 (s), 1450 (w), 1430 (m), 1365 (s), 1315 (m), 1275 (vs), 1180 (m), 1110 (s), 720 (s). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 1.34 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 3.77 (s, 3H, NCH_3), 4.31 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 7.38 (d, 4H, Ph), 7.50 (t, *J* = 7.3 Hz, 1H, Ph), 7.57 (d, *J* = 7.4 Hz, 2H, Ph), 8.01 (d, *J* = 8.7 Hz, 2H, Ph), 8.36 (s, 1H, NH). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): 14.42 ($OCH_2\underline{C}H_3$), 43.37 (NCH_3), 61.38 ($O\underline{C}H_2CH_3$), 124.54 (C_{aryl}), 128.23 (C_{aryl}), 128.79 ($\underline{C}_{aryl}$), 129.52 (C_{aryl}), 129.63 (C_{aryl}), 132.28 (C_{aryl}), 136.17 (C_{aryl}), 140.64 ($\underline{C}_{aryl}$−N), 165.73 (COO), 168.51 (C═O), 175.26 (C═S). ESI^+ MS (*m*/*z*): 343.1, 100%, $[M + H]^+$; 365.2, 40%, $[M + Na]^+$.

*Bis-[N-(4-ethoxycarbonylphenyl)-N-methyl-N′-benzoylthioureato]nickel(II) (**7**).* The synthesis of **7** from **6** was adopted from the general procedure.[16] Compound **6** (10.27 g, 30

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mmol) was dissolved in boiling EtOH (50 mL) and slowly added to a hot solution of $Ni(CH_3COO)_2{\cdot}4H_2O$ (3.72 g, 15 mmol) in 30 mL of MeOH, which resulted in the precipitation of a red-brown solid of **7**. The reaction mixture was refluxed for additional 30 min and then cooled to room temperature. Compound **7** was collected by suction filtration and dried in vacuo. Yield: 93.0% (10.32 g).

Anal. Calcd for $C_{36}H_{34}N_4NiO_6S_2$: C, 58.3; H, 4.6; N, 7.6; S, 8.7. Found: C, 58.3; H, 4.8; N, 7.3; S, 8.5. IR (KBr, cm^{-1}): 3065 (w), 2975 (w), 2925 (w), 2855 (w), 1720 (s), 1605 (w), 1525 (s), 1420 (s), 1375 (s), 1285 (s), 1110 (m), 1020 (m), 910 (m), 710 (m), 705 (m). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 1.41 (t, J = 7.0 Hz, 6H, $CH_2\underline{CH_3}$), 3.60 (s, 6H, NCH_3), 4.40 (q, J = 7.0 Hz, 4H, $\underline{CH_2}CH_3$), 7.3−8.1 (m, 18H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): 14.40 ($OCH_2\underline{C}H_3$), 41.94 (NCH_3), 61.23 ($O\underline{C}H_2CH_3$), 124.55 (C_{aryl}), 127.11 (C_{aryl}), 128.02 (C_{aryl}), 129.38 (C_{aryl}), 130.68 (C_{aryl}), 131.93 (C_{aryl}), 136.02 (C_{aryl}), 149.44 (C_{aryl}−N), 165.72 (COO), 165.93 (C═O), 175.44 (C═S). ESI^+ MS (m/z): 741.0, 50%, $[M + H]^+$; 762.9, 10%, $[M + Na]^+$.

*N-(4-Ethoxycarbonylphenyl)-N-methyl-N′-benzimidoyl Chloride (**8**).* The synthesis of **8** was adopted from the general procedure.[16] A solution of $SOCl_2$ (1.60 mL, 22.0 mmol) in 20 mL of dry CH_2Cl_2 was added dropwise into a stirred solution of compound **7** (8.16 g, 11.0 mmol). The reaction mixture was stirred at room temperature for an additional 2 h and then heated on reflux for 30 min. The formed precipitate of $NiCl_2$ was filtered off, and the filtrate was evaporated under reduced pressure. Compound **8** was obtained as yellow, microcrystalline solid. Yield: 65.0% (5.16 g).

Anal. Calcd for $C_{18}H_{17}ClN_2O_2S$: C, 59.9; H, 4.8; N, 7.8; S, 8.9. Found: C, 59.9; H, 4.8; N, 7.8; S, 8.9. IR (KBr, cm^{-1}): 3055 (w), 2981 (w), 2935 (w), 2900 (w), 1716 (s), 1639 (s), 1600 (m), 1505 (m), 1454 (m), 1365 (s), 1273 (s), 1164 (s), 1103 (s), 1014 (m), 910 (m), 775 (m), 690 (m). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 1.36 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 3.80 (s, 3H, NCH_3), 4.33 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 7.34 (d, J = 8.2 Hz, 4H, Ph), 7.45 (t, J = 7.3 Hz, 1H, Ph), 7.74 (d, J = 7.8 Hz, 2H, Ph), 8.01 (d, J = 8.3 Hz, 2H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): 14.27 ($OCH_2\underline{C}H_3$), 43.38 (NCH_3), 61.36 ($O\underline{C}H_2CH_3$), 125.25 (C_{aryl}), 128.48 (C_{aryl}), 129.12 (C_{aryl}), 130.10 (C_{aryl}), 130.79 (C_{aryl}), 132.92 (C_{aryl}), 133.62 (C_{aryl}), 144.39 (C_{aryl}−N), 147.68 (C−Cl), 165.49 (COO), 188.06 (C═S). ESI^+ MS (m/z): 361.0, 70%, $[M + H]^+$.

H_3L. *N*-[(Diethylamino)(thiocarbonyl)]benzimidoyl chloride (686 mg, 2.7 mmol), compound **4** (1.409 g, 2.5 mmol), and NEt_3 (2.02 g, 20 mmol) were stirred in 20 mL of dry EtOH for 6 h at room temperature and then at 40 °C for 1 h. The organic solvent was evaporated under reduced pressure to dryness. The residue was dissolved in 20 mL of THF, and brine solution (20 mL) was added. The organic layer was separated, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The residue was washed with diethyl ether and dried in vacuum to give H_3L as a colorless solid. Yield: 65% (742 mg).

Anal. Calcd for $C_{23}H_{28}N_4O_4S$: C, 60.5; H, 6.2; N, 12.3; S, 7.0. Found: C, 60.3; H, 6.3; N, 12.2; S, 7.2. IR (KBr, cm^{-1}): 3250 (br, s), 1720 (br, s), 1631 (br, s), 1573 (s), 1539 (s), 1489 (m), 1454 (s), 1423 (s), 1311 (m), 1257 (s), 1199 (s), 1138 (s), 1076 (m), 968 (w), 883 (w), 779 (m), 698 (m). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 1.07 (t, J = 7.0 Hz, 3H, CH_3), 1.13 (t, J = 7.0 Hz, 3H, CH_3), 3.52 (q, J = 7.0 Hz, 2H, $N\underline{CH_2}CH_3$), 3.78 (q, J = 7.0 Hz, 2H, $N\underline{CH_2}CH_3$), 3.99 (s, 4H, NCH_2CO), 4.64 (d, J = 5.2 Hz, 2H, $\underline{CH_2}NH$), 7.12 (t, J = 7.3 Hz, 1H, C_6H_4), 7.25 (t, J = 7.2 Hz, 1H, C_6H_4), 7.30 (d, J = 8.0 Hz, 1H, C_6H_4), 7.36 (d, J = 7.6 Hz, 1H, C_6H_4), 7.47 (m, 5H, Ph), 8.35 (s, br, 1H, NHCO), 12.76 (s, br, 1H, COOH). ^{13}C NMR (400 MHz, DMSO-d_6, ppm): 12.34, 13.45 ($CH_2\underline{C}H_3$), 46.42, 46.98 ($N\underline{C}H_2CH_3$), 56.56 ($N\underline{C}H_2$), 67.51 ($N\underline{C}H_2CO$), 118.21 (C_{aryl}), 125.23 (C_{aryl}), 127.48 (C_{aryl}), 127.90 (C_{aryl}), 128.87 (C_{aryl}), 129.55 (C_{aryl}), 130.04 (C_{aryl}), 132.68 (C_{aryl}), 135.34 (C_{aryl}), 149.54 (C_{aryl}−N), 166.24 (C═N), 172.50 (COO), 180.18 (C═S). ESI^+ MS (m/z): 457.1, 100%, $[M + H]^+$; 479.2, 60%, $[M + Na]^+$. ESI^- MS (m/z): 455.1, 100%, $[M - H]^-$.

H_3L−COOEt. The synthesis of H_3L−COOEt was adopted from the procedure described for H_3L except that the benzimidoyl chloride **8** was used.

Anal. Calcd for $C_{29}H_{30}N_4O_6S$: C, 61.9; H, 5.4; N, 10.0; S, 5.7. Found: C, 61.6; H, 5.2; N, 9.8; S, 5.8. IR (KBr, cm^{-1}): 3348 (br, s), 1712 (br, s), 1605 (s), 1542 (s), 1493 (m), 1446 (s), 1276 (s), 1202 (s), 1138 (s), 1099 (s), 1018 (m), 972 (w), 775 (m). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 1.40 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 3.56 (s, 3H, NCH_3), 3.83 (s, 4H, NCH_2CO), 4.37 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 4.49 (s, 2H, $PhC\underline{H_2}NH$), 6.86 (t, br, 1H, Ph), 6.93 (d, br, 1H, Ph), 7.14 (t, br, 1H, Ph), 7.19 (d, br, 1H, Ph), 7.47 (m, 7H, Ph), 7.91 (d, J = 8.6 Hz, 2H, Ph), 8.67 (s, br, 1H, NH) 12.13 (s, br, 2H, COOH). ^{13}C NMR (400 MHz, DMSO-d_6, ppm): 14.34 ($OCH_2\underline{C}H_3$), 42.89 (NCH_3), 61.15 ($O\underline{C}H_2CH_3$), 59.20 ($N\underline{C}H_2Ph$), 66.54 ($N\underline{C}H_2CO$), 120.01 (C_{aryl}), 124.43 (C_{aryl}), 125.51 (C_{aryl}), 126.70 (C_{aryl}), 128,99 (C_{aryl}), 129.12 (C_{aryl}), 130.68 (C_{aryl}), 130.97 (C_{aryl}), 131.03 (C_{aryl}), 131.48 (C_{aryl}), 133.20 (C_{aryl}), 135.76 (C_{aryl}), 148.57 (C_{aryl}−N), 152.95 (C_{aryl}−N), 165.30 ($Ph\underline{C}OO$), 166.93 (C═N), 172.62(COO), 180.77 (C═S). ESI^+ MS (m/z): 563.2, 100%, $[M + H]^+$; 585.2, 60%, $[M + Na]^+$; 601.1, 20%, $[M + K]^+$. ESI^- MS (m/z): 561.2, 100%, $[M - H]^-$.

H_3L−COOH. H_3L−COOEt (562 mg, 1 mmol) was added to a solution of NaOH (400 mg, 10 mmol) in MeOH (5 mL). The reaction mixture was stirred at room temperature for 12 h, and then the solvent was removed under vacuum. The resulting residue was dissolved in brine solution (5 mL). After being neutralized with 10 mmol of HCl, the mixture was extracted with THF (2 × 5 mL). The organic phases were collected, dried over $MgSO_4$, and the solvent was removed under vacuum to give compound H_3L−COOH as a slightly yellow powder. Yield: 80% (427 mg).

Anal. Calcd for $C_{27}H_{26}N_4O_6S$: C, 60.7; H, 4.9; N, 10.5; S, 6.0. Found: C, 60.4; H, 4.8; N, 10.3; S, 6.1. IR (KBr, cm^{-1}): 3368 (br, s), 1717 (s), 1605 (s), 1562 (s), 1423 (s), 1492 (m), 1423 (m), 1381 (m), 1272 (s), 1176 (s), 775 (m), 698 (m). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 3.58 (s, 3H, NCH_3), 3.98 (s, 4H, NCH_2CO), 4.55 (s, 2H, $PhC\underline{H_2}NH$), 6.87 (t, br, 1H, Ph), 6.96 (d, br, 1H, Ph), 7.21 (t, br, 1H, Ph), 7.29 (d, br, 1H, Ph), 7.40 (m, 7H, Ph), 7.94 (d, J = 8.2 Hz, 2H, Ph), 8.70 (s, br, 1H, NH), 12.74 (s, 3H, COOH). ^{13}C NMR (400 MHz, DMSO-d_6, ppm): 43.70 (NCH_3), 56.37 ($N\underline{C}H_2Ph$), 66.03 ($N-\underline{C}H_2CO$), 119.90 (C_{aryl}), 125.01 (C_{aryl}), 125.95 (C_{aryl}), 126.66 (C_{aryl}), 127.05 (C_{aryl}), 128.31 (C_{aryl}), 128.84 (C_{aryl}), 129.60 (C_{aryl}), 130.56 (C_{aryl}), 131.39 (C_{aryl}), 132.31 (C_{aryl}), 134.76 (C_{aryl}), 146.01 (C_{aryl}−N), 149.32 (C_{aryl}−N), 166.03 ($Ph\underline{C}OO$), 168.12 (C═N), 173.13 (COO), 180.21 (C═S). ESI^+ MS (m/z): 535.2, 40%, $[M + H]^+$; 557.2, 100%, $[M + Na]^+$; 573.1, 80%, $[M + K]^+$. ESI^- MS (m/z): 533.2, 100%, $[M - H]^-$.

Syntheses of the Complexes. *[ReO(L)] (**9**).* H_3L (46 mg, 0.1 mmol) and Et_3N (50 μL) were added to a stirred solution of $(NBu_4)[ReOCl_4]$ (58 mg, 0.1 mmol) in 5 mL of MeOH. The reaction mixture was heated under reflux for 30 min. After being cooled to room temperature, the formed purple solid of **9** was filtered off, washed with cold MeOH, and dried under vacuum. Yield: 67% (44 mg).

Compound **9** can also be synthesized from other precursors such as $[Re^VNCl_2(PPh_3)_2]$, $[Re^V(NPh)Cl_3(PPh_3)_2]$, or $[Re^{III}Cl_3(MeCN)(PPh_3)_2]$ by heating them with H_3L in the presence of a base (Et_3N), water, and air.

Anal. Calcd for $C_{23}H_{25}N_4O_5ReS$: C, 42.1; H, 3.8; N, 8.5; S, 4.9. Found: C, 42.0; H, 3.6; N, 8.3; S, 4.7. IR (KBr, cm^{-1}): 3055 (w), 2963 (m), 2926 (m), 1720 (vs), 1666 (vs), 1512 (s), 1442 (m), 1404 (m), 1350 (m), 1311 (m), 1041 (w), 964 (m), 941 (m), 910 (m), 771 (m), 702 (m). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 1.30 (t, J = 7.2 Hz, 3H, CH_3), 1.33 (t, J = 7.1 Hz, 3H, CH_3), 3.77 (m, 1H, $N\underline{CH_2}CH_3$), 3.84 (m, 1H, $N\underline{CH_2}CH_3$), 3.89 (s, 2H, $Ph\underline{CH_2}N$), 4.03 (m, 1H, $N\underline{CH_2}CH_3$), 4.09 (m, 1H, $N\underline{CH_2}CH_3$), 4.53 (d, J = 15.5 Hz, 1H, NCH_2CO), 4.83 (d, J = 14.0 Hz, 1H, NCH_2CO), 5.06 (d, J = 13.8 Hz, 1H, NCH_2CO), 5.68 (d, J = 15.6 Hz, 1H, NCH_2CO), 7.00 (d, J = 7.6 Hz, 1H, C_6H_4), 7.22 (t, J = 7.5 Hz, 1H, C_6H_4), 7.33 (m, 2H, C_6H_4), 7.44 (m, 3H, Ph), 7.48 (d, J = 7.5 Hz, 2H, Ph). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 1.26 (t, J = 7.2 Hz, 3H, CH_3), 1.29 (t, J = 7.2 Hz,

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Table 1. X-ray Structure Data Collection and Refinement Parameters

	[ReO(L)] (**9**)	[TcO(L)] (**10**)	[ReO(L−COOEt)]·1.25 MeOH (**11**)
formula	$C_{23}H_{25}N_4O_5ReS$	$C_{23}H_{25}N_4O_5STc$	$C_{30.25}H_{32}N_4O_{8.25}ReS$
MW	655.73	567.53	801.86
crystal system	monoclinic	monoclinic	triclinic
a/Å	32.448(3)	32.213(2)	9.949(1)
b/Å	7.160(1)	7.187(1)	10.980(1)
c/Å	20.521(2)	20.453(2)	16.796(2)
α/deg	90	90	100.54(1)
β/deg	100.69(1)	100.29(1)	92.32(1)
γ/deg	90	90	113.36(1)
V/Å^3	4684.8(9)	4659.2(8)	1643.0(3)
space group	$C2/c$	$C2/c$	$P\bar{1}$
crystal size	0.5 × 0.2 × 0.04	0.2 × 0.15 × 0.03	0.1 × 0.067 × 0.05
Z	8	8	2
D_{calc}/g cm^{-3}	1.859	1.618	1.621
μ/mm^{-1}	5.320	0.751	3.816
no. of reflns	14 462	20 479	17 975
no. of indep, R_{int}	6207, 0.1002	6270, 0.1119	8768, 0.1067
no. of parameters	326	326	380
R1/wR2	0.0477/0.0776	0.0505/0.1109	0.0668/0.1695
GOF	0.872	0.907	1.068
CSD	CCDC 1058104	CCDC 1058105	CCDC 1058106

3H, CH_3), 4.00 (m, 4H, N$\underline{CH_2}CH_3$), 4.10 (d, J = 18.3 Hz, 1H, Ph$\underline{CH_2}$N), 4.40 (d, J = 18.2 Hz, 1H, Ph$\underline{CH_2}$N), 4.78 (d, J = 15.2 Hz, 1H, N$\underline{CH_2}$CO), 4.82 (d, J = 14.1 Hz, 1H, N$\underline{CH_2}$CO), 5.37 (d, J = 14.5 Hz, 1H, N$\underline{CH_2}$CO), 5.63 (d, J = 15.6 Hz, 1H, N$\underline{CH_2}$CO), 7.13 (d, J = 7.6 Hz, 1H, C_6H_4), 7.29 (t, J = 7.4 Hz, 1H, C_6H_4), 7.43 (m, 2H, C_6H_4), 7.57 (m, 3H, Ph), 7.67 (d, J = 8.0 Hz, 2H, Ph). ^{13}C NMR (400 MHz, DMSO-d_6, ppm): 13.01, 13.23 (N$\underline{CH_2}\underline{CH_3}$), 46.75, 47.13 (N$\underline{CH_2}CH_3$), 64.03 (N$\underline{CH_2}$Ph), 65.37, 66.71 (N$\underline{CH_2}$CO), 119.38 ($C_{aryl}$), 127.84 ($C_{aryl}$), 128.57 ($C_{aryl}$), 128.78 ($C_{aryl}$), 129.56 ($C_{aryl}$), 130.83 ($C_{aryl}$), 131.54 ($C_{aryl}$), 132.67 ($C_{aryl}$), 137.02 ($C_{aryl}$), 153.81 ($C_{aryl}$−N), 170.44 (C═N), 173.34 (COORe), 173.67 (COORe), 183.61 (C═S). ESI$^+$ MS (m/z): 657.2, 100%, [M + H]$^+$.

*[TcO(L)] (**10**).* The technetium complex **10** was prepared from (NBu_4)[$TcOCl_4$] by the procedure described above as for its rhenium analogue **9**. Compound **10** was isolated as a green solid. Yield: 75% (43 mg).

Anal. Calcd for $C_{23}H_{25}N_4O_5TcS$: Tc, 17.4. Found: Tc, 17.5. IR (KBr, cm^{-1}): 3066 (w), 2954 (w), 2923 (w), 1701 (vs), 1654 (vs), 1500 (s), 1442 (m), 1407 (m), 1350 (m), 1311 (s), 1288 (m), 1045 (w), 944 (m), 910 (m), 771 (m). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 1.29 (m, 6H, CH_3), 3.79 (m, 2H, N$\underline{CH_2}$CH$_3$), 3.84 (s, 2H, Ph$\underline{CH_2}$N), 3.93 (m, 2H, N$\underline{CH_2}$CH$_3$), 4.43 (d, J = 15.3 Hz, 1H, N$\underline{CH_2}$CO), 4.79 (d, J = 14.1 Hz, 1H, N$\underline{CH_2}$CO), 5.01 (d, J = 14.1 Hz, 1H, N$\underline{CH_2}$CO), 5.11 (d, J = 15.3 Hz, 1H, N$\underline{CH_2}$CO), 7.04 (d, J = 7.5 Hz, 1H, C_6H_4), 7.23 (t, J = 7.6 Hz, 1H, C_6H_4), 7.45 (m, 7H, Ph).

*[ReO(L−COOEt)] (**11**).* H_3L−COOEt (56 mg, 0.1 mmol) and Et_3N (50 μL) were added to a stirred solution of (NBu_4)[$ReOCl_4$] (58 mg, 0.1 mmol) in 5 mL of MeOH. The reaction mixture was heated under reflux for 30 min. After being cooled to room temperature, the formed purple solid of **11** was filtered off, washed with cold MeOH, and dried under vacuum. Yield: 63% (48 mg).

Anal. Calcd for $C_{29}H_{27}N_4O_7ReS$: C, 45.7; H, 3.6; N, 7.4; S, 4.21. Found: C, 45.6; H, 3.6; N, 7.2; S, 4.1. IR (KBr, cm^{-1}): 2985 (w), 2931 (w), 2851 (w), 1717 (vs), 1527 (s), 1496 (m), 1388 (m), 1280 (s), 1226 (w), 1114 (w), 1096 (m), 1018 (w), 988 (w), 936 (w), 910 (m), 779 (m), 706 (w). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 1.33 (t, J = 6.9 Hz, 3H, OCH$_2\underline{CH_3}$), 3.85 (s, 3H, NCH_3), 4.14 (d, J = 18.1 Hz, 1H, Ph$\underline{CH_2}$N), 4.34 (q, J = 6.9 Hz, 2H, O$\underline{CH_2}$CH$_3$), 4.44 (d, J = 18.0 Hz, 1H, Ph$\underline{CH_2}$N), 4.78 (d, J = 15.5 Hz, 1H, N$\underline{CH_2}$CO), 4.90 (d, J = 15.5 Hz, 1H, N$\underline{CH_2}$CO), 5.32 (d, J = 13.5 Hz, 1H, N$\underline{CH_2}$CO), 5.69 (d, J = 16.1 Hz, 1H, N$\underline{CH_2}$CO), 7.20 (s, br, 1H, Ph), 7.28 (t, J = 7.4 Hz, 1H, Ph), 7.4−7.6 (m, 9H, Ph), 8.11 (d, J = 7.9 Hz, 2H, Ph). ^{13}C NMR (400 MHz, DMSO-d_6, ppm): 14.64 (OCH$_2\underline{CH_3}$), 43.04 (NCH_3), 61.59 (O$\underline{CH_2}$CH$_3$), 64.21 (N$\underline{CH_2}$Ph), 65.61 (N−$\underline{CH_2}$CO), 67.00 (N−$\underline{CH_2}$CO), 119.91 (C_{aryl}), 128.08 (C_{aryl}), 128.34 (C_{aryl}), 129.30 (C_{aryl}), 129,59 (C_{aryl}), 130.23 (C_{aryl}), 131.07 (C_{aryl}), 131.10 (C_{aryl}), 131.73 (C_{aryl}), 131.82 (C_{aryl}), 133.30 (C_{aryl}), 136.93-(C_{aryl}), 147.88 (C_{aryl}−N), 154.33 (C_{aryl}−N), 165.38 (Ph$\underline{C}$OO), 171.35 (C═N), 173.90 (COORe), 174.74 (COORe), 184.08 (C═S). ESI$^+$ MS (m/z): 763.1, 100%, [M + H]$^+$; 784.9, 10%, [M + Na]$^+$.

*[TcO(L−COOEt)] (**12**).* The technetium complex **12** was prepared from (NBu_4)[$TcOCl_4$] by the procedure described for its rhenium analogue **11**. Compound **12** was isolated as a green solid. Yield: 67% (45 mg).

Anal. Calcd for $C_{29}H_{27}N_4O_7TcS$: Tc, 14.6. Found: Tc, 14.6. IR (KBr, cm^{-1}): 2977 (w), 1701 (vs), 1523 (vs), 1454 (m), 1388 (m), 1276 (s), 1218 (m), 1114 (m), 1018 (w), 956 (m), 910 (m), 779 (m), 705 (m). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 1.18 (s, 3H, OCH$_2\underline{CH_3}$), 3.68 (d, J = 17.7 Hz, 1H, Ph$\underline{CH_2}$N), 3.96 (s, 3H, NCH_3), 4.36 (m, 3H, O$\underline{CH_2}$CH$_3$ + Ph$\underline{CH_2}$N), 4.49 (d, J = 18.0 Hz, 1H, N$\underline{CH_2}$CO), 4.74 (d, J = 15.4 Hz, 1H, N$\underline{CH_2}$CO), 4.93 (d, J = 15.4 Hz, 1H, N$\underline{CH_2}$CO), 5.15 (d, J = 18.0 Hz, 1H, N$\underline{CH_2}$CO), 7.1−7.4 (m, 11H, Ph), 8.08 (d, J = 7.6 Hz, 2H, Ph).

*[ReO(L−COOH)] (**13**).* H_3L−COOH (54 mg, 0.1 mmol) and Et_3N (50 μL) were added to a stirred solution of (NBu_4)[$ReOCl_4$] (58 mg, 0.1 mmol) in 5 mL of MeOH. The reaction mixture was heated under reflux for 30 min. After standing at room temperature for 24 h, the formed purple solid was filtered off, washed with cold MeOH, and dried under vacuum. Yield: 52% (38 mg).

Anal. Calcd for $C_{27}H_{23}N_4O_7ReS$: C, 44.1; H, 3.4; N, 7.6; S, 4.4. Found: C, 44.2; H, 3.3; N, 7.5; S, 4.3. IR (KBr, cm^{-1}): 3166 (br, m), 1705 (vs), 1685 (vs), 1535 (s), 1496 (m), 1389 (m), 1354 (m), 1307 (m), 1230 (m), 1172 (w), 1118 (w), 1080 (w), 984 (m), 941 (w), 914 (m), 864 (m), 783 (m), 698 (m). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 3.85 (s, 3H, NCH_3), 4.09 (d, J = 18.3 Hz, 1H, Ph$\underline{CH_2}$N), 4.44 (d, J = 18.3 Hz, 1H, Ph$\underline{CH_2}$N), 4.78 (d, J = 14.4 Hz, 1H, N$\underline{CH_2}$CO), 4.89 (d, J = 15.6 Hz, 1H, N$\underline{CH_2}$CO), 5.32 (d, J = 14.4 Hz, 1H, N$\underline{CH_2}$CO), 5.69 (d, J = 15.6 Hz, 1H, N$\underline{CH_2}$CO), 7.20(d, J = 7.6 Hz, 1H, Ph), 7.28 (t, J = 7.4 Hz, 1H, Ph), 7.4−7.6 (m, 9H, Ph), 8.09 (d, J = 8.4 Hz, 2H, Ph), 13.24 (s, 1H, COOH). ^{13}C NMR (400 MHz, DMSO-d_6, ppm): 42.57 (NCH_3), 63.71 (N$\underline{CH_2}$Ph), 65.11 (N−$\underline{CH_2}$CO), 66.49 (N−$\underline{CH_2}$CO), 119.43 (C_{aryl}), 127.39 (C_{aryl}), 127.84 (C_{aryl}), 128.69 (C_{aryl}), 129,10 (C_{aryl}), 129.71 (C_{aryl}), 131.02 (C_{aryl}), 131.22 (C_{aryl}), 131.35 (C_{aryl}), 132.01 (C_{aryl}), 132.81 (C_{aryl}), 135.70

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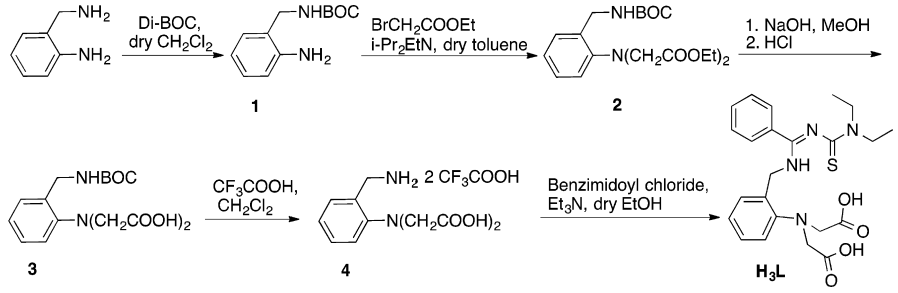
Scheme 1. Synthesis of the Potentially Pentadentate Ligand H_3L



(C_{aryl}), 144.06 (C_{aryl}–N), 153.85 (C_{aryl}–N), 166.44 (PhCOO), 170.93 (C=N), 173.41 (COORe), 174.05 (COORe), 183.58 (C=S). ESI^+ MS (m/z): 735.1, 100%, $[M + H]^+$; 757.2, 60%, $[M + Na]^+$. ESI^- MS (m/z): 733.1, 100%, $[M - H]^-$.

*[ReO(L–TriGlyCOOEt)] (**14**).* Compound **13** (37 mg, 0.05 mmol), *N,N′*-dicyclohexylcarbodiimide (14 mg, 0.07 mmol), and *N*-hydrobenzotriazole (9 mg, 0.07 mmol) were dissolved in 3 mL of dry DMF. The reaction mixture was stirred at room temperature for 30 min. Triglycine ethylester (17 mg, 0.07 mmol) then was added, and the mixture was stirred at room temperature for an additional 12 h. The solvent was removed under vacuum, and the residue was suspended in THF (5 mL). The insoluble urea was filtered off, and the filtrate was washed with 5 mL of brine solution. After the organic phase was dried over $MgSO_4$, the solvent was removed under vacuum. The residue was washed with cold MeOH and the red product was filtered off and dried under vacuum. Yield: 95% (45 mg).

Anal. Calcd for $C_{35}H_{36}N_7O_{10}ReS$: C, 45.1; H, 3.9; N, 10.5; S, 3.4. Found: C, 45.2; H, 3.8; N, 10.7; S, 3.4. IR (KBr, cm^{-1}): 3325 (m), 3062 (w), 2928 (m), 2850 (w), 1713 (vs), 1655 (vs), 1535 (s), 1497 (m), 1446 (w), 1384 (m), 1307 (m), 1219 (m), 1130 (w), 1084 (w), 980 (m), 941 (w), 910 (m), 864 (w), 787 (m), 605 (m). ^1H NMR (400 MHz, DMSO-d_6, ppm): 1.17 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 3.75 (d, J = 5.9 Hz, 2H, $NHC\underline{H_2}CO$), 3.85 (m, 5H, NCH_3 + $NHC\underline{H_2}CO$), 3.93 (d, J = 5.7 Hz, 2H, $NHC\underline{H_2}CO$), 4.07 (m, 3H, $OC\underline{H_2}CH_3$ + $NC\underline{H_2}Ph$), 4.43 (d, J = 18.4 Hz, 1H, $NC\underline{H_2}Ph$), 4.79 (d, J = 14.5 Hz, 1H, NCH_2CO), 4.89 (d, J = 15.7 Hz, 1H, NCH_2CO), 5.30 (d, J = 14.5 Hz, 1H, NCH_2CO), 5.68 (d, J = 15.7 Hz, 1H, NCH_2CO), 7.20 (d, J = 7.4 Hz, 1H, Ph), 7.28 (t, J = 7.4 Hz, 1H, Ph), 7.4–7.6 (m, 9H, Ph), 8.03 (d, J = 8.4 Hz, 2H, Ph), 8.24 (t, br, 1H, NH), 8.29 (t, br, 1H, NH), 8.98 (t, br, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, ppm): 14.07 ($OCH_2\underline{CH_3}$), 40.64 ($CONH\underline{CH_2}$), 41.76 ($CONH\underline{CH_2}$), 42.01 ($CONH\underline{CH_2}$), 42.98 (NCH_3), 60.44 ($O\underline{CH_2}CH_3$), 63.64 ($N\underline{CH_2}Ph$), 65.23 ($N–\underline{CH_2}CO$), 66.50 ($N–\underline{CH_2}CO$), 120.03 (C_{aryl}), 126.36 (C_{aryl}), 127.35 (C_{aryl}), 128.67 (C_{aryl}), 129.01 (C_{aryl}), 129.27 (C_{aryl}), 131.10 (C_{aryl}), 131.56 (C_{aryl}), 131.99 (C_{aryl}), 132.32 (C_{aryl}), 132.93 (C_{aryl}), 136.42 (C_{aryl}), 143.55 (C_{aryl}–N), 152.87 (C_{aryl}–N), 167.44 (PhCONH), 168.03 ($CH_2\underline{C}OOEt$), 169.40 ($CH_2\underline{C}ONH$), 169.69 ($CH_2\underline{C}ONH$), 171.02 (C=N), 173.56 (COORe), 174.15 (COORe), 183.60 (C=S). ESI^+ MS (m/z): 956.1718, 100%, $[M + Na]^+$, 972.1576, 90%, $[M + K]^+$.

X-ray Crystallography. The intensities for the X-ray determinations were collected on a STOE IPDS 2T instrument at 200 K with Mo Kα radiation (λ = 0.71073 Å) using a graphite monochromator. Standard procedures were applied for data reduction and absorption correction. Structure solution and refinement were performed with SHELXS97 and SHELXL97.[20] Hydrogen atom positions were calculated for idealized positions and treated with the "riding model" option of SHELXL. More details on data collections and structure calculations are contained in Table 1. Disordered solvent methanol is contained in the lattice of **11**. It has been modeled as three molecules with partial occupation. A similar situation has been found for the solid-state structure of the analogous technetium complex **12**, which also crystallizes in the triclinic space group $P\bar{1}$ (a = 9.993(1), b = 11.505(2), c = 16.440(2) Å, α = 100.31(1), β = 89.21(1), γ = 118.66(1)°). Because the disorder in the latter structure could not be resolved with an appropriate model, the refinement resulted in unsatisfactory R values. For this reason details of the crystallographic results obtained for **12** will not be discussed in this Article. The molecular structure of the complex, however, could be derived from the data set unambiguously and is in full agreement with the spectroscopic results.

Additional information on the structure determinations has been deposited with the Cambridge Crystallographic Data Centre.

RESULTS AND DISCUSSION

The pentadentate benzamidine ligand H_3L can be obtained from 2-aminobenzyl amine in a multistep synthesis, which is shown in Scheme 1. The nonsymmetric diamine was chosen to allow a selective protection of one amine group and to functionalize the other one, which gives access to ligands with high denticity. Thus, in the first step, the aliphatic amine group of 2-aminobenzyl amine is selectively protected by the reaction with 1 equiv of di-*tert.*-butyl dicarbonate in dry CH_2Cl_2 to form *o*-$NH_2C_6H_4CH_2NHBOC$ (**1**). The aromatic amine group then is converted to the iminodi(ethyl acetate) (**2**) by treatment with an excess amount of $BrCH_2COOEt$ in the presence of a supporting base. The reaction between **1** and $BrCH_2COOEt$ (with KI as catalyst) proceeds very slowly. Refluxing **1** with a large excess of $BrCH_2COOEt$ (ca. 6 equiv) in MeCN and with solid K_2CO_3 used as a supporting base for 6 days resulted in a mixture of **2** (60%) and monosubstituted product (40%). However, with the use of toluene as solvent and a homogeneous supporting base such as *i*-Pr_2EtN instead of solid K_2CO_3, the formation of **2** proceeds almost quantitatively with only 3 equiv of $BrCH_2COOEt$ and a reflux period of 2 days. Hydrolysis of the ester **2** with NaOH in MeOH at room temperature, followed by acidification with cold diluted HCl, gives the carboxylic acid **3**. The aliphatic amine of **3** is then deprotected by CF_3COOH/CH_2Cl_2 (1:1), giving the tetradentate amine **4** as trifluoroacetate salt. Because of the poor solubility of **4** in acetone or THF, the synthesis of the pentadentate benzamidine H_3L from *N,N*-diethylthiocarbonyl-*N′*-benzimidoyl chloride and **4** was carried out in dry EtOH. The ligand is obtained as a light yellow microcrystalline solid in high yields. No significant amount of side products by potential reactions of the benzimidoyl chloride and EtOH was detected.[21,22]

The IR spectrum of H_3L exhibits very strong broad bands in the region between 3500 and 2800 cm^{-1}, which are characteristic for the ν_{OH} stretches of free carboxylic groups. The absorption of the $\nu_{C=O}$ vibrations is very strong and broad and appears at 1720 cm^{-1}. It is partially overlapped with the strong absorption of the $\nu_{C=N}$ stretch at 1631 cm^{-1}. The ^1H NMR spectrum of H_3L shows two well-separated signal sets of two ethyl groups due to the hindered rotation of the NEt_2 moiety around the C(S)–NEt_2 bond.[10,11,23,24] While a singlet at 3.99 ppm is assigned to the methylene protons of $\underline{CH_2}CO$, a

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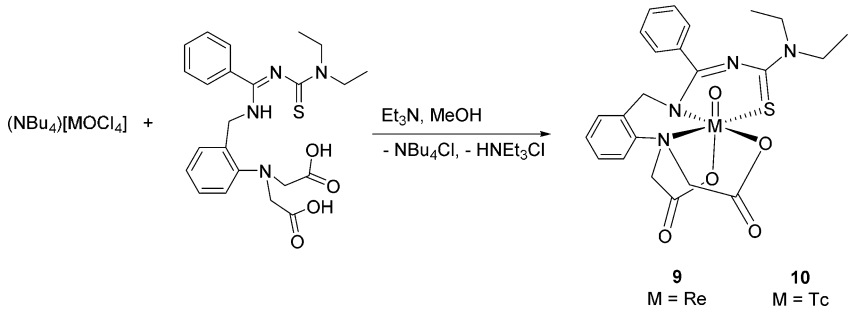
Scheme 2. Reactions of H_3L with $(NBu_4)[MOCl_4]$



doublet at 4.64 with J = 5.2 Hz is typical for the methylene protons of $\underline{CH_2}NH$. The chemical shifts of the aromatic protons belonging to the aminobenzylamine appear in the range from 6.8 to 7.3 ppm, which is at higher field as compared to those of the other phenyl group. Broad singlets at 8.35 and 12.76 ppm are assigned to the NH and COOH resonances, respectively.

The ligand H_3L reacts with the $(NBu_4)[MOCl_4]$ (M = Tc, Re) precursors in MeOH after addition of the supporting base Et_3N under formation of complexes of the composition [MO(L)] [M = Re (**9**), Tc (**10**)] (Scheme 2). While the rhenium complex is formed slowly and heating under reflux is required to complete the formation of the violet-purple powder, the technetium compound is readily precipitated from the reaction mixture at an ambient temperature as a green microcrystalline solid. Compounds **9** and **10** are stable as solids and in solution. Interestingly, compounds **9** and **10** are also obtained when H_3L is heated on reflux under aerobic conditions and without exclusion of water with other starting materials possessing different cores and contain the metal ions at different oxidation states such as $[M^{V}NCl_2(PPh_3)_2]$, $[M^{V}(NPh)Cl_3(PPh_3)_2]$, or $[M^{III}Cl_3(MeCN)(PPh_3)_2]$ in almost quantitative yields. This strongly suggests that the formation of the oxidometal(V) complexes of H_3L is thermodynamically preferred and $\{MN\}^{2+}$, $\{MNPh\}^{3+}$, or $\{M\}^{3+}$ (M = Re, Tc) complexes are readily converted when oxidation/hydrolysis is possible.

In the IR spectra of complexes **9** and **10**, no absorptions in the region above 3100 cm^{-1}, which correspond to ν_{N-H} and ν_{O-H} stretches in the free ligand, are observed. This is a strong hint for the triply deprotonated form of the ligand. While the $\nu_{C=O}$ bands of two nonequivalent carboxylate groups in **9** appear at 1720 and 1666 cm^{-1}, the corresponding stretches in **10** reveal strong bands at 1701 and 1654 cm^{-1}. For both compounds, the formation of a benzamidinato chelate, which is normally accompanied by a large delocalization of π electrons, is indicated by a strong bathochromic shift of the $\nu_{C=N}$ to the 1500 cm^{-1} region.[10,11,24] The medium absorption bands at 964 and 944 cm^{-1} are assigned to the $\nu_{Re=O}$ and $\nu_{Tc=O}$ stretches, respectively.[25] The ^1H NMR spectra of **9** and **10** in $CDCl_3$ show no signals of O−H or N−H protons. The spectra reflect the rigid arrangement around the tertiary nitrogen atoms of the (CS)−NEt_2 moieties. This results in magnetic nonequivalence of its four methylene protons as is indicated by four separated signals with ABX_3 splitting patterns as previously mentioned.[26] The signals of the four methylene protons of $N\underline{CH_2}CO$ appear in two pairs of doublets at 4.53/5.68 ppm, 4.83/5.06 ppm for **9** and 4.79/5.01 ppm, 4.43/5.11 ppm for **10** with typical geminal spin coupling constants (J = 14.0−15.5 Hz). This observation indicates that the two carboxylates and the tertiary aromatic nitrogen atom coordinate to the metal centers under formation of two five-membered chelate rings. Two methylene protons in each ring are magnetically nonequivalent due to their different positions, up and down with respect to the ring plane. Because of the dissociation of the protons of the neighboring nitrogen atoms, the resonances of the methylene protons of the benzylamine groups are high-field shifted by about 0.8 ppm and appear as singlets at about 3.89 ppm (Figure 1a).

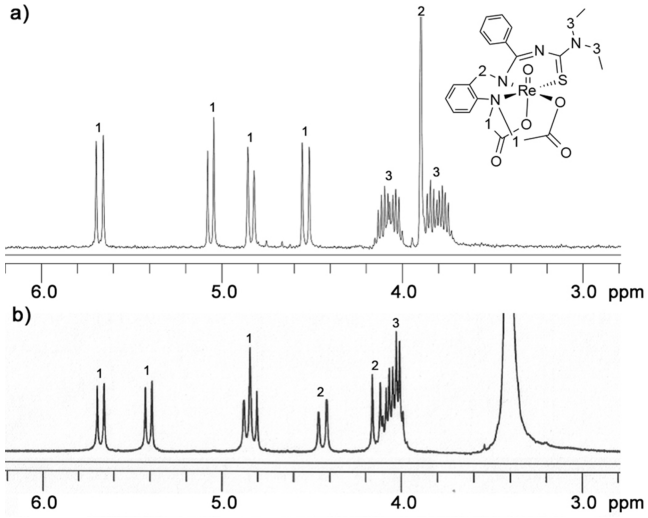


Figure 1. A part of the ^1H NMR spectrum of [ReO(L)] (a) in $CDCl_3$ and (b) in DMSO-d_6.

Interestingly, in the ^1H NMR spectrum of **1** measured in DMSO-d_6, this singlet is split into two doublets at 4.10 and 4.40 ppm with typical germinal coupling constants (J = 18.2 Hz) (Figure 1b). This can be explained by a restricted equilibrium between the chair and the boat conformations of the six-membered chelate ring in DMSO.

Single-crystal X-ray diffraction studies on complexes **9** and **10** confirm the conclusions drawn from the spectroscopic studies. An ellipsoid representation of the molecular structure of **10** is depicted in Figure 2. The equivalent molecular structure of the rhenium complex **9** is virtually identical and, thus, not presented as an extra figure. However, selected bond lengths and angles of both compounds are compared in Table 2, where the atomic labeling scheme for compound **9** is adopted from that of the technetium complex shown in Figure 2. The metal atoms reveal a distorted octahedral coordination environment with a terminal oxido ligand. The remaining five coordination positions are occupied by the donor atoms of $\{L\}^{3-}$. One of the carboxylate oxygen atoms is expectedly in *trans* position to the

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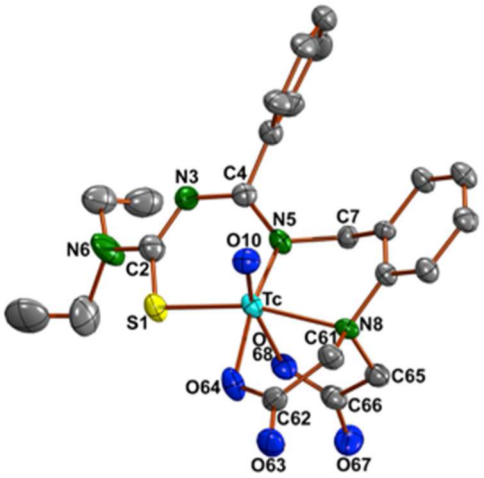

Figure 2. Molecular structure of [TcO(L)] (**10**). Hydrogen atoms were omitted for clarity.

oxido ligand. The distances from the metal atoms to the oxygen atoms *trans* to the oxido ligands are slightly shorter than the distances to the oxygen atoms in the equatorial coordination sphere. However, all of these distances fall into the range of rhenium−oxygen and technetium−oxygen single bonds found in some other carboxylato complexes.[27,28] The M−N bonds to the tertiary nitrogen atoms N8 are longer by about 0.25 Å than the M−N5 bonds. Nevertheless, the M−N5 bond lengths are in the same range observed before for other technetium or rhenium thiocarbamoylbenzamidinato complexes.[29] The M−O10 bond lengths of 1.662(6) Å in **9** and 1.659(3) Å in **10** are unexceptional.

For the use of ligands of the type H_3L in bioconjugation, an additional anchor like a carboxylic or an amino group should be introduced to the periphery of the ligands. Generally, the ligand skeleton of H_3L can be modified in three different positions: (i) the phenyl group of the benzamidine, (ii) the aromatic ring of aminobenzylamine, or (iii) the thiourea (CS)−NR^1R^2 moiety. The latter is the most convenient one and shall be used as a demonstration for the ready variability of the novel ligand system.[12,13] The desired pentadentate ligand H_3L−COOEt can be obtained by a multistep synthesis as is shown in Scheme 3. The syntheses of the benzoylthiourea **6** and its nickel complex **7**, which contains an ester group, were carried out similar to the standard procedure,[16] except using the secondary amine **5**, which was prepared from 4-aminobenzoic ethyl ester. Because of the poor solubility of the nickel complex **7** in CCl_4, dry CH_2Cl_2 was used as solvent for the synthesis of the corresponding benzimidoyl chloride **8**. The synthesis of H_3L−COOEt is similar to that of H_3L except using benzimidoyl chloride **8** instead of *N*,*N*-diethylthiocarbonyl-*N*′-benzimidoyl chloride. The reaction was also carried out in dry EtOH, and ligand H_3L−COOEt can be isolated in high yields.

The IR spectrum of H_3L−COOEt is characterized by a broad strong absorption ranging from 3450 to 2500 cm^{-1}, which is related to the carboxylic OH stretches. The $\nu_{C=O}$ stretches of protonated carboxylic acid groups appear as a broad strong band at 1712 cm^{-1}. Another strong absorption band at 1605 cm^{-1} is assigned to the $\nu_{C=N}$ vibration, which is typical for benzamidine-type compounds. The ^{1}H NMR spectrum of H_3L−COOEt shows the expected signal pattern. A triplet at 1.40 ppm and a quartet at 4.37 ppm, respectively, belong to the resonances of the methyl and methylene protons of the ethyl ester. No hindered rotation effects, which are normally discussed for thiourea moieties, are observed for this compound. This is reflected by a sharp singlet at 3.56 ppm corresponding to the resonance of the N−CH_3 protons. The signals corresponding to the methylene groups of N$\underline{CH_2}$CO and N$\underline{CH_2}$Ph are found as singlets at 3.83 and 4.49 ppm, respectively. Two broad signals at 8.67 and 12.13 ppm can be assigned to the NH and COOH resonances.

H_3L−COOEt readily reacts with $(NBu_4)[MOCl_4]$ (M = Re, Tc) in refluxing MeOH with the addition of base under formation of a purple solid of the composition [ReO(L−COOEt)] (**11**) or the green technetium analogue [TcO(L−COOEt)] (**12**) (Scheme 4). Both compounds were isolated as pure crystalline solids in high yields.

The information, which can be derived from the IR spectra of **11** and **12**, is similar to that discussed for compounds **9** and **10**: coordinated carboxylato groups and the formation of the benzamidine chelate rings with delocalized π-electrons. Medium absorption bands at 988 and 956 cm^{-1} are assigned to the $\nu_{Re=O}$ and $\nu_{Tc=O}$ vibrations.[25] Like the ^{1}H NMR spectrum of the uncoordinated ligand, those of **11** and **12** do not reveal a hindered rotation around the (CS−-NMe(p-C_6H_4COOEt) bonds. This is indicated by only one set of well-resolved signals corresponding to protons of the NMe(p-C_6H_4COOEt) moiety. The absence of NH and COOH resonances suggests $\{L-COOEt\}^{3-}$ being coordinated as a triply deprotonated ligand. The coordination of the ligand $\{L-COOEt\}^{3-}$ in the expected fashion is also clearly confirmed by the appearance of six doublet signals with geminal coupling

Table 2. Selected Bond Lengths (Å) and Angles (deg) in [ReO(L)] (9) and [TcO(L)] (10)

	9	10		9	10
Bond Lengths					
M−O10	1.662(6)	1.659(3)	S1−C2	1.75(1)	1.746(5)
M−S1	2.290(2)	2.296(1)	C4−N5	1.35(1)	1.349(6)
M−N5	2.022(7)	2.000(4)	C62−O63	1.22(1)	1.222(6)
M−N8	2.253(6)	2.253(4)	C62−O64	1.309(9)	1.285(6)
M−O64	2.078(6)	2.063(4)	C66−O67	1.20(1)	1.220(6)
M−O68	2.030(7)	2.031(3)	C66−O68	1.31(1)	1.292(6)
Angles					
O10−M− S1	104.1(2)	104.5(1)	O10−M−O68	162.5(2)	162.4(1)
O10−M−N5	97.5(3)	97.0(1)	S1−M−N8	166.2(2)	165.5(1)
O10−M−N8	86.8(3)	87.2(1)	N5−M−O64	166.7(3)	167.8(1)
O10−M−O64	93.6(3)	93.7(1)	S1−M−N5	93.1(2)	92.8(1)

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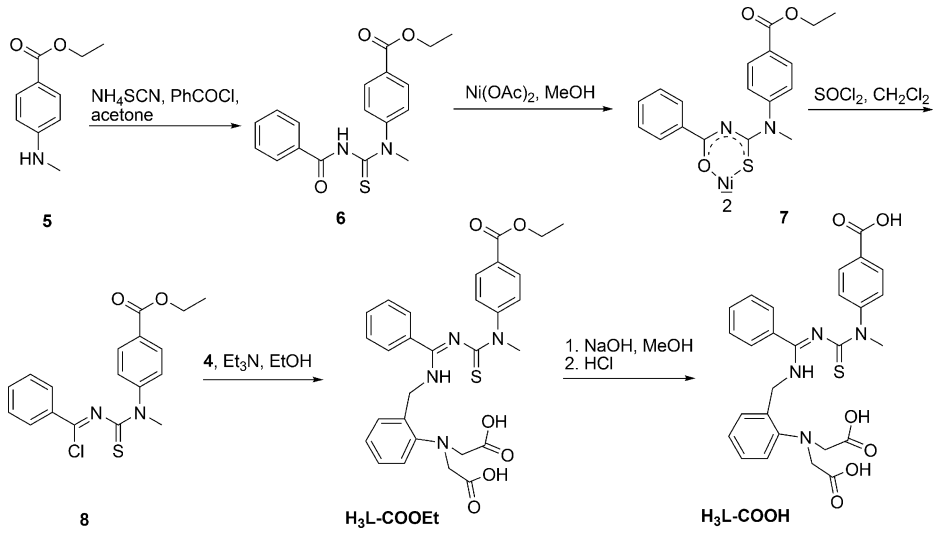
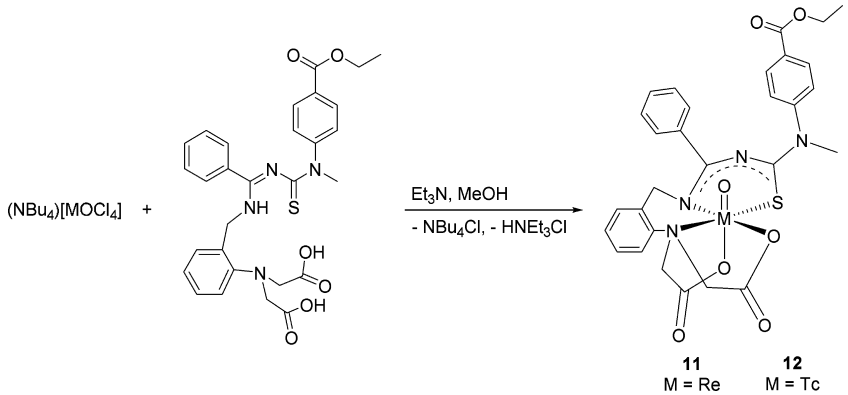
Scheme 3. Syntheses of $H_3L-COOEt$ and $H_3L-COOH$



Scheme 4. Reactions of $H_3L-COOEt$ with $(NBu_4)[MOCl_4]$ (M = Re, Tc)



patterns belonging to the six methylene protons as previously discussed for complexes **9** and **10**.

Single crystals of **11** suitable for X-ray diffraction were obtained by slow diffusion of MeOH into solutions of the complex in DMSO. Figure 3 illustrates the molecular structure of **11**. Selected bond lengths and angles are contained in Table 3. The structure of the analogous technetium complex is virtually the same. The metal atoms possess distorted octahedral environments; in each, one position is taken by a terminal oxido ligand and the five remaining positions are occupied by the donor atoms of $\{L-COOEt\}^{3-}$. The bond lengths and angles in their molecular structures are very similar to those of **9** and **10** with minor differences in the substituted group of the thiourea moiety.

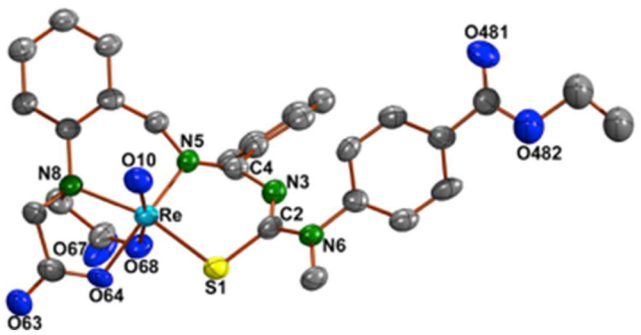


Figure 3. Molecular structure of [ReO(L−COOEt)] (**11**). Hydrogen atoms were omitted for clarity.

Table 3. Selected Bond Lengths (Å) and Angles (deg) in [ReO(L−COOEt)] (11)

Re−O10	1.651(8)	Re−O64	2.059(6)
Re−S1	2.294(2)	Re−O68	2.065(6)
Re−N5	2.047(7)	S1−C2	1.76(1)
Re−N8	2.219(7)	C4−N5	1.32(1)
O10−M−S1	105.0(3)	O10−M−O68	163.4(3)
O10−M−N5	96.9(3)	S1−M−N8	163.7(2)
O10−M−N8	87.8(3)	N5−M−O64	163.4(3)
O10−M−O64	98.3(3)	S1−M−N5	95.1(2)

Hydrolysis of the ester $H_3L-COOEt$ in a MeOH solution of NaOH gave the salt Na_4L-COO, which was subsequently treated with the exact amount of aqueous HCl required to obtain the acidic form of the ligand, $H_3L-COOH$. The yield of the hydrolysis is almost quantitative, and no side-reactions were detected. The IR spectrum of $H_3L-COOH$ is similar to that discussed for $H_3L-COOEt$ except for a slight bathochromic shift of about 5 cm^{-1} for the absorption band of the C═O vibrations. In the ^1H NMR spectrum of $H_3L-COOH$, the absence of resonances of the ethyl ester group is observed. The other signals appear in the same region as those in the spectrum of $H_3L-COOEt$.

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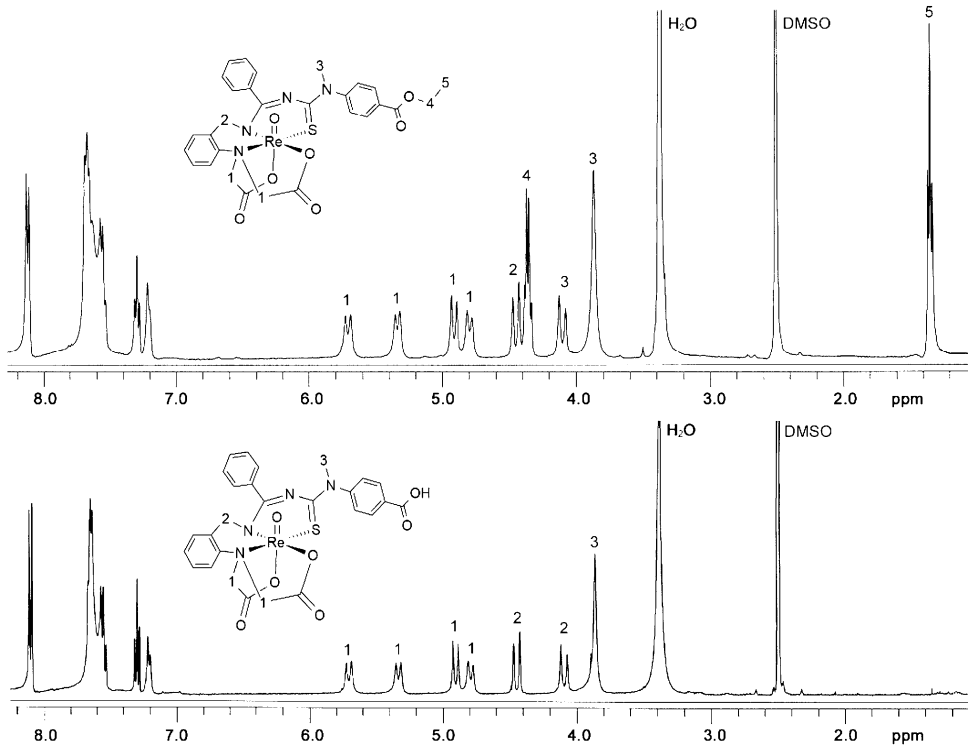
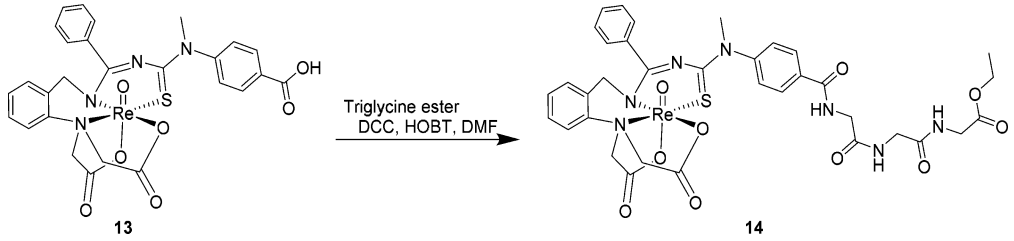


Figure 4. ^{1}H NMR spectrum of (a) [ReO(L−COOEt)] (**11**) and (b) [ReO(L−COOH)] (**13**).

Scheme 5. Coupling Reaction of [ReO(L−COOH)] with Triglycine Ethyl Ester and Formation of 14



Like the H_3L−COOEt ligand, H_3L−COOH readily reacts with $(NBu_4)[ReOCl_4]$ in MeOH after addition of Et_3N. This is indicated by an immediate change of the color of the reaction mixture from which a violet solid of the composition [ReO(L−COOH)] (**13**) was directly isolated. The amount of base, which is added, must not exceed 3 equiv of $(NBu_4)[ReOCl_4]$, to minimize the formation of the anion $[ReO(L−COO)]^{-}$, which is soluble in MeOH. Many attempts to obtain high-quality single crystals of **13** for an X-ray structure study failed. However, the structure of **13**, which is similar to that of **11**, can readily be derived from the spectroscopic data.

A very broad band between 3450 and 2500 cm^{-1} remains in the IR spectrum of **13** and confirms the existence of the free carboxylic group of the thiourea site. The other structural features are similar to those of compound **11**. The individual assignments of the bands are given in the Experimental Section. A part of the ^{1}H NMR spectra of **11** and **13** are compared in Figure 4. The ^{1}H NMR spectrum of **13** expectedly does not show any signals of ethyl ester protons, but reveals a broad signal at 13.24 ppm, which is typical for OH protons of carboxylic groups. The other resonances of **13** have almost the same chemical shifts as those in **11**. This strongly confirms the analogous structures of the two compounds.

The additional carboxylic group in the periphery of ligand H_3L−COOH is intended to act as a linker to couple its rhenium or technetium complexes to bioactive compounds such as peptides. For this purpose, we can consider two alternative routes. In the first approach, the free ligand is coupled to a targeting compound before being treated with the (radioactive) metal ions. This approach follows the classical kit-preparation of ^{99m}Tc radiopharmaceuticals and will give "one kit−one target" solutions. In the second approach, a two-step solution, the radioactive chelate is prepared first as a "bioconjucation kit" and treated with the suitable biomolecule in a subsequent step. This, however, requires a chemically robust chelate and ideally the opportunity of an even rough separation of the preformed chelate from the bulk chelator to ensure an effective bioconjugation in the carrier-free tracer chemistry. On the other hand, such a "bioconjugation kit" would deliver a "one complex−many targets" solution on the basis of an optimized metal chelate.

The ligand system introduced in this Article is not particularly suitable for the first approach of bioconjugation, because the presence of three carboxylic groups in H_3L−COOH would require a complicated protection of those of the iminodiacetic acid site before conjugation to, for example, a peptide. For the second approach, however, the very stable

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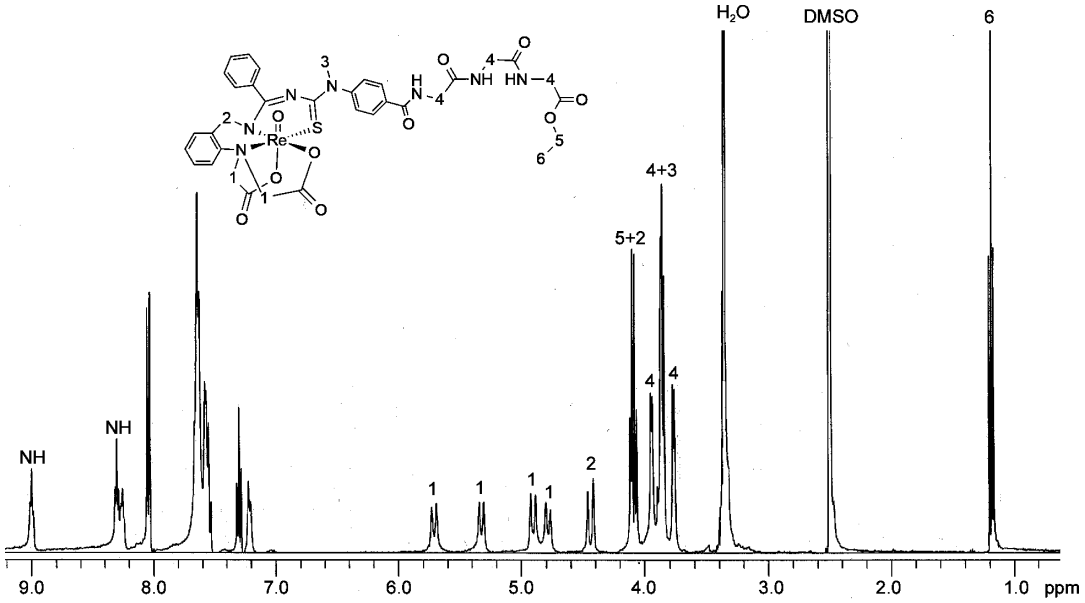

Figure 5. ^{1}H NMR spectrum of [ReO(L−TriGlyCOOEt)] (**14**).

metal chelate seems to be well suitable, because the iminodiacetic moiety is blocked by the formation of coordination bonds and the remaining carboxylic group of phenyl residue can selectively react with biomolecules. Thus, we undertook a "proof-of-principle" experiment. For this, a small peptide such as triglycine ethyl ester was used. The reaction of **13** and triglycine ethyl ester was done in dry DMF at room temperature with the addition of a slight excess of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *N*-hydroxybenzotriazole (HOBT) to give the coupling product [ReO(L−TriGlyCOOEt)] (**14**) with yields of over 95% (Scheme 5).

Compound **14** is sparingly soluble in alcohol, CH_2Cl_2, or $CHCl_3$, but soluble and stable in DMF or DMSO solutions. Good quality single crystals of **14** could not be obtained, but the structure of **14** is clearly elucidated by means of spectroscopic methods.

The IR spectrum of **14** exhibits a strong absorption at 3325 cm^{-1} corresponding to the NH stretches of the triglycine residue. The spectral features belonging to the skeleton of the rhenium complex are identical to those in **13**. The ^{1}H NMR spectrum of **14** (Figure 5) additionally confirms the presence of the triglycine ethyl ester by a triplet at 1.17 ppm and a quartet at 4.07 ppm belonging to ethyl ester protons, and three doublets at 3.75, 3.84, and 3.93 ppm and three triplets at 8.24, 8.29, and 8.99 ppm corresponding to the CH_2 and NH resonances, respectively. Moreover, the complex formation is clearly indicated by the presence of six doublets of the CH_2 protons of the chelate ring, which appear at 4.06 (overlapped with OCH_2 of the ethyl ester group), 4.43, 4.77, 4.89, 5.27, and 5.71 ppm with characteristic geminal coupling patterns. Additionally, the high-resolution mass spectrum of **14** shows only intense peaks at 956.1718 and 972.1576 corresponding to ions $[M + Na]^+$ (calcd 956.1699) and $[M + K]^+$ (calcd 972.1439).

CONCLUSIONS

The pentadentate H_3L is the first representative of a novel, versatile class of ligands, which are well-suited for the formation of stable complexes with rhenium(V) and technetium(V) centers. The use of this new class of compounds in further experiments, particularly such as the synthesis of bioconjugates with ^{186,188}Re or ^{99m}Tc, is planned for the future in collaboration with partner researchers, because such studies are presently not possible in our laboratories.

ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic data in CIF format. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.5b00769.

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Notes

The authors declare no competing financial interest.

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