Syntheses and First Crystal Structures of Rhenium Complexes Derived from ω-Functionalized Fatty Acids as Model Compounds of Technetium Tracers for Myocardial Metabolism Imaging

Christian M. Jung,[a] Werner Kraus,[b] Peter Leibnitz,[b] Hans-Jürgen Pietzsch,[a] Joachim Kropp,[c] and Hartmut Spies*[a]

Keywords: Rhenium / Technetium / Fatty acids / Drug research / Radiopharmaceuticals

In an attempt to develop new technetium-based radiopharmaceuticals for the noninvasive diagnosis of myocardial metabolism, we have synthesized three examples of novel metal-containing fatty acid derivatives according to the "3+1" mixed-ligand and the Schiff base/tricarbonyl design. The chelates contain the metal core in the oxidation states +5 and +1, respectively, and are attached to the end-position of a fatty acid chain. The complex formation was accomplished by ligand-exchange reactions with three different rhenium precursors, whereas the inactive rhenium metal was utilized as a surrogate of the technetium radionuclide. The molecular structures of the fatty acid complexes **7**, **10** and **14** were determined by single-crystal X-ray diffraction analyses and impressively show a general problem in technetium tracer research, namely the significant structural alterations of bioactive molecules by coordination even to small metal chelates.

Introduction

Naturally occurring long-chain fatty acids serve as the main energy source of the normoxic myocardium. Regional alterations in the myocardial fatty acid oxidation may indicate ischemic heart diseases and cardiomyophaties at an early stage and therefore possess a remarkable diagnostic potential in nuclear medicine. Although radio-iodinated fatty acids such as 15-(*p*-[^{123}I]iodophenyl)pentadecanoic acid (IPPA) and its β-methyl-branched derivative BMIPP have proven their applicability for myocardial metabolism imaging in numerous clinical trials, fatty acid scintigraphy has not yet reached widespread application in nuclear medicine.[1] Compared to the technetium-99m-based perfusion tracers that are mainly applied at present, radiolabelled fatty acids allow more convincing scans of viable myocardium. However, logistical disadvantages and disproportionately high costs of the accelerator-produced radionuclide iodine-123 still conflict with a major acceptance of these tracers in routine cardiac diagnostics. On the other hand, the low-price availability from the ^{99}Mo/^{99m}Tc generator combined with its optimal radiophysical properties, and the commercial distribution of pre-prepared instant kits for various clinical examinations have made technetium-99m the preferred radiolabel in nuclear medicinal imaging.[2] The progress in ^{99m}Tc tracer design to monitor specific endogenic functions is nevertheless severely limited by the effect of the artificial radiometal and its coordination chemistry on the in vivo behaviour of labelled bioactive molecules.

The synthesis of technetium-containing long-chain fatty acids for accessing regional discrepancies in myocardial energy production has been a goal of many research groups since 1975.[3] Although a variety of different chelating moieties were used to attach the radiometal at the fatty acid skeleton, low myocardial extraction and poor recognition as a substrate for the β-oxidation in living cells has prevented an application of these ^{99m}Tc-labelled agents in nuclear medicine. A characteristic feature of almost all the technetium-99m fatty acid analogues described so far is the focus on polar tetradentate N_2S_2 chelates with a central oxometal(V) core. In our attempt to create new technetium-labelled fatty acids with an improved myocardial profile, we therefore concentrate on alternative coordination moieties according to the "*n*+1" mixed-ligand approach[4] and the Schiff base/tricarbonyl design.[5] Since working with radioactive compounds affords great care and is subjected to some restrictions, the third-row congener rhenium was used

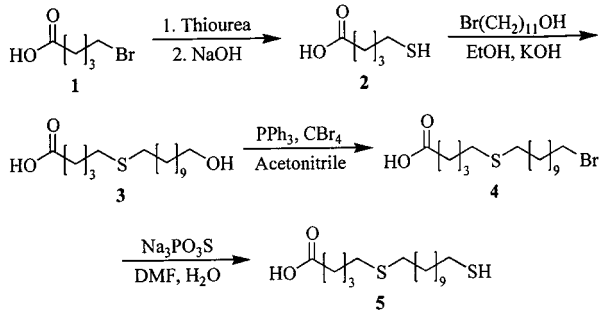
[a] Forschungszentrum Rossendorf e.V., Institut für Bioanorganische und Radiopharmazeutische Chemie,
Postfach 510119, 01314 Dresden, Germany
Fax: (internat.) + 49-(0)351/260-3232
E-mail: H.Spies@fz-rossendorf.de
[b] Bundesanstalt für Materialforschung und -prüfung,
Richard-Willstätter-Straße 11, 12489 Berlin, Germany
E-mail: W.Kraus@bam.de
[c] Medizinische Fakultät Carl Gustav Carus an der Technischen Universität Dresden, Klinik und Poliklinik für Nuklearmedizin,
Fetscherstraße 74, 01307 Dresden, Germany
E-mail: jkmed@rcs.urz.tu-dresden.de

in our preliminary studies as a surrogate for the radioactive technetium.

Results and Discussion

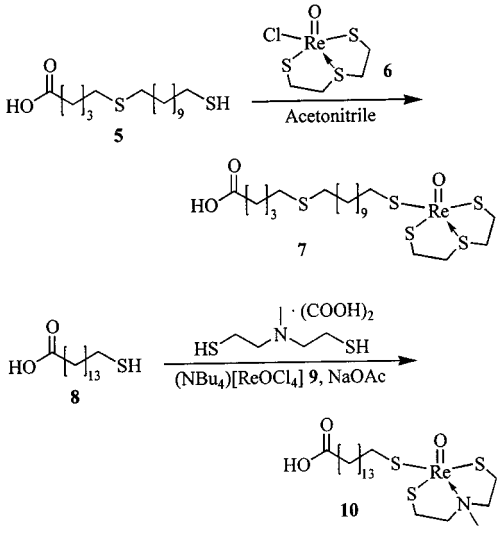
In this paper we report the synthesis and crystal structure of three new classes of rhenium-containing fatty acid analogues. From our point of view, success in the development of bioactive metal-based fatty acid tracers is primarily dependent on the choice of a suitable chelating moiety, which allows a strong binding of the bioligand to the metal centre but preserves the physiological integrity of the fatty acid. Since the carboxylic group probably plays a fundamental role in the substrate cognition in vivo we decided to functionalize fatty acid ligands in their ω-position. For the head structures we used the skeleton of the IPPA tracer,[6] which has been well tested in clinical trials, and the metabolism-blocking sulfur-inserted fatty acid analogue 14-(*R*,*S*)-[^{18}F]fluoro-6-thiaheptadecanoic acid (FTHA),[7] as well as the naturally occurring lauric acid.

Suitable ω-sulfanyl fatty acid ligands required for the "3+1" mixed-ligand concept were synthesized starting from the corresponding ω-bromo derivatives. Whereas the pentadecanoic acid starting material was reasonably accessible by acidic ring opening of the corresponding ω-hydroxylactone by hydrobromic acid,[8] the thia-inserted heptadecanoic acid analogue **4** was prepared in three steps starting from the commercially available 5-bromovaleric acid **1**. After nucleophilic substitution of the halide at the end position by a sulfanyl unit, the fatty acid body was built up by coupling to 11-bromo-1-undecanol under basic conditions. Conversion of the hydroxy group into a bromide was accomplished by an adopted version of the Appel reaction.[9] Sulfonyl groups in the ω-position of the fatty acids **5** and **8** were finally introduced by nucleophilic attack of sodium thiophosphate and subsequent acidic hydrolysis[10] (Scheme 1).



Scheme 1. Synthesis of ω-sulfanyl ε-thia fatty acid **5**

Coordination of the ω-sulfanyl fatty acid ligands **5** and **8** to the rhenium precursors **6**[11] and **9**[12] according the "3+1" approach offers access to the oxorhenium(V) complexes **7** and **10**, respectively. Preparation of **10** was accomplished in moderate yields by a one-pot synthesis of the tetrachlorooxorhenate **9**, the protected "SN(Me)S" tridentate and the ω-sulfanyl fatty acid **8** under basic conditions; complex **7** was obtained almost quantitatively by smooth chloride exchange of the thia fatty acid **5** at the preformed oxorhenium(V) precursor **6** (Scheme 2). The coordination sphere of these mixed-ligand complexes differs in the central donor atom of the tridentate chelator, being sulfur in the model compound **7** and nitrogen in complex **10**. Accompanied by the alteration of the tridentate ligand part is a change in colour from reddish-brown (for **7**) to dark green (for **10**). The infrared spectra of both complexes show a strong absorption band in the region of 955 cm^{-1}, which is distinctive of the central Re=O^{3+} moiety. In the ^{1}H NMR spectra of compound **7** the protons of the tridentate chelator give representative coupling patterns at δ_H = 4.27, 3.90, 3.09 and 1.95; the equivalent signals of the "SN(Me)S" ligand are partly widened and coincided and are observed between δ_H = 3.9−2.6.



Scheme 2. Syntheses of "3+1" mixed-ligand complexes **7** and **10**

Both complexes **7** and **10** were obtained as crystalline solids by slow solvent evaporation at room temperature and were investigated by X-ray analysis. As characteristic of "SSS"-coordinated "3+1" mixed-ligand complexes, **7** possesses a square-pyramidal coordination sphere around the central metal core. The distorted basal surface, stretched by the four sulfur donor atoms, exhibits a twisted orientation with respect to the planar arrangement of the fatty acid chain (Figure 1). An alteration of the tridentate to the "SN(Me)S" chelator results in a transition of the coordination sphere to a distorted trigonal-bipyramidal geometry. In **10** (Figure 2) the axial positions are occupied by the nitrogen donor of the tridentate ligand and the sulfur atom of the monodentate fatty acid derivative, respectively; the corner sites of the triangular plane, however, are taken up by the oxygen atom of the Re=O^{3+} unit and the two sulfanyl groups of the "SN(Me)S" ligand. In structures **7** and **10**, bond lengths and angles within the chelate moieties are of the order of magnitude expected for these types of rhenium coordination compounds (Table 1). However, a special order/disorder phenomenon was detected in the crystal packing of **10**. As frequently observed in this type of complexes

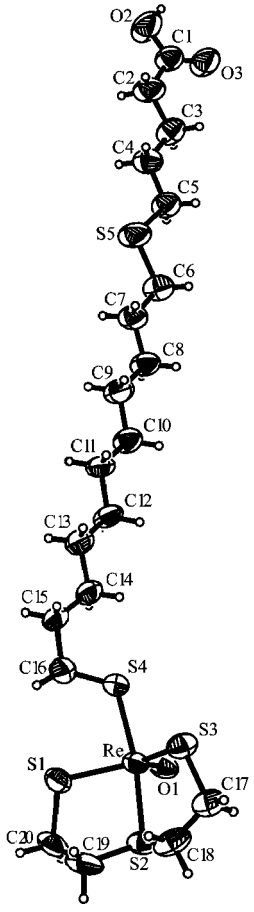


Figure 1. Molecular structure of "SSS"-coordinated "3+1" mixed-ligand complex **7**

Table 1. Selected bond lengths [Å] and angles [°] for "3+1" mixed-ligand complexes **7** and **10**

7		**10**	
Re−O(1)	1.684(8)	Re−O(1)	1.671(5)
Re−S(1)	2.303(3)	Re−N	2.208(7)
Re−S(2)	2.377(3)	Re−S(1)	2.273(4)
Re−S(3)	2.293(3)	Re−S(2)	2.265(3)
Re−S(4)	2.301(3)	Re−S(3)	2.295(3)
O(1)−Re−S(1)	114.2(3)	O(1)−Re−N	95.3(3)
O(1)−Re−S(2)	100.3(3)	O(1)−Re−S(1)	119.0(2)
O(1)−Re−S(3)	115.7(3)	O(1)−Re−S(2)	118.3(2)
O(1)−Re−S(4)	106.6(3)	O(1)−Re−S(3)	105.2(2)
S(1)−Re−S(2)	84.22(13)	N−Re−S(1)	82.72(16)
S(3)−Re−S(1)	129.88(14)	N−Re−S(2)	83.99(17)
S(3)−Re−S(2)	83.41(12)	N−Re−S(3)	159.44(18)
S(3)−Re−S(4)	81.05(11)	S(1)−Re−S(3)	88.54(8)
S(4)−Re−S(1)	88.76(11)	S(2)−Re−S(1)	121.99(11)
S(4)−Re−S(2)	152.78(12)	S(2)−Re−S(3)	84.96(10)

the "SN(Me)S" chelator can change its conformation by a flip-flop mechanism giving rise to a statistical distribution of two equal isomers within the crystal.[13]

Alberto et al. recently introduced the "*fac*-$[M(CO)_3]^+$" fragment as promising synthon for the labelling of biomolecules with technetium.[5] Due to the known tendency of the metal(I) core to interact strongly with soft donor compounds, bidentate aromatic Schiff base ligands are exceedingly suitable for coordinating the tricarbonylmetal(I) moiety. We therefore synthesized an appropriate fatty acid derivative; starting from commercially available ω-aminolauric acid (**11**), the corresponding Schiff base **12** was obtained by simple condensation of picolinaldehyde with the amino group of the analogous lauric acid salt. Since the resulting imines decompose even by neutralisation,[14] the protonation of the carboxyl function was carried out subsequent to the stabilizing attachment of the tricarbonylrhenium moiety. The two nitrogen donor atoms replace two bromide ions of the tricarbonylrhenium(I) precursor **13**.[15] The third halide substituent, however, is responsible for the compensation of the electrical charge and remains fixed in the coordination sphere of the metal(I) core (Scheme 3). Complex **14** was obtained as a deep orange compound and showed the characteristic carbonyl absorption bands at 2021 and 1902 cm^{-1} in the infrared spectrum. The imine proton of the fatty acid ligand was detected as a sharp singlet in the ^1H NMR spectrum at $\delta_H = 8.70$; the

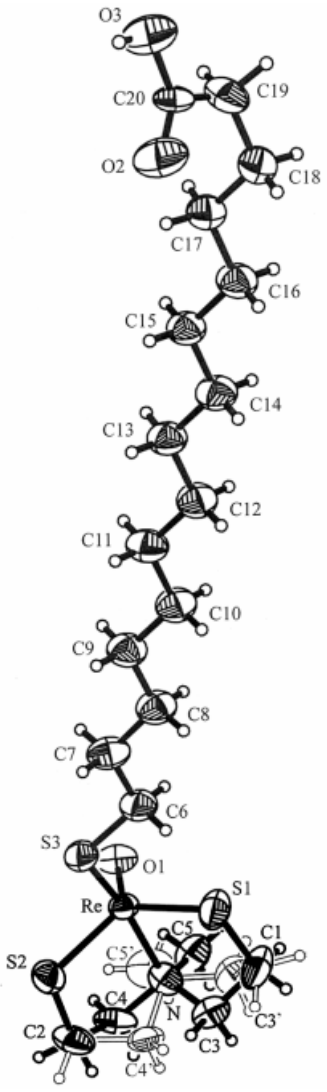
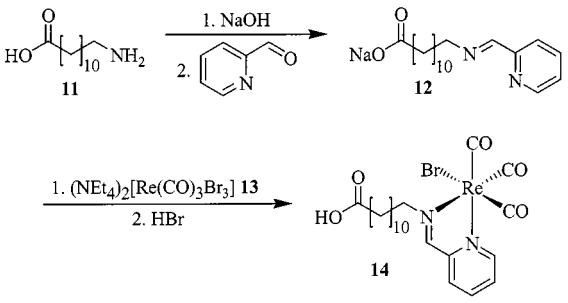


Figure 2. Molecular structure of "SN(Me)S"-coordinated "3+1" mixed-ligand complex **10**

^{13}C signals of the three carbonyl substituents were observed at δ_C = 196.6, 195.8 and 186.1.



Scheme 3. Synthesis of tricarbonylrhenium(I) complex **14**

Compound **14** crystallized upon slow concentration of a saturated solution in acetonitrile. As expected for this type of complex, the molecular structure shows an octahedral coordination sphere around the central rhenium(I) core. The three carbonyl moieties are arranged facial to each other, and the remaining coordination sites are occupied by the bidentate Schiff base ligand and a bromine atom (Figure 3, Table 2).

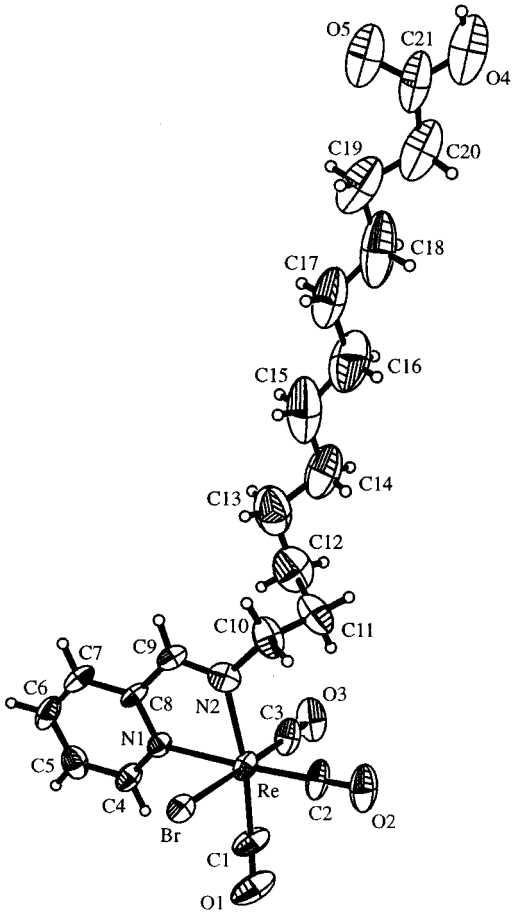


Figure 3. Molecular structure of tricarbonylrhenium(I) complex **14**

Table 2. Selected bond lengths [Å] and angles [°] for tricarbonylrhenium(I) complex **14**

14			
Re−C(1)	1.871(12)	C(1)−Re−C(2)	89.6(6)
Re−C(2)	1.883(12)	C(1)−Re−C(3)	88.6(6)
Re−C(3)	1.873(13)	C(3)−Re−C(2)	89.9(5)
Re−N(1)	2.159(7)	C(1)−Re−N(1)	97.2(5)
Re−N(2)	2.152(9)	C(1)−Re−N(2)	171.5(5)
Re−Br	2.6253(13)	C(2)−Re−N(1)	170.7(4)
O(1)−C(1)	1.158(14)	C(2)−Re−N(2)	98.6(5)
O(2)−C(2)	1.168(13)	C(3)−Re−N(1)	96.5(4)
O(3)−C(3)	1.137(14)	C(3)−Re−N(2)	93.9(5)
N(1)−C(8)	1.345(12)	C(1)−Re−Br(1)	92.6(4)
N(2)−C(9)	1.272(14)	C(2)−Re−Br(1)	89.2(4)
C(8)−C(9)	1.452(15)	C(3)−Re−Br(1)	178.5(4)
		N(1)−Re−Br(1)	84.3(2)
		N(2)−Re−Br(1)	85.0(2)
		N(2)−Re−N(1)	74.4(3)

Particularly conspicuous in the molecular structure of all three complexes, **7**, **10**, and **14**, are the proportions between the chelate moieties and the fatty acid ligands. The drastic structural alteration of the biomolecules, even by coordination to small-sized metal chelates, is certainly a main reason for the laborious progress in the development of new technetium-based radiotracers with the objective of assessment of specific endogenous processes and physiological functions. Nevertheless, structural integrity is only one of several parameters, besides others such as lipophilicity and polarity, that influence the in vivo behaviour of potential ^{99m}Tc radiotracers. Therefore further investigations concerning the biological profile of the technetium-99m analogues of **7**, **10** and **14** will be done to estimate the value of these compounds as potential radiotracers for myocardial metabolism imaging.

Experimental Section

General Remarks: All chemicals and solvents were of reagent grade and utilized without further purification, with the exception of picolinaldehyde, which was freshly distilled prior to use. 11-Bromo-1-undecanol and 12-aminolauric acid were purchased from Fluka. Sodium thiophosphate[16] and *N*-methyl-3-azapentane-1,5-dithiol−oxalic acid[17] were prepared according to the literature. The syntheses involving air-sensitive compounds were carried out under argon using the standard Schlenk technique. The standard workup procedure for product isolation was quenching the reaction mixture in an aqueous solution, followed by extracting thoroughly with $CHCl_3$, washing the extracts with saturated saline, drying owith $MgSO_4$ and evaporating the solvent under reduced pressure. Column chromatography was performed according to Still[18] by using Merck silica gel (0.040−0.063 mm). IR: Perkin−Elmer Specord 2000. NMR: Varian Inova-400. For ^1H NMR $CDCl_3$ (δ_H = 7.26) and CD_3OD (δ_H = 3.31) were used as solvents, for ^{13}C NMR $CDCl_3$ (δ_C = 77.0). Elemental analyses: LECO CHNS 932.

15-Sulfanylpentadecanoic Acid (8): 1.96 g (10.9 mmol) of sodium thiophosphate in 20 mL of H_2O was added to a solution of 1.75 g (5.45 mmol) of 15-bromopentadecanoic acid[8] in 50 mL of di-

methylformamide. The resulting slurry was stirred for 72 h while increasing the temperature from 25 to 50 °C. Afterwards, the mixture was quenched with 3.5% HCl (pH = 2) and stirred overnight. Dilution with additional 30 mL of H_2O and subsequent standard workup yielded a light yellow solid, which was purified by column chromatography (*n*-hexane/Et_2O/HOAc, 70:30:1). Yield: 1.22 g (82%). IR (KBr): $\tilde{\nu}$ = 1714 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.21−1.41 (m, 20 H, 10 × CH_2), 1.33 (t, ^3J = 7.7 Hz, 1 H, CH_2SH), 1.55−1.67 (m, 4 H, CH_2CH_2SH, CH_2CH_2COOH), 2.34 (t, ^3J = 7.5, 2 H, CH_2COOH), 2.52 (dt, ^3J = 7.4, CH_2SH, 2 H). $C_{15}H_{30}O_2S$ (274.47): calcd. C 65.46, H 11.02, S 11.68; found C 65.50, H 10.98, S 11.72.

5-Sulfanylvaleric Acid (2): A mixture of 5.00 g (27.6 mmol) of 5-bromovaleric acid (**1**) and 3.15 g (41.4 mmol) of thiourea in 50 mL of ethanol was heated under reflux for 16 h. After cooling off to room temperature, the solvent was evaporated under reduced pressure and the residue heated with 50 mL of 7.5 M NaOH for another 6 h. The mixture was carefully acidified with 2.5 M H_2SO_4, the organic layer separated and the aqueous phase extracted as usual. Purification of the remaining raw material was accomplished by distillation under vacuum. Yield: 3.04 g (82%). b.p. 102−104 °C/0.7 Torr. ^1H NMR ($CDCl_3$): δ = 1.35 (t, ^3J = 7.9, 1 H, CH_2SH), 1.59−1.80 (m, 4 H, $CH_2CH_2CH_2SH$), 2.37 (t, ^3J = 7.1, 2 H, CH_2COOH), 2.54 (dt, ^3J = 7.2, 2 H, CH_2SH), 10.2−11.3 (br, 1 H, COO*H*). ^{13}C NMR: δ = 23.3, 24.1 (CH_2S, CH_2CH_2COOH), 33.2, 33.4 (CH_2CH_2S, CH_2COOH), 179.8 (*C*OOH). $C_5H_{10}O_2S$ (134.20): calcd. C 44.75, H 7.51, S 23.89; found C 44.43, H 7.74, S 23.50.

17-Hydroxy-6-thiaheptadecanoic Acid (3): To a solution of 2.50 g (43.7 mmol) of KOH in 85 mL of ethanol was added, whilst stirring, 2.9 g (21.6 mmol) of **2** and subsequently 5.40 g (21.5 mmol) of 11-bromo-1-undecanol. After heating under reflux for 12 h, the mixture was acidified with 2.5 M H_2SO_4 and the solvent evaporated under reduced pressure. The residue was partitioned between 75 mL of H_2O and $CHCl_3$ and worked up by standard procedures. Crystallisation from MeOH at −15 °C yielded the pure fatty acid **3** as a colourless solid. Yield: 5.66 g (86%). IR (KBr): $\tilde{\nu}$ = 1690 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.19−1.39 (m, 14 H, 7 × CH_2), 1.47−1.76 (m, 8 H, CH_2CH_2OH, $CH_2CH_2SCH_2CH_2$, CH_2CH_2COOH), 2.33 (t, ^3J = 7.2, 2 H, CH_2COOH), 2.46 (t, ^3J = 7.4, 2 H), 2.48 (t, ^3J = 7.2, 2 H, CH_2SCH_2), 3.59 (t, ^3J = 6.7, 2 H, CH_2OH), 6.77 (br, 2 H, CH_2OH, COO*H*). $C_{16}H_{32}O_3S$ (304.49): calcd. C 63.11, H 10.59, S 10.53; found C 63.04, H 10.50, S 10.47.

17-Bromo-6-thiaheptadecanoic Acid (4): 646 mg (2.46 mmol) of PPh_3 was added, whilst stirring, to a solution of 817 mg (2.46 mmol) of CBr_4 and 250 mg (821 μmol) of **3** in 25 mL of acetonitrile at 0 °C. The mixture was allowed to reach ambient temperature and was stirred overnight. The solvent was evaporated under reduced pressure and the residue partitioned between 50 mL of H_2O and $CHCl_3$ followed by standard workup and column chromatography (*n*-hexane/Et_2O/HOAc, 75:25:1). Yield: 238 mg (79%). IR (KBr): $\tilde{\nu}$ = 1693 (C=O), 647 (C−Br) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.22−1.48 (m, 14 H, 7 × CH_2), 1.50−1.80 (m, 6 H, $CH_2CH_2SCH_2CH_2$, CH_2CH_2COOH), 1.85 (quint, ^3J = 7.1, 2 H, CH_2CH_2Br), 2.38 (t, ^3J = 7.2, 2 H, CH_2COOH), 2.49 (t, ^3J = 7.5, 2 H,), 2.52 (t, ^3J = 7.4, 2 H, CH_2SCH_2), 3.40 (t, ^3J = 6.9, 2 H, CH_2Br). $C_{16}H_{31}BrO_2S$ (267.39): calcd. C 52.31, H 8.50, S 8.73; found C 52.28, H 8.38, S 8.53.

17-Sulfanyl-6-thiaheptadecanoic Acid (5): ω-Sulfanyl ligand **5** was prepared from 200 mg (544 μmol) of **4** by the procedure described for **8**. Yield: 122 mg (70%). IR (KBr): $\tilde{\nu}$ = 1694 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.20−1.41 (m, 14 H, 7 × CH_2), 1.32 (t, ^3J = 7.8, 1 H, CH_2SH), 1.49−1.79 (m, 8 H, CH_2CH_2SH, $CH_2CH_2SCH_2CH_2$, CH_2CH_2COOH), 2.37 (t, ^3J = 7.2, 2 H, CH_2COOH), 2.44−2.55 (m, 6 H, CH_2SCH_2, CH_2SH). $C_{16}H_{32}O_2S_2$ (320.56): calcd. C 59.95, H 10.06, S 20.01; found C 59.97, H 10.08, S 20.12.

Oxorhenium(V) Complex 7: 50 mg (128 μmol) of chloro(3-thiapentane-1,5-dithiolato)oxorhenium(V) (**6**)[11] was dissolved in 6 mL of hot acetonitrile while stirring. To this mixture 45 mg (140 μmol) of the fatty acid **5** was added. The mixture was refluxed for 30 min and then concentrated to dryness. The residue was purified by flash chromatography ($CHCl_3$/EtOAc/HOAc, 60:40:1). Crystals suitable for single crystal analysis were obtained by slow evaporation of a saturated $CHCl_3$/acetonitrile solution of **7** at room temperature. Yield: 81 mg (94%). IR (KBr): $\tilde{\nu}$ = 1703 (C=O), 958 (Re=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.23−1.41 (m, 12 H, 6 × CH_2), 1.46−1.60 (m, 4 H), 1.64 (quint, ^3J = 7.3, 2 H), 1.74 (quint, ^3J = 7.4, 2 H, $CH_2CH_2SCH_2CH_2$, CH_2CH_2COOH, $CH_2CH_2CH_2SRe$), 1.88 (quint, ^3J = 7.6, 2 H, CH_2CH_2SReO"SSS"), 1.95 (ddd, J_1 = 4.9, J_2 = 9.9, J_3 = 14.6, 2 H, A-part ABCD system "SSS"), 2.38 (t, ^3J = 7.3, 2 H, CH_2COOH), 2.49 (t, ^3J = 7.3, 2 H), 2.52 (t, ^3J = 7.1, 2 H, $CH_2SCH_2CH_2CH_2$), 3.09 (dt, J_1 = 4.0, J_2 = 13.8, 2 H, B-part ABCD system "SSS"), 3.83 (t, ^3J = 7.5, 2 H, CH_2SReO"SSS"), 3.90 (dd, J_1 = 3.8, J_2 = 10.2, 2 H, C-part ABCD system "SSS"), 4.27 (dd, J_1 = 4.7, J_2 = 13.1, 2 H, D-part ABCD system "SSS"). $C_{20}H_{39}O_3ReS_4$ (674.06): calcd. C 35.64, H 5.83, S 23.79; found C 35.46, H 5.81, 23.86.

Oxorhenium(V) Complex 10: A mixture of 140 mg (510 μmol) of **8**, 109 mg (452 μmol) of *N*-methyl-3-azapentane-1,5-dithiol−oxalic acid, 265 mg (452 μmol) of tetrachlorooxorhenate **9**[12] and 4 mL of 1 M methanolic NaOAc in 25 mL of MeOH was stirred at 40 °C for 24 h. The solvent was removed under reduced pressure and the remaining brown solid partitioned between 25 mL of H_2O and $CHCl_3$. After standard workup, the pure complex was isolated by column chromatography ($CHCl_3$/EtOAc/HOAc, 50:50:1) and subsequent crystallisation from ethanol. Yield: 191 mg (68%). IR (KBr): $\tilde{\nu}$ = 1705 (C=O), 950 (Re=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.20−1.38 (m, 18 H, 9 × CH_2), 1.47 (quint, ^3J = 7.4, 2 H, $CH_2CH_2CH_2SRe$), 1.63 (quint, ^3J = 7.4, 2 H, CH_2CH_2COOH), 1.85 (quint, ^3J = 7.4, 2 H, CH_2CH_2SRe"SNS"), 2.35 (t, ^3J = 7.6, 2 H, CH_2COOH), 2.63 (m, 2 H, "SNS"), 3.16−3.22 (m, 4 H, "SNS", CH_2SReO"SNS"), 3.35 (s, 3 H, NCH_3), 3.54 (m, 2 H, "SNS"), 3.5−3.9 (br, 2 H, "SNS"). $C_{20}H_{40}NO_3ReS_3$ (624.95): calcd. C 38.44, H 6.45, N 2.24, S 15.39; found C 38.52, H 6.65, N 2.21, S 15.47.

Sodium 12-{[(Pyridin-2-yl)methylene]amino}undecanoate (12): 200 mg (777 μmol) of amino fatty acid **11** was dissolved in 5 mL of MeOH, containing 31 mg (775 μmol) of NaOH. The solution was filtered and then concentrated to dryness. The residue was redissolved in 5 mL of MeOH and 125 mg (1.15 mmol) of freshly distilled picolinaldehyde was added whilst stirring at 0 °C. The mixture was stirred for additional 12 h at room temperature before removing the solvent and washing the residue carefully with several portions of acetone and Et_2O. Schiff base sodium salt **12** was obtained as a light brown powder without any further purification steps. Yield: 248 mg (87%). IR (KBr): $\tilde{\nu}$ = 1648 (CH=N), 1561 (C=O) cm^{-1}. ^1H NMR (CD_3OD): δ = 1.23−1.42 (m, 14 H, 7 × CH_2), 1.59 (m, 2 H), 1.73 (m, 2 H CH_2CH_2N, CH_2CH_2COONa), 2.14 (t, ^3J = 7.6, CH_2COONa, 2 H), 3.68 (t, ^3J = 7.0, 2 H, CH_2N), 7.48 (m, 1 H, $H_{5\text{-Ar}}$), 7.91 (m, 1 H, $H_{4\text{-Ar}}$), 7.99 (m, 1 H, $H_{3\text{-Ar}}$), 8.37 (s, 1 H, CH=N), 8.61 (m, 1 H, $H_{6\text{-Ar}}$). $C_{18}H_{27}N_2NaO_2$ (326.41): calcd. C 66.23, H 8.34, N 8.58; found C 65.94, H 8.53, N 8.87.

Table 3. Crystallographic data and structure refinement for complexes **7**, **10** and **14**

	7	**10**	**14**
Empirical formula	$C_{20}H_{39}O_3ReS_5$	$C_{20}H_{40}NO_3ReS_3$	$C_{21}H_{28}BrN_2O_5Re$
Formula mass	674.01	624.91	654.56
Crystal system	orthorhombic	monoclinic	triclinic
Space group	*Pbca*	$P2_1/c$	$P\bar{1}$
a [Å]	9.0585(3)	16.17(2)	6.6516(14)
b [Å]	13.1617(4)	11.082(16)	8.1605(16)
c [Å]	45.3602(15)	14.18(2)	23.325(5)
α [°]	90	90	89.678(4)
β [°]	90	92.15(3)	86.915(4)
γ [°]	90	90	74.811(4)
V [Å^3]	5408.1(3)	2538(6)	1220.0(4)
Z	8	4	2
$D_{calcd.}$ [g cm^{-3}]	1.656	1.635	1.782
Absorption coefficient [mm^{-1}]	4.898	5.054	6.649
F(000)	2704	1256	636
Crystal size [mm^{-1}]	0.450 × 0.360 × 0.054	0.21 × 0.11 × 0.05	0.4 × 0.28 × 0.1
θ range [°]	1.80−29.03	2.23−23.43	0.87−20.00
Index ranges	$-11 \le h \le 12$	$-17 \le h \le 17$	$-6 \le h \le 6$
	$-17 \le k \le 17$	$-12 \le k \le 10$	$-6 \le k \le 7$
	$-61 \le l \le 48$	$-15 \le l \le 15$	$-20 \le l \le 22$
Reflections collected	30609	10503	3785
Independent reflections	6759 [R_{int} = 0.0704]	3639 [R_{int} = 0.0608]	2282 [R_{int} = 0.0705]
Absorption correction	Ψ scan	Ψ scan	Ψ scan
Max. and min. transmission	0.350, 0.173	0.31671, 0.20085	0.409, 0.253
Refinement method	full-matrix least squares on F^2	full-matrix least squares on F^2	full-matrix least squares on F^2
Data/restraints/parameters	6654/0/263	3639/14/280	2282/11/271
Goodness-of-fit on F^2	1.161	0.666	0.866
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0841, *wR*2 = 0.2088	*R*1 = 0.0345, *wR*2 = 0.0910	*R*1 = 0.0416, *wR*2 = 0.1147
R indices (all data)	*R*1 = 0.0928, *wR*2 = 0.2136	*R*1 = 0.0454, *wR*2 = 0.0983	*R*1 = 0.0454, *wR*2 = 0.1238
Largest diff. peak and hole [eÅ^{-3}]	2.170, −2.066	0.948, −1.670	0.898, −1.825

(Tricarbonyl)rhenium(I) Complex 14: 45 mg (130 μmol) of fatty acid ligand **12** was dissolved in 2 mL of MeOH and added to a solution of 100 mg (130 μmol) of tricarbonylrhenium(I) precursor **13**[15] in 1 mL of MeOH. The mixture immediately turned to a deep orange colour and became cloudy within 15 min. After stirring overnight at room temperature, the solvent was removed in a nitrogen stream. Then 1 mL of $CHCl_3$ and 1 mL of 4 M aqueous HBr were added and the mixture was vigorously stirred for another 24 h. Afterwards, the organic layer was separated and the aqueous phase thoroughly extracted in the usual manner. Purification of the obtained residue was accomplished by column chromatography ($CHCl_3$/EtOAc/HOAc, 100:25:4). Crystals of complex **14** suitable for single-crystal X-ray analysis were obtained by slow crystallization of **14** from an acetonitrile solution at room temperature. Yield: (74%). IR (KBr): $\tilde{\nu}$ = 2021, 1902 (C≡O), 1713 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.22−1.43 (m, 14 H, 7 × CH_2), 1.62 (quint, ^3J = 7.2, 2 H, CH_2CH$_2$COOH), 1.94−2.35 (m, 2 H, CH_2CH$_2$N), 2.34 (t, ^3J = 7.4, 2 H, CH_2COOH), 4.03 (m, 1 H), 4.26 (m, 1 H, CH_2N), 7.56 (m, 1 H, $H_{5\text{-Ar}}$), 7.90 (m, 1 H, $H_{4\text{-Ar}}$), 8.05 (m, 1 H, $H_{3\text{-Ar}}$), 8.70 (s, 1 H, CH=N), 9.04 (m, 1 H, $H_{6\text{-Ar}}$). $C_{21}H_{28}BrN_2O_5Re$ (654.57): calcd. C 38.53, H 4.31, N 4.28, Br 12.21; found C 38.40, H 4.35, N 4.24, Br 12.31.

X-ray Crystallographic Studies: Crystal data and details of structure determinations for complexes **7**, **10,** and **14** are listed in Table 3. Using Mo-K_α radiation, reflection intensities were collected at room temperature (293 K) with a Siemens SMART diffractometer, equipped with a CCD area detector. The structures were solved by direct methods using SHELXS-90 and refined with SHELXL-97.[19] An empirical absorption correction (Ψ-scan) was applied. All non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were calculated corresponding to their geometrical conditions and refined using the riding model. Atomic numbering schemes are shown in Figure 1 (for **7**), Figure 2 (for **10**) and Figure 3 (for **14**). Selected bond lengths and angles are listed in Tables 1 and 2. For complex **7** only crystals of poor quality were available, reflected in a relatively high *R* value for this compound. CCDC-156312 (**7**), -172606 (**10**) and -172605 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

This work was funded by grants from the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie.

[1] [1a] N. Tamaki, K. Morita, Y. Kuge, E. Tsukamoto, *J. Nucl. Med.* **2000**, *41*, 1525−1534. [1b] F. F. Knapp Jr., J. Kropp, *Eur. J. Nucl. Med.* **1995**, *22*, 361−381.
[2] J. R. Dilworth, S. J. Parrott, *Chem. Soc. Rev.* **1998**, *27*, 43−55.
[3] [3a] W. C. Eckelman, S. M. Karesh, R. C. Reba, *J. Pharm. Sci.* **1975**, *64*, 704−706. [3b] F. H. Liang, F. Virzi, D. J. Hnatovich, *Int. J. Radiat. Appl. Instrum. Part B, Nucl. Med. Biol.* **1987**, *14*, 63−67. [3c] R. H. Mach, H. F. Kung, P. Jungwiwattanaporn, Y.-Z. Guo, *Int. J. Radiat. Appl. Instrum. Part B, Nucl. Med. Biol.* **1991**, *18*, 215−226. [3d] H. Alagui, M. Vidal, F. Riché, A. du Moulinet d'Hardemare, J. P. Mathieu, R. Pasqualini, *Technetium and Rhenium in Chemistry and Nuclear Medicine*,

SGEditoriale, Padova, **1995**, vol. 4, p. 325−327. [3e] G. S. Jones Jr., D. R. Elmaleh, H. W. Strauss, A. J. Fischman, *Nucl. Med. Biol.* **1994**, *21*, 117−123. [3f] G. S. Jones Jr., D. R. Elmaleh, H. W. Strauss, A. J. Fischman, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2399−2404. [3g] W. Chun-Ying, J. Shu-Ren, F. Ping, Z. Xiang, C. Zheng-Ping, C. Guo-Xian, *Nucl. Sci. Tech.* **1998**, *9*, 29−32.

[4] H. Spies, H.-J. Pietzsch, B. Johannsen, *Technetium, Rhenium and other Metals in Chemistry and Nuclear Medicine*, SGEditoriali, Padova, **1999**, vol. 5, p. 101−108.

[5] [5a] R. Alberto, R. Schibli, A. P. Schubiger, U. Abram, H.-J. Pietzsch, B. Johannsen, *J. Am. Chem. Soc.* **1999**, *121*, 6076−6077. [5b] R. Waibel, R. Alberto, J. Willuda, R. Finnern, R. Schibli, A. Stichelberger, A. Egli, U. Abram, J.-P. Mach, A. Plückthun, P. A. Schubiger, *Nature Biotechnol.* **1999**, *17*, 897−901. [5c] N. Metzler-Nolte, *Angew. Chem.* **2001**, *113*, 1072−1076; *Angew. Chem. Int. Ed.* **2001**, *40*, 1040−1043.

[6] H.-J. Machulla, K. Dutschka, D. van Beuningen, T. Chen, *J. Radioanal. Chem.* **1981**, *65*, 279−286.

[7] T. R. DeGrado, *J. Labelled Compd. Radiopharm.* **1991**, *29*, 989−995.

[8] C. Galli, L. Mandolini, *Gazz. Chim. Ital.* **1975**, *105*, 367−376.

[9] R. Appel, *Angew. Chem.* **1975**, *87*, 863−874; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801−811.

[10] C. Bieniarz, M. J. Cornwell, *Tetrahedron Lett.* **1993**, *34*, 939−942.

[11] T. Fietz, H. Spies, H.-J. Pietzsch, P. Leibnitz, *Inorg. Chim. Acta* **1995**, *231*, 233−236.

[12] R. Alberto, R. Schibli, A. Egli, P. A. Schubiger, W. A. Herrmann, G. Artus, U. Abram, T. A. Kaden, *J. Organomet. Chem.* **1995**, *493*, 119−127.

[13] P. Leibnitz, G. Reck, H.-J. Pietzsch, H. Spies, *Structures of Technetium and Rhenium Complexes* (Ed.: Forschungszentrum Rossendorf), Wissenschaftlich-Technische Berichte FZR-311, Dresden, **2001**, p. 21.

[14] S. Ohta, M. Okamoto, *Chem. Pharm. Bull.* **1980**, *28*, 1917−1919.

[15] R. Alberto, A. Egli, U. Abram, K. Hegetschweiler, V. Gramlich, P. A. Schubiger, *J. Chem. Soc., Dalton Trans.* **1994**, 2815−2820.

[16] S. K. Yasuda, J. L. Lambert, *J. Am. Chem. Soc.* **1954**, *76*, 5356.

[17] M. Friebe, Dissertation, Technische Universität Dresden, **1999**.

[18] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923−2925.

[19] G. M. Sheldrick, *SHELXL-97*, Universität Göttingen, **1997**.

Received November 13, 2001
[I01455]