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Rhenium complexes with phosphine-containing peptides. Synthesis and characterization of oxorhenium(v) complexes with *N*-{*N*-[3-(diphenylphosphino)propionyl]glycyl}-L-*S*-benzylcysteine and its methyl ester

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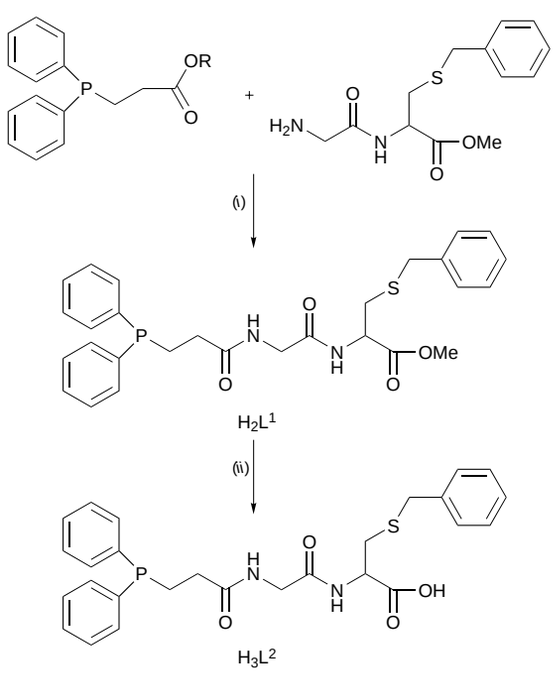
The co-ordination of dipeptides modified with a phosphine group to the $Re{=}O^{3+}$ core has been studied, and the new donor sets PN_2X (X = O or S) achieved. *N*-{*N*-[3-(Diphenylphosphino)propionyl]glycyl}-L-*S*-benzylcysteine (H_3L^2) and its methyl ester derivative (H_2L^1) have been used for preparing six-co-ordinated oxorhenium(v) complexes, providing a new chelating system for targeting $^{186/188}$Re to protein bioactive molecules. The complexes have been characterized by means of UV/VIS, IR, FAB and ^{1}H NMR spectroscopy. The crystal structures of $[ReO(L^2)(OH_2)]\cdot H_2O\cdot MeOH$ and $[ReO(L^1)Cl]$ have been established. In both the complexes the co-ordination geometry is distorted octahedral. The ligands are tetradentate, co-ordinating the $Re{=}O^{3+}$ moiety through the phosphine phosphorus, the two deprotonated amide nitrogens and the O or S atom from the carboxylate or thioether groups. When the cysteine carboxylic moiety is free, it can replace, in organic solvents, the thioether sulfur to give a stable complex, the fourth donor atom in the equatorial plane being a carboxylate oxygen. In basic medium $[ReO(L^1)Cl]$ underwent substitution of Cl^- by OH^-, evidence for the high stability of the PN_2S donor set.

In the last few years the discovery and radiotherapeutic application of $^{186/188}$Re-based radiopharmaceuticals[1] has greatly changed the landscape of rhenium co-ordination chemistry. A possible way for rhenium to explicate its own therapeutic action is to link it with a bioactive molecule with a high affinity for cancer cells. This may open up the field of radioimmunotherapy and provide an update in the battle against cancer.[2] Bioactive molecules can be rhenium-labelled *via* the preformed-chelate or chelator–conjugate approaches.[3] To date, well known chelating moieties such as diaminodithiol,[4] N_2S_2,[5,6] sulfanylacetyltriglycine[7] and hexamethylpropyleneamineoxime[8] have been tested for labelling of bioactive molecules with technetium or rhenium and the results are promising. Nevertheless, these compounds must be entirely incorporated into the biological molecule, thus introducing significant structural modifications. The co-ordinating properties of amido N, thiolato S and phosphino P atoms towards rhenium(v) have been well investigated[9] so that in this work we have concentrated on PN_2O and PN_2S systems obtained by a coupling reaction between a diphenylphosphinopropionic active ester and the dipeptide glycyl-*S*-benzyl or its methyl ester derivative (Scheme 1). In this reaction the addition of a phosphine group is the only change introduced in the peptide. These compounds have been designed for investigating how phosphine groups can stabilize the chelating system. This work is part of a project to synthesize phosphine-modified peptides for the successful labelling of peptides with a high affinity for receptors.[10]



Scheme 1 R = *N*-Succinimido. (*i*) 1,4-Dioxane; (*ii*) NaOH

Experimental

Methods and materials

All chemicals were of reagent grade and used without purification. The complexes $[ReOCl_3(PPh_3)_2]$ **1** and $[ReOCl_2(OEt)(PPh_3)_2]$ **2** were prepared as reported in the literature.[11] Elemental analyses were performed on a Carlo Erba model 1106 elemental analyser. Infrared spectra were recorded in the range 4000–400 cm^{-1} on a Perkin-Elmer 1760-Infrared Fourier-transform spectrometer using KBr pellets, ^{1}H NMR spectra on a Varian Gemini 200 spectrometer (200 MHz) using $SiMe_4$ as internal standard (^{1}H), ^{31}P NMR spectra on a Bruker AC-200 spectrometer using 85% aqueous H_3PO_4 as external reference (^{31}P), UV/VIS spectra in a suitable solvent on a Perkin-Elmer Lambda 15 spectrophotometer or the photodiode array of an

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HPLC UV/VIS detector and positive-ion FAB mass spectra using a 3-nitrobenzyl alcohol matrix on a VG 30-250 spectrometer (VG Instrument) at the probe temperature. For the mass spectral measurements Xe was used as the primary beam gas and the ion gun was operated at 8 keV (*ca.* 1.28×10^{-15} J) and 100 μA. Data were collected over the range *m*/*z* 100–1000 at 0.7 s per scan. The HPLC experiments were performed on a Pharmacia LKB instrument with a 2156 solvent conditioner, a 2140 Rapid Spectra Detector, a 2140 rsd optical unit and a 2249 gradient pump. The chromatograms were collected at 254 nm. The signals and the UV/VIS spectra in the wavelength range 220–450 nm were elaborated with a Wavescan EG HPLC analysis program.

Syntheses

***N*-{*N*-[3-(Diphenylphosphino)propionyl]glycyl}-L-*S*-benzylcysteine methyl ester (H_2L^1).** A 1,4-dioxane solution (100 cm^3) of *N*-glycyl-L-*S*-benzylcysteine methyl ester hydrochloride (1.91 g, 6.0 mmol), deaerated with Ar, was treated with NEt_3 (0.91 cm^3, 6.5 mmol) and the $NHEt_3Cl$ was filtered off after 10 min of stirring. To the solution under Ar was added 3-(diphenylphosphino)propionylsuccinimide (2.14 g, 6 mmol) and left at room temperature for 12 h. The formation of the coupling product was detected by TLC (CH_2Cl_2–MeOH, 95:5). The mixture was evaporated to dryness under reduced pressure. The oily mixture was redissolved in ethyl acetate (100 cm^3) deaerated with Ar, and washed twice with an acidic solution (pH ≈ 3), water (100 cm^3), 10% $NaHCO_3$ (100 cm^3), again with water (100 cm^3), dried over Na_2SO_4 and treated with light petroleum (b.p. 30–60 °C) resulting in a white fine powder. Yield: 1.96 g (63%). The ^1H and ^{31}P NMR spectra were consistent with the formula[12] (Found: C, 64.1; H, 5.8; N, 5.3; S, 6.4. Calc. for $C_{28}H_{31}N_2O_4PS$: C, 64.3; H, 6.0; N, 5.4; S, 6.1%).

***N*-{*N*-[3-(Diphenylphosphino)propionyl]glycyl}-L-*S*-benzylcysteine (H_3L^2).** A methanol solution (20 cm^3) of H_3L^1 (0.5 g, 0.96 mmol) deaerated with Ar was treated with a deaerated 1 mol dm^{-3} NaOH water solution (1 cm^3). The reaction mixture was left at room temperature for 14 h under Ar. The reaction was monitored by TLC ($CHCl_3$–MeOH–$MeCO_2H$, 90:8:2). The reaction rate can be increased by adding a further amount of NaOH. The mixture was acidified with 1 mol dm^{-3} HCl until pH 3. A white precipitate of the acid form of H_3L^2 was recovered and dried. Yield 0.4 g, 78%. ^1H NMR [$(CD_3)_2SO$]: δ 2.20–2.49 [4 H, m, $(CH_2)_2$], 2.52–2.77 (2 H, m, β-CH_2 of Cys), 3.74 (4 H, s, CH_2 of Gly + SCH_2), 4.42–4.45 (1 H, m, α-CH_2 of Cys), 7.22–7.44 (15 H, m, Ph), 8.17–8.25 (2 H, t + d, NH) and 12.92 (1 H, s, CO_2H). ^{31}P NMR ($CDCl_3$): δ −17.7 (Found: C, 63.6; H, 5.5; N, 5.3; S, 6.4. Calc. for $C_{27}H_{29}N_2O_4PS$: C, 63.8; H, 5.8; N, 5.5; S, 6.3%).

Chloro(*N*-{*N*-[3-diphenylphosphino)propionyl]glycyl}-L-*S*-benzylcysteinato-*P*,*N*,*N*,*S*)oxorhenium(v), [ReO(HL^2)Cl] 3. *Method* (*a*). A suspension of complex **1** (0.58 g, 0.70 mmol) in EtOH (25 cm^3) was treated with H_3L^2 (0.40 g, 0.79 mmol) dissolved in EtOH (25 cm^3). The mixture was deaerated with Ar and then refluxed for 30 min, until the starting yellow-green solid completely disappeared and the solution was light violet. The solution was evaporated to low volume until a dark violet powder formed. The latter was recrystallized from hot EtOH. Small light violet crystals were recovered after slow evaporation of the mixture (yield 0.24 g, 47%). From the mother-liquors a light brown powder of complex **4** was also recovered (yield 0.05 g, 9%). A drop of a concentrated HCl solution increased the yield of complex **3** and **4** disappeared.

Method (*b*). Solid H_3L^2 (0.36 g, 0.71 mmol) was added to a CH_2Cl_2 solution (25 cm^3) of complex **1** (0.59 g, 0.71 mmol) and stirred for 1 h in an argon atmosphere at room temperature. The resulting green solution was treated with argon-degassed EtOH (75 cm^3). Within an hour the solution became red-violet and brilliant violet crystals were recovered after slow evaporation. After filtration of **3** the mother-liquors gave yellow-brown crystals of complex **4**. Yields: 0.25 g, 48% of **3** and 0.35 g, 25% of **4** (Found: C, 43.7; H, 3.7; Cl, 4.6; N, 3.7; P, 4.0; S, 4.0. Calc. for $C_{27}H_{27}ClN_2O_5PReS$: C, 43.5; H, 3.6; Cl, 4.7; N, 3.8; P, 4.1; S, 4.3%). IR (KBr, cm^{-1}): 1785, 1614 [ν(C=O)]; 967 [ν(Re=O)]. Positive-ion FAB mass spectrum: *m*/*z* (relative intensity) 709 (*M* − Cl, 70), 617 (*M* − Cl − CH_2Ph, 100) and 573 (*M* − Cl − CH_2Ph − CO_2H, 64%). UV/VIS [CH_2Cl_2, λ/nm (log ε)]: 273 (3.94) and 453 (2.24).

Aqua(*N*-{*N*-[(3-diphenylphosphino)propionyl]glycyl}-L-*S*-benzylcysteinato-*P*,*N*,*N*,*O*)oxorhenium(v), [ReO(L^2)(OH_2)] 4. A suspension of complex **2** (0.58 g, 0.7 mmol) in EtOH (25 cm^3) was treated with H_3L^2 (0.36 g, 0.7 mmol) dissolved in EtOH (25 cm^3). The mixture was deaerated with Ar and then refluxed for 30 min, until the starting yellow-green solid completely disappeared and the solution was bright brown. The solution was evaporated to low volume until a yellow-brown powder precipitated. The latter was recrystallised from hot MeOH. Yield 0.37 g, 68%. A small amount of **3** (yield 0.03 g, 5%) was also recovered (Found: C, 43.5; H, 4.5; N, 3.5; P, 4.1; S, 4.2. Calc. for $C_{28}H_{34}N_2O_8PReS$: C, 43.3; H, 4.4; N, 3.6; P, 4.0; S, 4.1%). NMR [$(CD_3)_2SO$]: ^1H, δ 2.61–4.12 [6 H, m, $P(CH_2)_2$ + β-CH_2 of Cys], 3.64, 3.75 (dd, 2 H, J_{gem} = 12, SCH_2Ph), 4.44, 4.55 (2 H, dd, J_{gem} = 19 Hz, CH_2 of Gly), 4.73 (1 H, m, α-CH of Cys) and 7.31–8.07 (15 H, m, aromatic); ^{31}P, δ 7.14. IR (KBr, cm^{-1}): 1667 [ν(C=O)] and 1005 [ν(Re=O)]. Positive-ion FAB mass spectrum: *m*/*z* (relative intensity) 709 (*M* − H_2O, 60), 617 (*M* − H_2O − CH_2Ph, 25) and 573 (*M* − H_2O − CH_2Ph − CO_2H, 100%). UV/VIS [EtOH, λ/nm (log ε)]: 266 (3.90) and 464 (2.05).

Chloro(*N*-{*N*-[3-(diphenylphosphino)propionyl]glycyl}-L-*S*-benzylcysteinato methyl ester-*P*,*N*,*N*,*S*)oxorhenium(v), [ReO(L^1)Cl] 5. *Method* (*a*). A suspension of complex **1** (0.56 g, 0.67 mmol) in EtOH (25 cm^3) was treated with H_2L^1 (0.350 g, 0.67 mmol) dissolved in EtOH (25 cm^3). The mixture was deaerated with Ar and then refluxed for 2 h, until the starting yellow-green solid completely disappeared and the solution was red-violet. The solution was evaporated to dryness under vacuum giving a violet oil, which was redissolved in CH_2Cl_2 and Et_2O added until the solution became opalescent. Red-violet crystals were recovered after slow evaporation of the mixture (yield 0.2 g, 37%). Recrystallization was from hot EtOH.

Method (*b*). Solid H_2L^1 (0.37 g, 0.71 mmol) was added to a CH_2Cl_2 solution (25 cm^3) of complex **1** (0.59 g, 0.71 mmol) and stirred for 1 h under an argon atmosphere at room temperature. The resulting green solution was treated with Ar-degassed EtOH (75 cm^3). Within an hour it had become red-violet and brilliant violet crystals were recovered after slow evaporation. Yield 0.4 g, 74% (Found: C, 44.6; H, 4.0; Cl, 4.5; N, 3.9; P, 4.4; S, 4.5. Calc. for $C_{28}H_{29}ClN_2O_5PReS$: C, 44.3; H, 3.9, Cl, 4.7; N, 3.7; P, 4.1; S, 4.3%). ^1H NMR: ($CDCl_3$) δ 2.69–3.82 [6 H, m, $P(CH_2)_2$ + β-CH_2 of Cys], 3.85 (3 H, s, OCH_3), 3.95, 4.20 (2 H, dd, J_{gem} = 12, SCH_2Ph), 4.88, 5.29 (2 H, m, CH_2 of Gly), 5.52 (1 H, dd, *J* = 3, 7, α-CH of Cys), 6.78–7.92 (15 H, m, aromatic); [$(CD_3)_2SO$] δ 2.50–4.04 [6 H, m, $P(CH_2)_2$ + β-CH_2 of Cys], 3.79 (3 H, s, OCH_3), 4.22, 4.45 (2 H, dd, J_{gem} = 12, SCH_2Ph), 4.71, 4.94 (2 H, dd, J_{gem} = 19 Hz, CH_2 of Gly), 5.36 (1 H, m, α-CH of Cys) and 6.81–7.62 (15 H, m, aromatic). ^{31}P NMR ($CDCl_3$): δ −1.5. IR (KBr, cm^{-1}): 1744, 1639 [ν(C=O)], 969 [ν(Re=O)]. Positive-ion FAB mass spectrum: *m*/*z* (relative intensity) 759 (*M*, 7), 724 (*M* − Cl, 65), 709 (*M* − Cl − Me, 8), 652 (*M* − Me − CH_2Ph, 12), 631 (*M* − Cl − CH_2Ph, 100), 617 (*M* − Cl − Me − CH_2Ph, 9) and 573 (*M* − Cl − CH_2Ph − CO_2Me, 72%). UV/VIS [EtOH, λ/nm (log ε)]: 274 (3.94), 472 (2.29) and 548 (sh).

(*N*-{*N*-[(3-diphenylphosphino)propionyl]glycyl}-L-*S*-benzylcysteinato methyl ester-*P*,*N*,*N*,*S*)hydroxooxorhenium(v), [ReO(L[1])(OH)] 6. A stoichiometric amount (1:1) of KOH (0.78 cm^3 of 0.25 mol dm^{-3} KOH in EtOH) was added dropwise to a solution of complex **5** (0.15 g, 0.2 mmol) in CH_2Cl_2–EtOH (1:1, 50 cm^3). The initial violet solution immediately turned yellow-brown. After 5 min it was filtered from a white precipitate (KCl) and light petroleum (150 cm^3) was added. The brown solid was recovered by decantation and recrystallized from hot EtOH. Good brown crystals were obtained (yield 0.12 g, 80%) (Found: C, 45.6; H, 5.5; N, 3.7; P, 4.0; S, 4.4. Calc. for $C_{28}H_{30}N_2O_7PReS$: C, 45.4; H, 5.3; N, 3.8; P, 4.2; S, 4.3%). ^{1}H NMR ($CDCl_3$): δ 2.50–3.46 [4 H, m, $P(CH_2)_2$], 3.68–3.74 (2 H, m, β-CH_2 of Cys), 3.79 (3 H, s, OCH_3), 3.88, 4.13 (2 H, dd, J_{gem} = 12 Hz, SCH_2Ph), 4.76, 5.59 (2 H, m, CH_2 of Gly), 5.50 (1 H, m, α-CH of Cys) and 6.72–7.96 (15 H, m, aromatic). ^{31}P NMR ($CDCl_3$): δ −2.7. IR (KBr, cm^{-1}): 1743 [ν(C=O)], 939, 909 [ν(Re=O)]. Positive-ion FAB mass spectrum: *m*/*z* (relative intensity) 724 (*M* − OH, 54), 631 (*M* − OH − CH_2Ph, 100) and 573 (*M* − OH − CH_2Ph − CO_2Me, 47%). UV/VIS [EtOH, λ/nm (log ε)]: 273 (3.94) and 453 (2.24).

HPLC Experiments

The compounds were analysed using a PRP-1 reversed-phase column with a binary gradient [A, 20 mmol dm^{-3} methanol–ammonium acetate (3:2); B, MeOH] programmed as follows: 0–8 min from 100% A to 86% B; 8–25 min 86% B isocratic; 25–27 min from 86% B to 100% A. Injection of all the compounds gave the following retention times: **3**, 11.18; **4**, 11.17; **5**, 15.99; **6**, 15.98 min. The UV spectra collected at the peak maxima showed the same features for **3** and **4**, with a maximum at 266 nm, and for **5** and **6** with a maximum at 273 nm. Even the solution of **6**, in basic medium for some hours, gave the same chromatogram (t_R = 11.18 min) and UV spectrum (λ_{max} = 266 nm) as those of **3** and **4**.

Crystallography

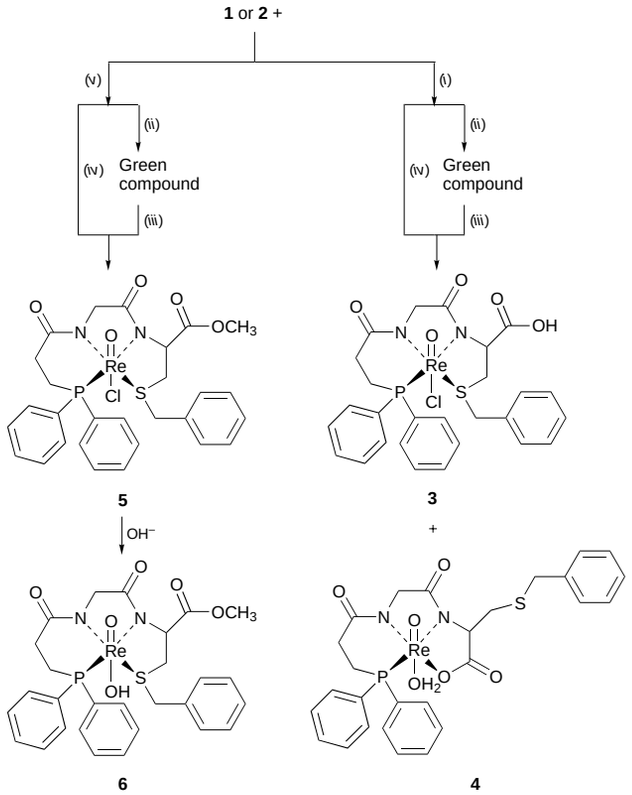
Details of crystal data, intensity measurement, data processing and refinement for both complexes are summarized in Table 1. Cell parameters were determined from 50 reflections at 2θ > 21°. For the calculation of the structure factors, corrections for Lorentz-polarization effects and absorption (using an empirical method based on ψ scans of five reflections at χ *ca.* 90°) were made. The structures were solved by standard heavy-atom methods and in **4** all atoms, except oxygen and carbon atoms of water and methanol molecules, were refined anisotropically. Refinements were based on *F* and H-atom parameters refined as riding models with U = 0.08 $Å^2$. For **4** a difference map, calculated after the refinement, was essentially featureless, apart from some disorder in the vicinity of the MeOH molecule and some peaks up to 1.8 e $Å^{-3}$ (at *ca.* 1 Å from Re), probably attributable to inadequate absorption correction. For **5**, owing to the paucity of observed reflections, the anisotropy was applied only to Re, Cl, P and S atoms; the refined model proved to be the correct enantiomorph. Selected bond distances and angles are given in Table 2.

Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 186/459.

Results

Synthesis

The syntheses of compounds H_2L^1 and H_3L^2 were achieved as in Scheme 1. The methyl ester hydrolysis occurs in KOH basic solution. The reactions of oxorhenium(v) complexes **1** or **2**



Scheme 2 (*i*) H_3L^2; (*ii*) CH_2Cl_2; (*iii*) EtOH; (*iv*) EtOH, heat; (*v*) H_2L^1

with H_2L^1 or H_3L^2 result in ligand-exchange reactions in which both the ligands behave as tetradentate, replacing all the groups in the equatorial plane normal to the Re=O axis (Scheme 2). The reaction of $[ReOCl_2(OEt)(PPh_3)_2]$ **2** with H_3L^2 was performed in two different solvents by using stoichiometric (1:1) quantities. The reaction in EtOH was conducted at high temperature for a long time; it results in complex **4** in moderate yield and a small amount of **3** was recovered from the mother-liquors. The reaction in CH_2Cl_2 rapidly produced an intermediate green compound and, after addition of a protonated solvent, such as MeOH or EtOH, complex **4** was recovered in high yield. Also in CH_2Cl_2 a small amount of a violet powder of **3** was obtained. In an attempt to characterize the green compound, a light green powder was recovered from the green solution, but purification procedures result in decomposition. Since the green compound is transformed into the final $[ReO(L^2)(OH_2)]$ or $[ReO(HL^2)Cl]$ complex just by addition of a protonated solvent, the green intermediate should contain the ligand with the two amide nitrogens still protonated. Using $[ReOCl_3(PPh_3)_2]$ as starting material gave the same behaviour, but complex **3** became predominant in both methods. The difference is attributed to the higher acidity of the solution when two chlorides are released by the starting complex, which enforces protonation of the carboxylic moiety and favours co-ordination of the thioether group. Upon addition of some drops of an ethanolic 0.1 mol dm^{-3} HCl solution, only complex **3** is obtained from both reactions.

The reaction of complex **1** or **2** with H_2L^1 gave violet complex **5**, which was collected and characterized. The reaction of **1** with H_2L^1 has been previously described[12] and complex **5** was also detected. The reaction in CH_2Cl_2 gave the same green solution which became violet on addition of EtOH. The availability of the thioether group for the fourth co-ordination site in the equatorial plane, with respect to the oxorhenium(v) core, makes the reaction with H_2L^1 easier than that with H_3L^2 and evidentiates that the behaviour of H_3L^2 with the oxorhenium core is the same even when the ligand is joined *via* the carboxylate group to any type of peptide. By

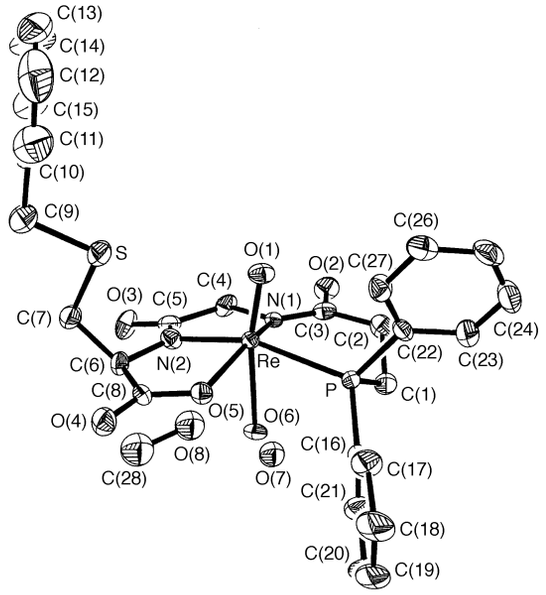


Fig. 1 An ORTEP[14] view of complex **4**, showing the atom labelling scheme and the thermal ellipsoids drawn at 50% probability

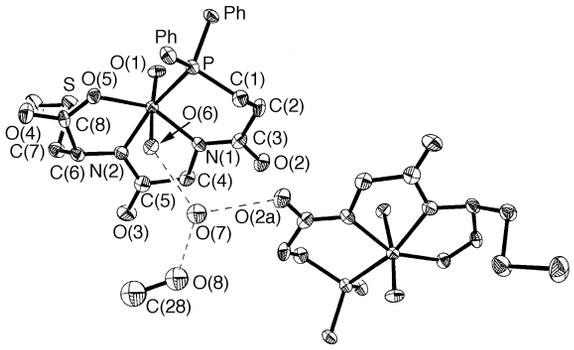


Fig. 2 Hydrogen-bonding arrangement (dashed lines) involving the solvent water molecule; O(2a) denotes the carbonyl oxygen at $1 - x$, $-y$, $-z$

treatment of product **5** with a stoichiometric amount of KOH in EtOH the chloride ion *trans* to Re=O is immediately substituted by a hydroxide anion producing complex **6**. When a further amount of KOH was added and the reaction mixture left in basic medium for some hours, hydrolysis of the methyl ester group of **6** was also observed.

Characterization

Elemental analyses, as given in the Experimental section, are consistent with the proposed formulations. The IR spectra of all the recovered complexes exhibit M=O stretching vibrations in the range 1005–909 cm^{-1}. The spectra show also vibrations characteristic of ν(MeOC=O) at 1743, ν(OC=O) at 1667 and ν(NC=O) at 1639–1614 cm^{-1}. The positive-ion FAB mass spectra showed the presence of the parent peak only in the case of complex **5**. The major fragment containing Re=O and the entire ligand was observed with the other compounds. Further fragments revealed the loss of the benzyl group and of the carboxyl moiety. Thus all the compounds exhibit the same fragmentation with the addition of 15 mass units due to the methoxy group of the ester moiety when it is present. The UV/VIS spectra are consistent with charge transfers from the ligand to the metal for similar rhenium complexes and have been used to determine the species during HPLC experiments. Under the HPLC conditions in the Experimental section only two species have been detected, one containing H_3L^2 and one H_2L^1. A previous experiment[12] determined the two species directly by injection into the chromatograph of the mixture obtained upon hydrolysis of the methyl ester function of complex **5** in basic medium. In the present study, after isolation of complexes **4** and **6**, and determination of their UV/VIS absorptions, two HPLC peaks at t_R 15.99 and at 11.7 min have been assigned respectively to complex **6** and to a species, the UV spectrum of which is the same as that of a solution of **4** at pH 7.5. This species has not yet been identified but it reversibly transforms into complex **4** at lower pH (≤7).

The phosphorus NMR spectra show signals at usual values for a co-ordinated tertiary phosphine, considerably shifted downfield with respect to the value for the free phosphine. Proton NMR spectra show for all the complexes the disappearance of the triplets at δ 6.10 and 8.17, and of the doublets at δ 6.67 and 8.25, attributed to the amide protons of free H_2L^1 and H_3L^2, respectively, which confirms the deprotonation of the amide nitrogen in the complexes. Another usual behaviour is the significant downfield shift of the resonances of all the protons close to the co-ordinated groups. This is particularly evident (>1 ppm) for the methylene protons of glycine. The high complexity of the proton NMR spectra suggests the possibility of different conformers in solution and prevents complete attribution of the proton chemical shifts.

Crystal structure of complex 4

The crystal structure (Fig. 1) consists of monomeric, neutral monoxorhenium(V) complex units. Methanol and water of crystallization are also present in the lattice and the water molecule (Fig. 2) is involved in a hydrogen-bonding network. In particular, atom O(7) is hydrogen-bonded to O(6) of the co-ordinated water (at 2.55 Å), to carbonyl O(2) (at $1 - x$, $-y$, $-z$) (separation 2.70 Å) and to O(8) of MeOH (at 2.75 Å), the pertinent angles around O(7) averaging 113(1)°. The tetradentate PN_2O ligand occupies the four equatorial positions of a distorted octahedron around the metal atom; the axial positions are occupied by the oxo-atom [O(1)] and by the water ligand [O(6)], with an O(1)–Re–O(6) angle of only 166.6(3)°. The metal is displaced from the equatorial PN_2O plane by 0.43 Å towards O(1), a common situation for five- and six-co-ordinate Re=O structures. The tetradentate co-ordination mode of the triply deprotonated ligand leads to a tricyclic (6,5,5) system around rhenium, with the two five-membered metallocycles in envelope (C_s) configuration (torsion angles in the range −15.1 to 12.6°), while the six-membered chelate ring is in an approximately boat (C_{2v}) configuration with atoms N(1) and C(1) 0.25 and 0.72 Å above the mean plane formed by the remaining four atoms. The (6,5,5) rings are inclined to the basal PN_2O plane at dihedral angles of 13.0, 12.8 and 12.1°, respectively. In the PN_2O_3 polyhedron the Re atom is +0.91 Å away from the N(1), O(1),N(2) plane and −1.42 Å from the P,O(6),O(5) plane, the angle between the two triangles being 10.7°. This departure from 0° represents a measure of the octahedral distortion, as in the basal plane does the dramatic contraction of the O(5)–P–N(1) angle (72.8°) and the O(5)···P and P···N(1) separations (3.36 and 3.27 Å, respectively) considerably greater than those involving N(2) [*i.e.* N(1)···N(2) 2.61 and N(2)···O(5) 2.58 Å]. The angles between the Re=O(1) bond and the equatorial donors are remarkably larger than 90° [from 93.5(2)° for O(1)–Re–P to 108.8(3)° for O(1)–Re–N(2)] and the angle between the normal to the PN_2O plane and the O(1)···O(6) line is 2.3°. The bond lengths and angles do not differ significantly from the expected values[15] and do not deserve any comment. Only the N(1)–Re and N(2)–Re distances [2.016(8) and 1.990(8) Å, respectively] are of note, being markedly shorter than the amine to Re^V bonds (mean 2.16 Å)[16] and the Re–N (Schiff base) distances (mean 2.12 Å),[16] but they compare favourably with the average value found in [ReO(Cl){$PPh_2(C_6H_4NH$-*o*)}$_2$] (2.02 Å),[17] [ReO(Cl){$PPh_2(C_6H_4O$-*o*)}{$PPh_2(C_6H_4NH$-*o*)}] (1.99 Å)[18] and [ReO{(*o*-$Ph_2PC_6H_4$)-$HN(CH_2)_3NH(C_6H_4PPh_2$-*o*)}X] (X = OMe or O_2CCF_3)

Table 1 Structure determination summary for complexes **4** and **5***

	4	**5**
Empirical formula, *M*	$C_{28}H_{34}N_2O_8PReS$, 775.8	$C_{28}H_{29}ClN_2O_5PReS$, 758.2
Colour, habit	Violet octahedrons	Dark red parallelepipeds
Crystal size/mm	0.12 × 0.12 × 0.20	0.06 × 0.15 × 0.20
Crystal system, space group	Monoclinic, $P2_1/c$	Orthorhombic, $P2_12_12_1$
a/Å	14.805(3)	11.952(3)
b/Å	10.781(3)	17.049(4)
c/Å	20.325(6)	18.608(4)
β/°	106.87(2)	
U/Å^3	3104(1)	3792(1)
D_c/Mg m^{-3}, *F*(000)	1.660, 1544	1.328, 1496
μ(Mo-Kα)/mm^{-1}	4.08	3.40
Index ranges	$0 \leqslant h \leqslant 17$, $0 \leqslant k \leqslant 12$, $-24 \leqslant l \leqslant 23$	$0 \leqslant h \leqslant 14$, $0 \leqslant k \leqslant 20$, $0 \leqslant l \leqslant 22$
Independent reflections	5476	3758
Observed reflections [$F_o > 4\sigma(F_o)$]	4258	1828
Weighting scheme, w^{-1}	$\sigma^2(F) + 0.0063F^2$	$\sigma^2(F) + 0.0099F^2$
Number of parameters refined	355	178
Final *R*, *R*′ (observed data)	0.063, 0.069	0.049, 0.063
Goodness of fit	0.97	0.54
Largest difference peak/e Å^{-3}	1.10 (0.8 Å from Re)	1.24 (0.9 Å from Re)

* Details in common: $T = 294$ K; $Z = 4$; Siemens R3m/V diffractometer; Mo-Kα radiation (λ 0.710 73 Å); ω–2θ scan mode; scan speed 3.0–14.65° min^{-1}; 2θ range 4.5–50°; function minimized $\Sigma w(\Delta F)^2$; SHELXTL-PLUS[13] program.

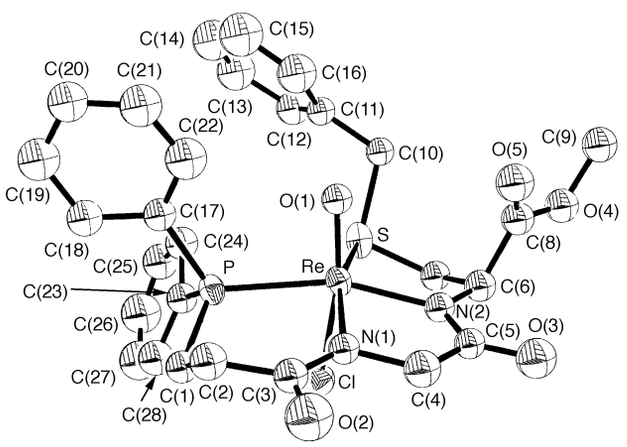


Fig. 3 An ORTEP drawing of complex **5** showing the atom labelling scheme and the thermal ellipsoids drawn at 50% probability

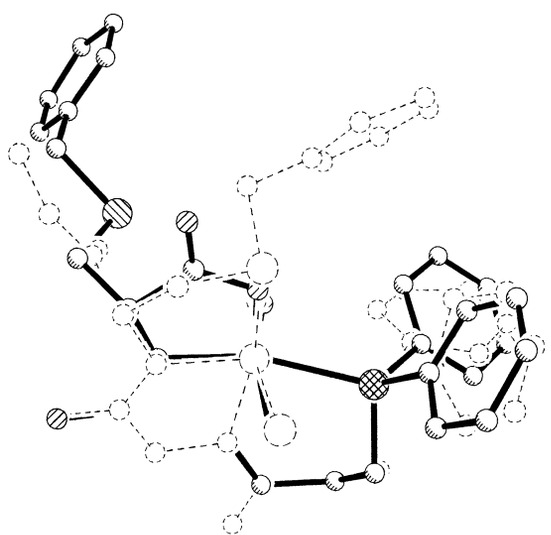


Fig. 4 Superimposition of complexes **4** (—) and **5** (- - -)

(2.03 Å).[19] The Re–N distances are at the higher end of the 1.91–2.04 Å range observed in oxorhenium(v) complexes with deprotonated nitrogen-donor atoms and, as expected, the negatively charged amide nitrogen atoms are more effective σ donors than are the neutral amines.

Crystal structure of complex 5

The structure is found to contain discrete monomeric neutral molecules in which the metal atom has a distorted-octahedral environment, as seen in Fig. 3. The complex represents the first example of an Re^V=O core with a PN_2SCl donor set. The geometry could also be described as distorted square pyramidal, a typical geometry for oxorhenium complexes, and within this description the metal atom is displaced from the mean plane of the PN_2S donor atom set by 0.34 Å towards the oxo-O(1) atom, the insertion of the chloride occurring *trans* to O(1) [O(1)–Re–Cl 162.6°]. In the co-ordination polyhedron the Re atom is −1.35 Å from the N(1),N(2),Cl plane and +1.12 Å from the P,S,O(1) plane, the angle between the two triangular faces being 8.0°. The tetradentate dianionic ligand forms around Re a three (6,5,5)-membered chelate ring system, in which the six-membered ring adopts a 'boat' arrangement, the middle ring is roughly planar, while in the remaining ring the conformation is 'twist-envelope'. The ligand chain is highly wrapped [up to 0.62 and 0.36 Å for C(1) and C(7), respectively; down to 0.28 and 0.32 Å for P and S] and this produces significant departures of the rhenium valence angles from those anticipated for a regular octahedral geometry. The angles between the Re=O(1) bond and the equatorial nitrogen donors are remarkably different from 90° (105.8 and 105.5°), while they are close to 90° with the sulfur (91.6°) and phosphorus atom (93.5°). The CO_2Me moiety is roughly perpendicular to the mean equatorial plane, the angle being 78.3°, while the benzyl ring makes an angle of 48.9° with the same plane. The bond distances and angles (Table 2) are in good agreement with data for similar six-co-ordinate oxorhenium(v) complexes.[16] In particular, the Re–S distance of 2.485(6) Å, between Re and a neutral sulfur donor atom, is considerably longer than the 2.29–2.38 Å expected for a rhenium–thiolate interaction and it is of the order of a rhenium–thioether distance.[20] In accordance with this result, the separation between Re and an anionic nitrogen donor [2.01(2) Å] is remarkably shorter than the mean value (2.12 Å) observed for Re–N separations involving neutral nitrogen-donor atoms. Comparison of this complex with the parent **4** (Fig. 4), in which the quadridentate ligand is doubly deprotonated, shows that around the $[ReO]^{3+}$ core the co-ordinating mode of the portion from P to N(2) is identical, the weighted root-mean-square deviation, derived from the BMFIT pro-

Table 2 Selected bond lengths (Å) and angles (°)

Complex **4**

Re–P	2.451(2)	N(1)–C(3)	1.35(1)
Re–N(1)	2.016(8)	N(1)–C(4)	1.48(1)
Re–N(2)	1.990(8)	N(2)–C(5)	1.37(1)
Re–O(1)	1.681(6)	N(2)–C(6)	1.44(1)
Re–O(5)	2.043(6)	O(5)–C(8)	1.31(1)
Re–O(6)	2.247(6)	S–C(7)	1.83(1)
P–C(1)	1.81(1)	S–C(9)	1.82(1)
P–Re–N(1)	93.6(2)	Re–P–C(1)	104.6(3)
P–Re–N(2)	157.7(2)	Re–N(1)–C(3)	132.1(6)
P–Re–O(5)	96.3(2)	Re–N(1)–C(4)	114.3(6)
N(1)–Re–N(2)	81.2(3)	Re–N(2)–C(5)	118.6(7)
N(1)–Re–O(5)	151.5(3)	Re–N(2)–C(6)	119.1(6)
N(2)–Re–O(5)	79.6(3)	Re–O(5)–C(8)	116.3(6)
O(1)–Re–O(6)	166.6(3)	C(7)–S–C(9)	96.9(6)

Complex **5**

Re–Cl	2.494(6)	N(1)–C(3)	1.34(3)
Re–S	2.485(6)	N(1)–C(4)	1.48(3)
Re–P	2.451(6)	N(2)–C(5)	1.31(3)
Re–N(1)	2.02(2)	N(2)–C(6)	1.48(3)
Re–N(2)	2.00(2)	P–C(1)	1.78(2)
Re–O(1)	1.66(2)	S–C(7)	1.74(2)
Cl–Re–S	75.9(2)	P–Re–N(1)	93.0(5)
Cl–Re–P	76.7(2)	N(1)–Re–N(2)	79.9(7)
Cl–Re–O(1)	162.6(5)	P–Re–N(2)	160.9(6)
Cl–Re–N(1)	89.2(5)	Re–N(1)–C(3)	132(2)
Cl–Re–N(2)	85.4(6)	Re–N(1)–C(4)	112(1)
S–Re–P	98.2(2)	C(3)–N(1)–C(4)	116(2)
S–Re–O(1)	91.6(5)	Re–N(2)–C(5)	117(2)
S–Re–N(1)	158.7(5)	Re–N(2)–C(6)	122(2)
S–Re–N(2)	83.7(6)	C(5)–N(2)–C(6)	121(2)
P–Re–O(1)	93.5(5)		

gram,[21] being only 0.07 Å, when the fitting is performed using the pertinent eight atoms. In the present compound the potential sulfur donor atom attached to the benzyl group has no interactions with the metal atom (at 3.94 Å) or the oxometal group (at 3.56 Å).

Discussion

The compound H_3L^2 and its methyl ester derivative H_2L^1 show a high affinity for the oxorhenium(v) core, so allowing the synthesis of six-co-ordinated complexes in which the common skeleton is made of the $[ReOPN_2]^+$ moieties, whereas the remaining co-ordination positions donate suitable electron density for thermodynamic stabilization. This idea comes from the behaviour of H_3L^2, which yields complex **3** or **4** only when a highly nucleophilic carboxylate group is available. The co-ordination of the group *trans* to Re=O arises from competition of the CO_2^- and SCH_2Ph groups. When the fourth equatorial position is occupied by the carboxylate, the co-ordination site *trans* to Re=O is filled by a water molecule. When the same equatorial position is occupied by thioether sulfur, the last position is taken by a Cl^- found in the solution. The methyl ester derivative, instead, can give only complex **5**, because it lacks the co-ordinating carboxylic group; thus, only a chloride ion can be placed *trans* to Re=O. The same anion can easily be replaced with an hydroxide group at pH $\geqslant$ 7.

The positive-ion FAB mass fragmentation spectra gave a strong indication of the stability of the $[ReOPN_2]^+$ moiety. The same fragment at *m*/*z* 573 (corresponding to an $ReOPN_2S$ moiety) was found for all the complexes, even when the carboxylate group is co-ordinated in the fourth equatorial site. The relative intensity of the fragment peaks shows that loss of the benzyl group is preferred in presence of the co-ordinated thioether sulfur (high intensity of the fragment containing the CO_2Me group), while both carboxyl and benzyl groups are easily released in the case of complex **4**. Comparison of the above complexes with those derived from *N*,*N*′-bis[*o*-(diphenylphosphino)phenyl]propane-1,3-diamine[22] shows that the phosphine group provides the oxorhenium(v) core with an amount of electron density similar to that from a thioether sulfur, an inference that can be justified by looking at the electron density demand at the position *trans* to Re=O, as shown by the different substituents bound to this position. For example, the density offered to the central Re^V=O core by the third amido nitrogen in $[ReO(L)]^-$ (L = sulfanylacetyltriglycinate)[23] is insufficient. So, the thioether sulfur must co-ordinate as thiolate with reductive deprotection of the sulfur atom. Thiolate sulfur allows a five-co-ordinated square-pyramidal configuration. The H_3L^2 ligand did not exhibit deprotection of cysteine sulfur during co-ordination, even though there is preliminary evidence that this happens with corresponding nitridotechnetium complexes.[24]

Conclusion

The complexes $[ReOCl_3(PPh_3)_2]$ and $[ReOCl_2(OEt)(PPh_3)_2]$ undergo exchange reaction with the dipeptide H_3L^2 modified with a phosphine moiety. The polydentate ligand immediately substitutes the PPh_3 group and then behaves differently according to the solvent and to the pH conditions. By using protonated solvents, the amide groups can lose their proton and co-ordinate as anions. The other co-ordination positions can involve reversible reactions, but the $[ReOPN_2]^+$ moiety is shown to be stable. This behaviour of the $ReO(L^2)$ complexes demonstrates that the phosphine moiety can enhance the bonding ability of the two deprotonated amide nitrogens towards $Re{=}O^{3+}$, the fourth co-ordination site on the equatorial plane having only a secondary role. This result endorses the strategy of modifying a bioactive peptide with a phosphine group. This kind of substitution ensures that the rhenium radioisotopes can be addressed to exactly where the modification has been made, and that the labelling will remain stable.

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