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FULL PAPER

Complexes of phosphine–phenolate ligands with the $[Re{=}O]^{3+}$ and $[Re(HNNC_5H_4N)(NNC_5H_4N)]^{2+}$ cores

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Complexes incorporating the $[Re{=}O]^{3+}$ core have been synthesised with ligands containing the new methyl substituted phosphine–phenolate PO and PO_2 donor sets, (2-hydroxy-5-methylphenyl)diphenylphosphine (H(MePO)) and bis(2-hydroxy-5-methylphenyl)phenylphosphine ($H_2(Me_2PO_2)$). The analogous *tert*-butyl ligands, (5-*tert*-butyl-2-hydroxyphenyl)diphenylphosphine (H(*t*-BuPO)) and bis(5-*tert*-butyl-2-hydroxyphenyl)phenylphosphine ($H_2(t\text{-}Bu_2PO_2)$), were also prepared. Reaction of either *mer*-$[ReOCl_3(PPh_3)_2]$ or $[NH_4][ReO_4]$ in CH_3OH with H(MePO) led to formation of $[ReOCl(MePO)_2]$ (**1**) in good yield. Reaction of $[NH_4][ReO_4]$ with $H_2(Me_2PO_2)$ in CH_3OH afforded $[ReO(Me_2PO_2)(H(Me_2PO_2))]$ (**2**), also in good yield. X-Ray crystallographic analyses of **1** and **2** demonstrated that both complexes are neutral and octahedral, and contain the oxo moiety. Two complexes have been structurally characterised from the reaction of (*o*-hydroxyphenyl)diphenylphosphine (HPO) with $[Re(Hhypy)(hypyH)Cl_3]$: $[Re(Hhypy)(hypy)(PO)(HPO)]Cl$ (**3**) and $[ReCl(Hypy)(hypy)(PO)]$ (**4**) (hypy = NNC_5H_4N, Hhypy = $HNNC_5H_4N$, hypyH = NNC_5H_4NH). X-Ray crystallography demonstrated that both are Re(III) complexes; **3** is monocationic with an N_3OP_2 coordination sphere while **4** is neutral with a ClN_3OP coordination sphere. $[Re(Hhypy)(hypy)(HPO_2)(H_2PO_2)]Cl$ (**5**) and $[Re(Hhypy)(hypy)(H(Me_2PO_2))(H_2(Me_2PO_2))]Cl$ (**6**) were synthesised by reaction of $[Re(Hhypy)(hypyH)Cl_3]$ in CH_3OH with bis(*o*-hydroxyphenyl)phenylphosphine (H_2PO_2) and $H_2(Me_2PO_2)$ respectively. Compounds **5** and **6** were shown by ^1H and ^{31}P NMR spectroscopies to have the same N_3OP_2 coordination sphere as $[Re(Hhypy)(hypy)(PO)(HPO)]Cl$, with the addition of several uncoordinated, protonated phenolic donors.

Introduction

Intense effort has been focused on the extension of the well-known diagnostic radiopharmaceuticals of technetium (^{99m}Tc) to its third row congener rhenium (^{186}Re, ^{188}Re) for use as radiotherapeutic cancer agents.[1–7] Rhenium-186 is capable of delivering a sizeable dose of radiation (β_{max} = 1.07 MeV) over an extended period of time due to its relatively long (3.8 day) half-life. Rhenium-188 delivers a dose with higher tissue-penetrating power (β_{max} = 2.12 MeV), and with higher intensity due to its 17 hour half-life. Since rhenium-188 can be obtained from a $^{188}W/^{188}Re$ generator, it offers a distinct advantage over isotopes such as rhenium-186 that must be synthesised off-site by neutron activation, or many other isotopes requiring sizable infrastructure for their preparation.

The challenges that must be overcome to extend this chemistry to rhenium are significant, however. Foremost from the clinical standpoint are the much stricter target to background ratios that must be achieved in therapeutic *vs.* diagnostic use. Rhenium is more kinetically inert than technetium and it is also much more difficult to reduce from $[MO_4]^-$ (M = Tc, Re), the preferred starting material in nuclear medicine. For these reasons, it may require considerable research to extend working technetium systems to rhenium systems.

One such approach originally envisioned for technetium is the bifunctional chelate approach (Scheme 1). Conjugation to a biologically active molecule (BAM) is achieved using a bifunctional linker that can attach to the complex. One highly successful system uses *N*-oxysuccinimidylhydrazinonicotinamide (HYNIC) as the linker.[8–16] This linker can be attached to a BAM *via* the activated ester functional group, and to a metal complex through the hydrazine. Unlike small molecule diagnostic systems, the metal complex is designed from the start to behave only as a spectator. The role of the BAM is to direct the metal and its incumbent radiation dose to the biological target. The resulting bioconjugate must be stable enough to withstand conditions *in vivo* and at the same time, must not deactivate the BAM. Since the HYNIC ligand can only act as a monodentate or bidentate ligand, ancillary ligands for the metal centre must be very carefully designed into the system, otherwise the strict *in vivo* requirements may not be met. The system shows promise since it is theoretically possible to design a wide variety of radiopharmaceutical agents from one type of reaction.

The chemistry of rhenium with various hydrazines has been well documented.[17–36] Most of these compounds are mixed complexes of a hydrazine with phosphines and halogens and many of the complexes have been made by convenient reduction of *mer*-$[ReOCl_3(P)_2]$ (P = PPh_3 or PMe_2Ph) to form bis-(hydrazine) complexes.[20–23,25,26,30] One system in particular has been proposed as a model of the HYNIC system, with 2-hydrazinopyridine ($H_2NHNC_5H_4N$, H_3hypy) acting both as a model for HYNIC and as reductant towards $[ReO_4]^-$.[37–41] The resulting $[Re(Hhypy)(hypy)]^{2+}$ core is a useful model in the study and design of ternary complexes of rhenium for use in the HYNIC system.

Phosphinophenol ligands of the type HPO and H_2PO_2 and related systems have been reported to form oxo, nitrido and imido complexes with rhenium and technetium.[42–46] In this

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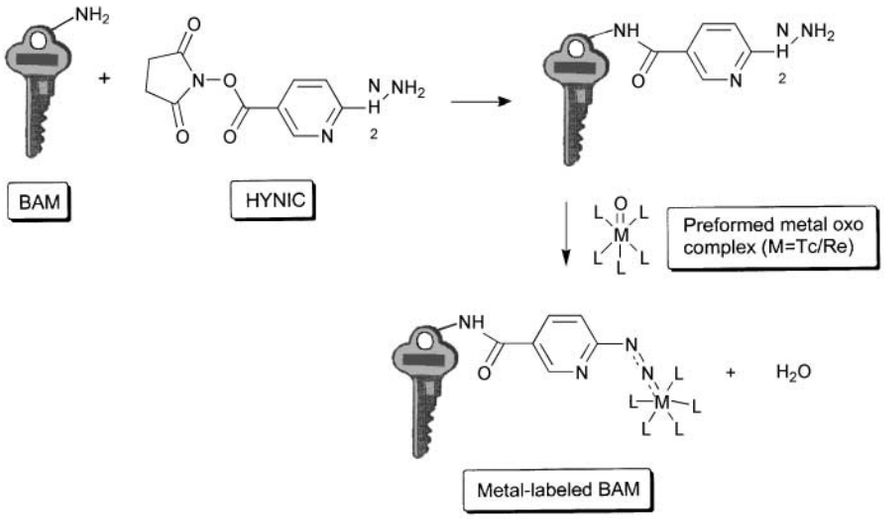
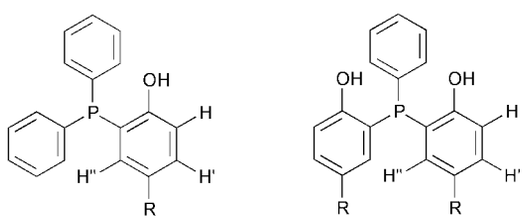


Scheme 1

study, we report the synthesis of the new alkyl derivatives H(MePO), $H_2(Me_2PO_2)$ and the *tert*-butyl analogues as ancillary ligands for rhenium. In this study $[Re{=}O]^{3+}$ complexes have been synthesised and characterised to evaluate PO_x ligands as ancillary ligands in HYNIC model complexes, after subsequent reaction with hydrazines. The reactivity of the PO_x ligands with the aforementioned $[Re(Hhypy)(hypy)]^{2+}$ core was also investigated as an alternative route to HYNIC model complexes.



Experimental

Materials

(*o*-Hydroxyphenyl)diphenylphosphine (HPO),[47] bis(*o*-hydroxyphenyl)phenylphosphine (H_2PO_2),[42] *mer*-$[ReOCl_3(PPh_3)]$[48] and $[Re(Hhypy)(hypyH)Cl_3]$ (Hhypy = $HNNC_5H_4N$, hypyH = NNC_5H_4NH)[40,41] were synthesised by published methods. All solvents were of HPLC grade and were obtained from Fisher. When anhydrous solvents were required they were dried using conventional procedures.[49] Reactions were carried out under Ar, although all of the product metal complexes were found to be air and moisture stable. Chemicals used in the ligand syntheses, NEt_3, and hydrazines were obtained from commercial sources (Aldrich, Fischer) and were used without further purification. $[NH_4][ReO_4]$ was a gift from Johnson-Matthey and was also used without purification.

Instrumentation

Mass spectra were obtained with either a Kratos MS 50 (electron impact ionisation, EIMS) or a Kratos Concept II H32Q instrument (Cs^+-LSIMS with positive ion detection). Infrared (IR) spectra in the range 4000–500 cm^{-1} were recorded as KBr disks with a Mattson Galaxy Series 5000 FTIR spectrophotometer. Microanalyses for C, H, N, and Cl were performed by Mr P. Borda in the UBC chemistry department. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker AC-200E (^1H 200 MHz, ^{13}C 50 MHz) NMR spectrometer with δ referenced downfield from external $SiMe_4$ $^{31}P\{^1H\}$ NMR spectra were recorded on Bruker AC-200E (81 MHz) and Bruker AMX-500 (202.5 MHz) spectrometers with δ referenced to external 85% aqueous phosphoric acid.

Preparation of compounds

1-Methoxymethoxy-4-methylbenzene. The compound was synthesised by a published procedure, with some modifications.[50] A mixture of *p*-cresol (27 g, 0.25 mol), dimethoxymethane (86 g, 1.13 mol), and *p*-toluenesulfonic acid (250 mg, 1.45 mmol) were dissolved in 600 mL dichloromethane and refluxed overnight in a Soxhlet extractor equipped with 3 Å molecular sieves. The reaction mixture was allowed to cool and was treated with *ca.* 3 mL of triethylamine to neutralise the acid catalyst. The solution was then washed with two 200 mL portions of 1 M NaOH followed by two 200 mL portions of water, and then dried over $CaCl_2$. Evaporation of the solvent afforded a yellow residue that was distilled (40 °C, 0.1 mmHg) to give the product as a colourless liquid, yield 19.5 g (51%). ^1H NMR ($CDCl_3$) δ: 7.21 (d, 2H, aromatic *H*, $^3J_{HH'} = 9$ Hz), 7.08 (d, 2H, aromatic *H′*, $^3J_{HH'} = 9$ Hz), 5.24 (s, 2H, mom CH_2), 3.58 (s, 3H, mom CH_3), 2.42 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 155.37 (s, 1C), 131.17 (s, 1C), 130.03 (s, 2C), 116.34 (s, 2C), 94.69 (s, 1C), 55.76 (s, 1C), 20.55 (s, 1C).

(2-Methoxymethoxy-5-methylphenyl)diphenylphosphine. The compound was synthesised by a published procedure, with some modifications.[47] To an ice-cooled solution of 1-methoxymethoxy-4-methylbenzene (8.5 g, 55.8 mmol) in 75 mL petroleum ether (bp 35–60 °C) were added *n*-BuLi in *n*-hexane (1.6 M, 39.4 mL, 63.0 mmol) in 11 mL petroleum ether and TMEDA (6.5 g) in 11 mL petroleum ether. The mixture was stirred overnight, during which time a yellow precipitate formed. The mixture was heated to 40 °C for 30 minutes and was then cooled to 0 °C; chlorodiphenylphosphine (12.3 g, 55.8 mmol) was then added *via* syringe. The resultant mixture was stirred overnight again, during which time it warmed to room temperature. The solvent was removed and the residue dissolved in a mixture of 250 mL 0.1 M Na_2HPO_4 solution and 150 mL chloroform. The chloroform phase was separated and the water phase was further extracted with 2 × 50 mL chloroform. The organic phases were combined and washed with one 50 mL portion of water, dried over $CaCl_2$, and then dried *in vacuo* to afford a yellow oil. To this oil was added 30 mL methanol after which the solution was allowed to stand in a freezer overnight to afford a white precipitate. After the precipitate was removed by filtration, it was washed with several portions of cold methanol and dried overnight *in vacuo*, yield 12.6 g (67%). ^1H NMR ($CDCl_3$) δ: 7.46–7.30 (overlapped

multiplets, 10H), 7.19–7.02 (overlapped multiplets, 2H), 6.58 (dd, 1H), 5.08 (s, 2H, mom CH_2), 3.00 (s, 3H, mom CH_3), 2.18 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 156.88 (d), 136.87 (d), 134.24 (s), 133.96 (d), 133.83 (s), 131.32 (d), 130.82 (s) 128.67 (s), 128.42 (d), 126.52 (s), 94.33 (s, 1C, mom CH_2), 55.94 (s, 1C, mom CH_3), 20.75 (s, 1C, CH_3). $^{31}P\{^1H\}$ ($CDCl_3$, 81 MHz) δ: −15.79 (s).

(2-Hydroxy-5-methylphenyl)diphenylphosphine, H(MePO)·CH_3OH. This compound was synthesised by a published procedure, with some modifications.[47] (2-Methoxymethoxy-5-methylphenyl)diphenylphosphine (12.5 g, 37.1 mmol) was suspended in 350 mL anhydrous methanol. This suspension was saturated with HCl gas generated from concentrated H_2SO_4 and ammonium chloride (26.7 g, 0.5 mol). After the suspension clarified to a solution, the latter was allowed to stir for 5 hours, after which time it was concentrated into an oil and was then dissolved in 50 mL of boiling methanol. Water (*ca.* 50 mL) was slowly added to the boiling solution until the solution became cloudy. Cooling the solution afforded a white solid which was dried overnight *in vacuo*, yield 3.9 g (91%). Anal. Calcd (found) for $C_{19}H_{17}OP{\cdot}CH_3OH$: C, 74.06 (74.24); H, 6.53 (6.51%). EIMS: *m*/*z* = 292 ([MeHPO]$^+$). ^1H NMR ($CDCl_3$) δ: 7.43–7.31 (overlapping multiplets, 10H), 7.10 (dd, 1H, aromatic *H*, $^3J_{HH'}$ = 8 Hz), 6.83 (dd, 1H, aromatic *H*′, $^3J_{HH'}$ = 8 Hz), 6.75 (dd, 1H, aromatic *H*″, $^4J_{H'H''}$ = 6 Hz, 3.45 (s, 3H, CH_3OH), 2.17 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 157.15 (d), 134.86 (s), 134.59 (d), 133.52 (d), 132.39 (s), 129.99 (d), 129.10 (s), 128.71 (d), 120.12 (s), 115.56 (s), 20.60 (s). $^{31}P\{^1H\}$ ($CDCl_3$, 81 MHz) δ: −25.50 (s).

1-*tert*-Butyl-4-methoxymethoxybenzene. The same procedure was used as for 1-methoxymethoxy-4-methylbenzene with the following substitutions: 4-*tert*-butylphenol (18.8 g, 0.125 mol), dimethoxymethane (43 g, 0.565 mol) and *p*-toluenesulfonic acid (125 mg, 0.726 mmol) were used in 250 mL of dichloromethane. The yield after distillation (61–64 °C, 0.1 mmHg) was 13.8 g (57%). ^1H NMR ($CDCl_3$) δ: 7.30 (d, 2H, aromatic *H*, $^3J_{HH'}$ = 9 Hz), 7.00 (d, 2H, aromatic *H*′, $^3J_{HH'}$ = 9 Hz), 5.12 (s, 2H, mom CH_2), 3.43 (s, 3H, mom CH_3), 1.31 (s, 9H, C(CH_3)$_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 155.28 (s, 1C), 144.61 (s, 1C), 126.38 (s, 2C), 116.01 (s, 2C), 94.62 (s, 1C, mom CH_2), 55.80 (s, 1C, mom CH_3), 34.24 (s, 1C, $C(CH_3)_3$), 31.69 (s, 3C, C(CH_3)$_3$).

(5-*tert*-Butyl-2-methoxymethoxyphenyl)diphenylphosphine. The same procedure was used as for (2-methoxymethoxy-5-methylphenyl)diphenylphosphine with the following substitutions: 1-*tert*-butyl-4-methoxymethoxybenzene (5.42 g, 27.9 mmol) in 40 mL petroleum ether, *n*-BuLi in *n*-hexane 1.6 M (19.7 mL, 31.5 mmol) in 5 mL petroleum ether, TMEDA (3.25 g) in 5 mL of petroleum ether, and chlorodiphenylphosphine (6.12 g, 27.9 mmol) were used to yield 5.54 g (53%) of white solid. ^1H NMR ($CDCl_3$) δ: 7.43–7.29 (overlapped multiplets, 11H), 7.07 (dd, 1H), 6.74 (dd, 1H), 5.08 (s, 2H, mom CH_2), 3.21 (s, 3H, mom CH_3), 1.13 (s, 9H, C(CH_3)$_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 156.57 (d), 144.47 (s), 136.73 (d), 134.16 (s), 133.76 (s), 131.01 (d), 128.67 (s), 128.33 (d), 127.04 (s), 125.45 (d), 112.96 (s), 94.20 (s, 1C, mom CH_2), 55.95 (s, 1C, mom CH_3), 34.23 (s, 1C, $C(CH_3)_3$), 31.30 (s, 3C, C(CH_3)$_3$). $^{31}P\{^1H\}$ ($CDCl_3$, 81 MHz) δ: −14.88 (s).

(5-*tert*-Butyl-2-hydroxyphenyl)diphenylphosphine, H(*t*-BuPO). The same procedure was used as for H(MePO) with the following substitutions: (5-*tert*-butyl-2-methoxymethoxyphenyl)diphenylphosphine (4.2 g, 11 mmol) and 200 mL methanol were used to yield a white solid 2.3 g (63%). ^1H NMR ($CDCl_3$) δ: 7.73–7.22 (overlapped multiplets, 13H), 1.05 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 158.91 (d), 143.03 (d), 133.50 (d), 133.30 (s), 132.80 (s), 130.75 (d), 129.09 (d), 121.53 (s), 120.17 (s), 116.63 (s), 33.94 (s, 1C, $C(CH_3)_3$), 30.91 (s, 3C, C(CH_3)$_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 81 MHz) δ: −4.19 (s).

Bis(2-methoxymethoxy-5-methylphenyl)phenylphosphine. The same procedure was used as for (2-methoxymethoxy-5-methylphenyl)diphenylphosphine with the following substitutions: 1-methoxymethoxy-4-methylbenzene (10.7 g, 70.3 mmol) in 100 mL petroleum ether, *n*-BuLi in *n*-hexane (1.6 M, 50 mL, 80 mmol) in 11 mL petroleum ether, TMEDA (8.19 g) in 11 mL petroleum ether, and dichlorophenylphosphine (6.26 g, 35 mmol) were used to yield a white solid 9.22 g (64%). ^1H NMR ($CDCl_3$) δ: 7.45–7.26 (br, 5H), 7.10 (dd, 2H, aromatic *H*, $^3J_{HH'}$ = 8 Hz), 7.02 (dd, 2H, aromatic *H*′, $^3J_{HH'}$ = 8 Hz), 6.58 (dd, 2H, aromatic *H*″, $^4J_{H'H''}$ = 6 Hz), 5.05 (m, 4H, mom CH_2), 3.21 (s, 6H, mom CH_3), 2.15 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 156.63 (d), 136.34 (d), 134.13 (d), 133.88 (s), 130.91 (s), 130.40 (s), 128.25 (d), 127.98 (s), 125.60 (d), 113.42 (s), 94.08 (s, mom CH_2), 55.56 (s, mom CH_3), 20.51 (s, CH_3). $^{31}P\{^1H\}$ ($CDCl_3$, 81 MHz) δ: −25.77 (s).

Bis(2-hydroxy-5-methylphenyl)phenylphosphine, $H_2(Me_2PO_2)$. The same procedure was used as for H(MePO) with the following substitutions: bis(2-methoxymethoxy-5-methylphenyl)-phenylphosphine (7.20 g, 17.5 mmol) and 400 mL methanol were used. The resulting methanol solution of product was stored at room temperature overnight to obtain a white powder, yield 5.3 g (84%). Anal. Calcd (found) for $C_{20}H_{19}O_2P{\cdot}CH_3OH{\cdot}$HCl: C, 64.53 (63.46); H, 6.19 (5.91%). EIMS: *m*/*z* = 322 ([$Me_2H_2PO_2$]$^+$). ^1H NMR (pyridine-d^5) δ: 7.75 (m, 2H), 7.40–7.24 (overlapping multiplets, 5H), 7.18–7.06 (overlapping multiplets, 4H), 2.03 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR (pyridine-d^5) δ: 159.22 (d), 138.86 (d), 135.02 (s), 134.87 (d), 131.41 (s), 128.91 (d), 128.87 (s), 124.29 (d), 116.04 (s), 20.91 (s). $^{31}P\{^1H\}$ NMR (pyridine-d^5, 81 MHz) δ: −27.02 (s).

Bis(5-*tert*-butyl-2-methoxymethoxyphenyl)phenylphosphine. The same procedure was used as for (2-methoxymethoxy-5-methylphenyl)diphenylphosphine with the following substitutions: 1-*tert*-butyl-4-methoxymethoxybenzene (12.5 g, 64.6 mmol) in 100 mL of petroleum ether, *n*-BuLi in *n*-hexane (1.6 M, 45.7 mL, 73 mmol) in 11 mL petroleum ether, TMEDA (9.7 g) in 11 mL petroleum ether, and dichlorophenylphosphine (5.55 g, 31.7 mmol). The yield was 9.33 g (59%). ^1H NMR ($CDCl_3$) δ: 7.36–7.26 (br with overlapped multiplets, 7H), 7.05 (dd, 2H, aromatic *H*′, $^3J_{HH'}$ = 8.5 Hz), 6.76 (dd, 2H, aromatic *H*″, $^4J_{H'H''}$ = 6 Hz), 5.06 (m, 4H, mom CH_2), 3.20 (s, 6H, mom CH_3), 1.11 (s, 18H, C(CH_3)$_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 156.90 (d), 144.40 (s), 136.84 (d), 133.94 (d), 131.35 (s), 128.20 (d), 128.15 (s), 126.80 (s), 125.31 (d), 113.10 (s), 94.28 (s, 2C, mom CH_2), 55.83 (s, 2C, mom CH_3), 34.16 (s, 2C, $C(CH_3)_3$), 31.28 (s, 6C, C(CH_3)$_3$). $^{31}P\{^1H\}$ ($CDCl_3$, 81 MHz) δ: −25.97 (s).

Bis(5-*tert*-butyl-2-hydroxyphenyl)phenylphosphine, $H_2(t\text{-}Bu_2PO_2)$. The same procedure was used as for H(MePO) with the following substitutions: bis(5-*tert*-butyl-2-methoxymethoxyphenyl)phenylphosphine (9.30 g, 18.8 mmol) and 400 mL methanol were used to prepare a white powder, yield 8.0 g (96%). EIMS: *m*/*z* = 406 ([*t*-$Bu_2H_2PO_2$]$^+$). ^1H NMR (pyridine-d^5) δ: 7.47–7.16 (overlapped multiplets, 11H), 1.14 (s, 18H, C(CH_3)$_3$). $^{13}C\{^1H\}$ NMR (pyridine-d^5) δ: 159.39 (d), 142.43 (s), 139.50 (d), 134.66 (d), 132.31 (s), 128.89 (d), 128.77 (s), 127.74 (s), 123.48 (d), 115.66 (s), 34.62 (s, 1C, $C(CH_3)_3$), 31.99 (s, 3C, C(CH_3)$_3$). $^{31}P\{^1H\}$ NMR (pyridine-d^5, 81 MHz) δ: −26.69 (s).

[ReOCl(MePO)$_2$], (1). *Method A. mer*-[$ReOCl_3(PPh_3)_2$] (84 mg, 0.10 mmol) and H(MePO)·CH_3OH (74 mg, 0.23 mmol) were dissolved in ethanol (10 mL), and refluxed under Ar for 30 minutes. Three drops of triethylamine were added and the subsequent mixture was refluxed for a further 60 minutes. The solvent was removed; the green solid was redissolved into a minimum amount of CH_2Cl_2. Diethyl ether (20 mL) was added and the solution was cooled; the resulting white precipitate of [$NHEt_3$]Cl was removed by filtration and *n*-pentane (200 mL)

was added to the green solution to produce a green precipitate, after partial removal of solvent. The green precipitate was filtered off, washed liberally with *n*-pentane and dried *in vacuo* to yield 48 mg (59%). The product was soluble in acetone, acetonitrile, $CHCl_3$ and CH_2Cl_2, but insoluble in Et_2O and *n*-pentane. Anal. Calcd (found) for $C_{38}H_{32}ClO_3P_2Re$: C, 55.64 (55.72); H, 3.93 (3.97); Cl, 4.32 (4.22%). (+)LSIMS: *m*/*z* = 785 ($[M - Cl]^+$). IR (cm^{-1}): 957 (Re=O). ^1H NMR (CD_2Cl_2) δ: 7.8–6.0 (overlapping, 26 H, aromatic *H*), 2.26 (s, 3H, CH_3), 2.20 (s, 3H, CH_3). $^{31}P\{^1H\}$ NMR (CD_2Cl_2, 202.5 MHz) δ: 15.25 (d, $^2J_{PP'}$ = 10 Hz), 2.05 (d, $^2J_{PP'}$ = 10 Hz). Crystals suitable for X-ray structure analysis were grown by slow diffusion of pentane into a CH_2Cl_2 solution of the complex.

Method B. To a 25 mL ethanol solution of $[NH_4][ReO_4]$ (78.8 mg, 0.294 mmol) and H(MePO)·CH_3OH (248 mg, 0.765 mmol) was added one drop of concentrated HCl. This solution was refluxed for two hours under Ar; triethylamine (150 mg, 0.15 mmol) was then added, and the solution was further refluxed overnight. The resulting green solution was filtered, and then purified on a silica gel column using 20 : 1 $CHCl_3/CH_3OH$ eluent (TLC R_f 0.69, green). After removal of the solvent, the solid was recrystallised from a saturated solution of $CHCl_3$ and *n*-pentane, and was dried *in vacuo* overnight. The resulting olive green solid was found to be identical to **1** synthesised by method A, yield 118 mg (49%).

[ReO(Me_2PO_2)(H(Me_2PO_2))], (2). To a 20 mL ethanol solution of $[NH_4][ReO_4]$ (30 mg, 0.11 mmol) and $H_2(Me_2PO_2)$·CH_3OH·HCl (100 mg, 0.25 mmol) was added one drop of concentrated HCl. This solution was refluxed for several hours under Ar, triethylamine (100 mg, 0.1 mmol) was then added, and the solution was further refluxed overnight. The resulting green solution was filtered and then purified on a silica gel column using 20 : 1 $CHCl_3/CH_3OH$ eluent (TLC R_f 0.75, green). After removal of the solvent, a green solid was isolated and dried *in vacuo*, yield 40 mg (43%). Anal. Calcd (found) for $C_{40}H_{35}O_5P_2Re·H_2O$: C, 55.74 (55.62); H, 4.33 (4.33%). (+)LSIMS: *m*/*z* = 845 ($[M + H]^+$). IR (cm^{-1}): 965 (Re=O). ^1H NMR (CD_3OD) δ: 7.9–5.7 (overlapping, 22H aromatic *H*), 2.27 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.09 (s, 3H, CH_3). $^{31}P\{^1H\}$ NMR (CD_3OD, 202.5 MHz) δ: 21.14 (d, $^2J_{PP'}$ = 4 Hz), 12.69 (d, $^2J_{PP'}$ = 4 Hz). Crystals suitable for X-ray structure analysis were grown by slow evaporation of an acetonitrile/methanol/acetone solution of the complex.

[Re(Hhypy)(hypy)(PO)(HPO)]Cl, (3). *Method A.* [Re(Hhypy)(hypyH)Cl_3] (62 mg, 0.118 mmol) and HPO (93 mg, 0.294 mmol) were dissolved in 15 mL methanol. The reaction flask was flushed with Ar for 20 minutes, after which time triethylamine (32 mg, 0.317 mmol) was added. The solution began to turn red immediately and was refluxed overnight. The resulting red solution contained a mixture of **3** and **4** (*vide infra*), from which **3** was separated on a silica gel column using 10 : 1 $CHCl_3$/MeOH eluent (R_f = 0.12, red). After removal of the solvent, the red product was recrystallised from CH_2Cl_2/CH_3OH, and dried *in vacuo*, yield 80 mg (64%). Anal. Calcd. (found) for $C_{46}H_{41}ClN_6O_2P_2Re·CH_2Cl_2$: C, 52.35 (53.11); H, 4.02 (4.03); N, 7.79 (8.13%). (+)LSIMS: *m*/*z* = 955 ($[M]^+$). IR (cm^{-1}): 1580 ($\nu_{N=N}$), 1550 ($\nu_{N=N}$). ^1H NMR (CD_2Cl_2) δ: 8.66 (dd, 1H, α-nitrogen *H*, $^3J_{HP}$ = 1.2 Hz, $^3J_{HP'}$ = 5.1 Hz), 7.9–6.4 (overlapping multiplets, 36H, 2.25 (s, 1H, phenolic *H*). ^{31}P NMR (CD_2Cl_2, 81 MHz) δ: 33.0 (d, $^2J_{PP}$ = 202 Hz), 14.1 (d, $^2J_{PP}$ = 202 Hz). Crystals suitable for X-ray structure analysis were grown by slow diffusion of cyclohexane into a chlorobenzene/toluene solution of the isolated complex.

Method B. $[NH_4][ReO_4]$ (100 mg, 0.373 mmol) and 2-hydrazinopyridine·2HCl (270 mg, 1.492 mmol) were combined and stirred into 40 mL methanol. The solution colour quickly changed to purple; the reaction solution was refluxed for 30 minutes. After allowing the solution to cool, HPO·HCl (500 mg 1.59 mmol) in 10 mL methanol was added, followed by NEt_3 (300 mg, 2.97 mmol). The mixture was refluxed overnight, and afforded a red mixture of products. The products were separated on silica gel as above and isolated: **3** (190 mg, 48%), **4** (26 mg, 10%).

[ReCl(Hhypy)(hypy)(PO)], (4). [ReCl(Hhypy)(hypy)(PO)] (20 mg, 24%) was isolated, on a silica gel column using 10 : 1 $CHCl_3/CH_3OH$ eluent, as a byproduct of the [Re(Hhypy)(hypy)(PO)(HPO)]Cl reaction (R_f = 0.54). IR (cm^{-1}): 1579 ($\nu_{N=N}$), 1551 ($\nu_{N=N}$). (+)LSIMS: *m*/*z* = 677 ($[M - Cl]^+$). ^1H NMR (CD_2Cl_2) δ: 8.02 (d, 1H, α-nitrogen *H*, $^3J_{HP}$ = 6.1 Hz), 7.7–6.5 (overlapped multiplets, 22H). ^{31}P NMR (CD_2Cl_2, 81 MHz) δ: 25.5 (s). Crystals suitable for X-ray structure analysis were obtained by slowly evaporating a solution of the complex in CH_2Cl_2/MeOH.

[Re(Hhypy)(hypy)(HPO_2)(H_2PO_2)]Cl (5). This complex was synthesised using method A for **3** with the substitution of H_2PO_2 for HPO. (+)LSIMS: *m*/*z* = 987 ($[M]^+$). ^1H NMR (CD_3OD) δ: 8.50 (dd, 1H, α-nitrogen *H*, $^3J_{HP}$ = 1.0 Hz, $^3J_{HP'}$ = 4.9 Hz), 7.9–6.0 (overlapping multiplets, 34H). ^{31}P NMR (CD_3OD, 81 MHz) δ: 31.8 (d, $^2J_{PP}$ = 207 Hz), 13.5 (d, $^2J_{PP}$ = 207 Hz).

[Re(Hhypy)(hypy)(H(Me_2PO_2))(H_2(Me_2PO_2)]Cl (6). This complex was synthesised using method A of the synthesis for **3** with the substitution of $H_2(Me_2PO_2)$ for HPO. Only the major product was isolated and characterised. Recrystallisation from CH_2Cl_2/CH_3OH afforded pure product, yield 60 mg (45%). Anal. Calcd (found) for $C_{50}H_{46}N_6O_4P_2Re·CH_2Cl_2$: C, 54.30 (54.70); H, 4.29 (4.51); N, 7.45 (7.51%). (+)LSIMS: *m*/*z* = 1043 ($[M]^+$). ^1H NMR (CD_2Cl_2) δ: 8.45 (dd, 1H, α-nitrogen *H*, $^3J_{HP}$ = 1.1 Hz, $^3J_{HP'}$ = 5.0 Hz), 7.9–6.4 (overlapping multiplets, 30H), 2.17 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.80 (s, 3H, CH_3). ^{31}P NMR (CD_2Cl_2, 81 MHz) δ: 32.8 (d, $^2J_{PP}$ = 205 Hz), 12.8 (d, $^2J_{PP}$ = 205 Hz).

X-Ray crystallographic analyses of 1, 2 and 3

Data for **1**, **2** and **3** were collected on a Rigaku/ADSC CCD diffractometer at UBC at −100(1) °C. All data were processed and corrected for Lorentz and polarisation effects, and absorption (semi-empirical, based on symmetry analysis of redundant data). Structures **1** and **3** were solved using heavy-atom Patterson methods,[51] while the structure of **2** was solved by direct methods.[52] All three structures were expanded using Fourier techniques.[53] Final refinements for **1**, **2** and **3** were carried out using SHELXL-97.[54] Selected crystallographic data for the complexes appear in Table 1.

Final unit cell parameters for **1** (**2**, **3**) were obtained by least-squares on the setting angles for 18480 (20525, 22660) reflections with 2θ = 5.8–55.8° (6.0–55.9°, 6.2–55.8°). Compound **1** was found to crystallise in space group *C*2/*c* with two molecules of *n*-pentane in the asymmetric unit. All non-hydrogen atoms other than the *n*-pentane carbons were refined anisotropically. All hydrogens were included in fixed positions. Additionally, one phenyl ring [C(27)–C(32)] was disordered and modelled as a rigid group in two separate orientations, with relative populations of 0.72 and 0.28 for the major and minor orientations, respectively. Compound **2** crystallises in space group $P2_12_12_1$ with two molecules of acetonitrile in the asymmetric unit. All non-hydrogen atoms were refined anisotropically. The lone hydroxyl hydrogen was refined isotropically, while all others were included in fixed positions. The enantiomer reported here was chosen based on a refinement of the Flack parameter and by the results of a parallel refinement of both enantiomers. Compound **3** crystallises in space group $P\bar{1}$, with two chloride counter ions in the asymmetric unit. All non-hydrogen atoms were refined anisotropically, while all hydrogens were included in fixed positions. While it was evident that

Table 1 Selected crystallographic data for **1**, **2**, **3** and **4**

	1	**2**	**3**	**4**
Chemical formula	$C_{48}H_{56}ClO_3P_2Re$	$C_{44}H_{41}N_2O_5P_2Re$	$C_{46}H_{41}ClN_6O_2P_2Re$	$C_{28}H_{23}ClN_6OPRe$
Formula weight	964.58	925.97	993.48	712.14
Crystal system	Monoclinic	Orthorhombic	Triclinic	Orthorhombic
Space group	$C2/c$	$P2_12_12_1$	$P\bar{1}$	$P2_12_12_1$
a/Å	29.371(1)	9.5519(3)	14.9440(8)	12.294(2)
b/Å	16.9227(5)	18.9971(6)	16.1173(7)	14.500(4)
c/Å	17.6075(9)	21.824(1)	19.003(1)	14.999(5)
α/°	90.0	90.0	81.996(2)	90.0
β/°	105.453(2)	90.0	77.802(2)	90.0
γ/°	90.0	90.0	78.955(2)	90.0
V/Å^3	8435.3(5)	3960.2(2)	2118.4(1)	2673.8(12)
Z	8	4	4	4
Density/g cm^{-3}	1.519	1.553	1.511	1.769
Wavelength/Å	0.71069	0.71069	0.71069	1.54184
μ/mm^{-1}	3.063	3.198	2.962	10.651
T/K	173(1)	173(1)	173(1)	153(5)
$R1(F_o)$	0.038	0.032	0.042	0.0260
$wR2(F_o^2)$	0.111	0.078	0.106	0.0676

the large void spaces in the lattice allowed for the inclusion of disordered CH_3OH solvent, the solvent molecules were indeed extremely disordered and impossible to model properly. As a consequence, PLATON[55] was used to correct the data. The corrected data set improved the $R1$ value from 0.052 to 0.042.

X-Ray crystallographic analysis of 4

Data for **4** were collected on a Nonius CAD4 diffractometer at Rutgers with graphite monochromatised Cu-Kα radiation ($\lambda = 1.5418$ Å) at −120 °C. The three check reflections measured every hour showed less than 1% intensity variation. The data were corrected for Lorentz effects and polarisation, and absorption, the latter by a numerical SHELX-76[56] method. The structures were solved by direct methods using SHELXS-86.[57] All atoms were refined using SHELXL-97[54] based upon F_o^2. The U_{iso} parameters of H4, H8, H16 and H18 were fixed to 1.2 times the equivalent isotropic U of N4, C8, C16 and C18, respectively. Scattering factors (f_o, f', f'') are as described in SHELXL-97.[54]

CCDC reference numbers 168621–168624.

See http://www.rsc.org/suppdata/dt/b1/b104274m/ for crystallographic data in CIF or other electronic format.

Results and discussion

Alkyl HPO and H_2PO_2 ligands

A series of *para*-substituted alkyl HPO and H_2PO_2 derivatives have been synthesised by modifying the published preparations for HPO[47] and H_2PO_2[42] (Scheme 2). The synthetic methodology was relatively unchanged except for the use of *para*-substituted phenols in the first step. After mom protection, the *para*-substituted phenols were *ortho* lithiated and then reacted with the appropriate chlorophenylphosphines, which were then subsequently deprotected. It should be noted that the difficulty of isolating pure product increases dramatically both with the size and number of alkyl substituents.

The formulation of H(MePO)·CH_3OH is supported by the presence of exactly one equivalent of methanol in the ^{1}H NMR spectrum. Indeed, the elemental analysis was found to be consistent with this formulation.

The methyl and *t*-butyl derivatives have enhanced solubility in organic solvents compared to the unsubstituted compounds. In particular, the H_2PO_2 system shows remarkably higher solubility on going from the unsubstituted to the *t*-butyl-substituted compound. In addition to enhancing solubility, the alkyl substituents also provide a convenient ^{1}H and ^{13}C NMR handle in metal complexes.

It was hoped that the soft/hard phosphine–phenolate mixed donors would stabilise intermediate oxidation states of rhenium, and stabilise the resulting complexes towards hydrolysis. A bidentate phosphine–phenolate ligand should also prove more hydrolytically stable than a phosphine/chloro pair of monodentate ligands.

Me_xPO_x Complexes with the $[Re{=}O]^{3+}$ core

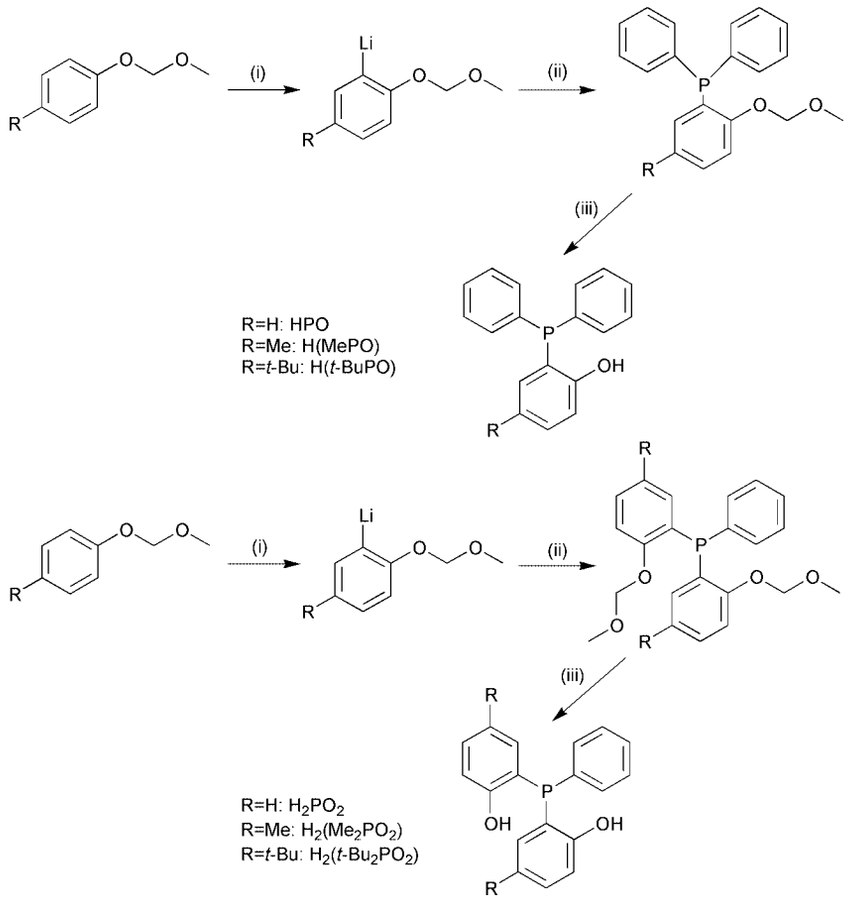
$[ReOCl(MePO)_2]$ (**1**) was prepared in good yield by reaction of H(MePO) with *mer*-$[ReOCl_3(PPh_3)_2]$ under basic conditions. The complex was also made from $[NH_4][ReO_4]$ by reduction of the metal in the presence of H(MePO) and HCl. After sufficient time for the reduction, the reaction was brought to basic conditions; the complex was formed and isolated in good yield. Although complexes of this type are represented in the literature,[42,43] this is the first report of their synthesis from an $[ReO_4]^-$ precursor. The complex is soluble in organic solvents such as methanol and dichloromethane, but is insoluble in diethyl ether or less polar solvents.

The diagnostic Re=O stretch in the IR spectrum of **1** at 957 cm^{-1} is consistent with values for related rhenium oxo complexes.[42,43] The (+)LSIMS spectrum shows only a small trace of the parent peak at m/z 820 and is dominated by the parent minus chloride cation peak at m/z 785. The presence of one chloride was verified by elemental analysis. The complex does not precipitate upon addition of sodium tetraphenylborate indicating that it is neutral and not cationic in solution.

The ^{1}H NMR spectrum of **1** shows two methyl resonances, as expected for a bis complex of low symmetry. The two doublets in the ^{31}P NMR spectrum possess a $^2J_{PP}$ coupling constant of 10 Hz, consistent with two mutually *cis* phosphorus nuclei in dichloromethane solution. The related complex $[ReOCl(PO)_2]$ is also *cis*-(P,P) when synthesised in alcohol solution. The addition of the methyl group does not create enough steric hindrance for the complex to revert to the *trans*-(P,P) stereoisomer.

Single crystals for an X-ray structural analysis of **1** were obtained by slow diffusion of pentane into a dichloromethane solution of the purified complex (Table 2, Fig. 1). The complex is a neutral, distorted octahedral $[Re{=}O^{3+}]$ complex with a mononuclear P_2O_3Cl coordination sphere. Two pentane molecules are incorporated in the crystal lattice per complex, for a total of 16 in the unit cell. As expected, the MePO ligands act as uninegative, bidentate chelates with the oxo group and the chloride filling the remaining octahedral coordination sites. One Me–PO ligand occupies two equatorial sites and the other occupies both an equatorial site and the axial site *trans* to the oxo group.

The Re=O bond length of 1.680 Å is identical to that in the reported structure of $[ReOCl(PO)_2]$.[43] The Re–P bond lengths



Scheme 2 (i) Petroleum ether, 273 K, *n*-BuLi, TMEDA; (ii) Ph_2PCl, 273 K; (iii) HCl(g), anhydrous MeOH.

Table 2 Selected bond lengths (Å) and angles (°) in $[ReOCl(MePO)_2]$ (**1**)

Re=O(3)	1.680(4)	Cl(1)–Re–O(3)	98.23(16)
Re–Cl(1)	2.264(4)	P(1)–Re–O(1)	100.69(5)
Re–P(1)	2.4457(15)	P(1)–Re–O(2)	83.41(12)
Re–P(2)	2.4206(17)	P(1)–Re–O(3)	91.00(14)
Re–(O1)	2.013(4)	P(2)–Re–O(1)	160.08(10)
Re–O(2)	2.044(3)	P(2)–Re–O(2)	77.96(12)
Cl(1)–Re–P(1)	162.66(10)	P(2)–Re–O(3)	87.18(14)
Cl(1)–Re–P(2)	94.44(12)	O(1)–Re–O(2)	82.57(15)
Cl(1)–Re–O(1)	81.89(15)	O(1)–Re–O(3)	112.70(16)
Cl(1)–Re–O(2)	91.57(14)	O(2)–Re–O(3)	162.80(15)

are comparable, with Re–P *trans* to the chloride slightly elongated compared to Re–P *trans* to the phenolic O donor. This is contrary to the reported $[ReOCl(PO)_2]$ structure wherein both bond lengths are *ca.* 0.04 Å longer and the opposite effect was observed.

The bond angles indicate that the coordination in **1** is best described as distorted octahedral. Most of the bond angles are similar to those in $[ReOCl(PO)_2]$ with one notable exception: the bidentate phenol ring that is coordinated both through an axial and equatorial position is twisted away from the chloride. This effect is likely a combination of the increased steric bulk of the methyl group and the shortened Re–Cl bond length.

$[ReO(Me_2PO_2)(H(Me_2PO_2))]$ (**2**) was synthesised from $[NH_4][ReO_4]$ by reducing perrhenate in the presence of the ligand and HCl. After reduction, addition of excess base formed a green complex that was soluble in ethanol. This enhanced solubility is presumably due to the methyl groups since the analogue $[ReO(PO_2)(HPO_2)]$ is insoluble in ethanol. Pure **2** was isolated in reasonable yield after purification using silica gel chromatography. The formation of a rhenium oxo complex is evident from the 965 cm^{-1} band in the infrared spectrum, and its formulation is supported by the (+)LSIMS spectrum. As expected for a bis complex, the ^1H NMR spectrum shows four methyl

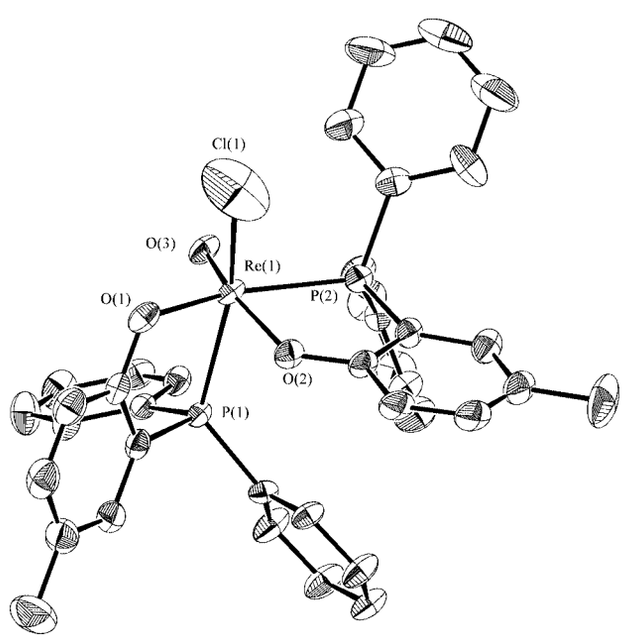


Fig. 1 ORTEP[62] diagram of $[ReOCl(MePO)_2]$, **1** (with the solvent molecules and H-atoms omitted); 50% thermal probability ellipsoids.

resonances. The ^{31}P NMR spectrum shows two doublets with a $^2J_{PP}$ coupling constant of 4 Hz, consistent with two mutually *cis* phosphorus nuclei in solution. At 25 °C, there is no indication of any exchange between the free arm of the bidentate ligand with the tridentate Me_2PO_2 ligand.

Single crystals were isolated from a slowly evaporated acetonitrile/methanol/acetone solution of the purified complex. The discrete, mononuclear compound has a distorted octahedral geometry with a P_2O_4 donor set (Table 3, Fig. 2). One Me_2PO_2 ligand is bound in a facial, tridentate fashion with P

Table 3 Selected bond lengths (Å) and angles (°) in [ReO(Me_2PO_2)-(H(Me_2PO_2))] (**2**)

Re=O(5)	1.666(4)	P(2)–Re–O(1)	79.7(1)
Re–P(1)	2.410(2)	P(2)–Re–O(2)	160.9(1)
Re–P(2)	2.458(2)	P(2)–Re–O(3)	82.3(1)
Re–O(1)	2.035(4)	P(2)–Re–O(5)	93.9(2)
Re–O(2)	2.018(4)	O(1)–Re–O(2)	88.1(2)
Re–O(3)	2.003(4)	O(1)–Re–O(3)	85.1(2)
P(1)–Re–P(2)	108.24(5)	O(1)–Re–O(5)	163.6(2)
P(1)–Re–O(1)	75.0(1)	O(2)–Re–O(3)	82.0(2)
P(1)–Re–O(2)	82.4(1)	O(2)–Re–O(5)	101.5(2)
P(1)–Re–O(3)	155.0(1)	O(3)–Re–O(5)	109.2(2)
P(1)–Re–O(5)	93.0(1)		

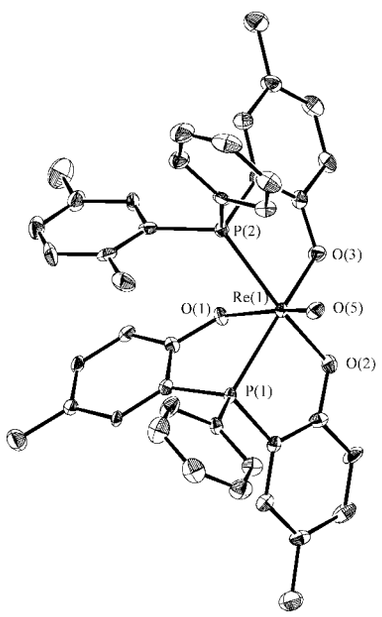


Fig. 2 ORTEP diagram of [ReO(Me_2PO_2)(H(Me_2PO_2))], **2** (with the solvent molecules and H-atoms omitted); 50% thermal probability.

and O atoms occupying equatorial positions, and the remaining oxygen occupying the axial position *trans* to the oxo linkage. The second Me_2PO_2 ligand is bound in an equatorial bidentate fashion with the remaining O protonated and uncoordinated to Re. The addition of acetonitrile to the crystal growing solution was necessary and suitable crystals could not be obtained without it. Indeed, the crystal structure shows two acetonitrile molecules per complex, one of which is hydrogen bound to the free phenolic OH with an N–O contact of 2.82(1) Å.

A search of the Cambridge Crystallographic Database[58] reveals that **2** is the second rhenium PO_2 complex structure to be reported, after [ReO(PO)(PO_2)].[42] It is the first reported structure of a bis PO_2 complex. The Re=O bond length in **2** (1.666(4) Å) is consistent; Re–P bond lengths are typical, but the bidentate Re–P bond is significantly longer than its tridentate analogue. This may be caused by the additional steric hindrance of the free phenolic OH and its concomitant hydrogen-bonded acetonitrile. The 163.6(2°) O(1)–Re–O(5) angle is far from linear and suggests that the tridentate ligand is under strain. In both cases, the phosphine atoms lie within a few degrees of the ideal 90°, relative to the oxo.

There are examples in the literature of the successful bioconjugation of $[Tc{=}O]^{3+}$ complexes with the bifunctional chelate HYNIC.[10,12,13,15,16,38] Typically, a HYNIC-labelled biomolecule is reacted with pertechnetate in the presence of the ligand and a reducing agent. In some cases, the reducing agent is not necessary due to the reductive capacity of the hydrazine.[8] Reactions of various hydrazines with **1** and **2** were attempted in order to extend this type of chemistry to rhenium, and to test the feasibility of this approach. Under no conditions would a hydrazine complex form with **1** or **2**, even at a 20 : 1 hydrazine : Re ratio. None of 2-hydrazinopyridine, 2-hydrazino-2-imidazoline, phenylhydrazine, *N*,*N*-phenylmethylhydrazine or *N*,*N*-dimethylhydrazine produced any product. In each case, **1** or **2** were recovered from the reaction mixture in near quantitative yield. In order to drive the elimination of the Re=O oxygen atom as water (as in Scheme 1), temperatures as high as 180 °C were used, but all attempts were unsuccessful. Addition of $NaBH_4$ as a reducing agent did not promote formation of complex by reduction/complexation. An alternative route to HYNIC bioconjugates of PO_x and hydrazines is possible: preformation of PO_x/hydrazine-containing metal complexes, followed by subsequent conjugation to the biomolecule. The kinetic inertness of rhenium may require conditions too harsh for the biomolecule to tolerate. This synthetic route is advantageous because the complex is formed before the introduction of the biomolecule.[5] The capacity of the PO_x ligands to form hydrazine complexes was then explored with this alternative route in mind.

$[Re(HNNC_5H_4N)(NNC_5H_4N)]^{2+}$: the $[Re(Hhypy)(hypy)]^{2+}$ core

There has been a burgeoning interest in synthesizing complexes with the $[Re(Hhypy)(hypy)]^{2+}$ core as models for the HYNIC bioconjugation of metal complexes.[39,40] The [Re(Hhypy)-(hypyH)Cl_3] parent complex was synthesised from $[ReO_4]^-$ in methanol with 2-hydrazinopyridine hydrochloride.[40,41] The ligand reduced Re(VII) to Re(III) after which the oxidised organodiazenes (hypy) coordinated to the metal in a unique bidentate bent diazene and a monodentate linear diazenido fashion with the pyridine nitrogen protonated in the latter case (hypyH). The chloro complex is not expected to be stable *in vivo*. Since the initiation of our studies, others have tried to stabilise the core through the formation of ternary complexes, demonstrating that thiols, including HPS (the thiol equivalent of HPO), could be used to form complexes with the [Re(Hhypy)-(hypy)]$^{2+}$ core.[39]

In order to stabilise this core towards hydrolysis *in vivo*, we thought that the H_xPO_x ligands could be bound to the metal as ancillary ligands. Recently, a variety of tethered "3 + 2" rhenium oxo complexes with mixed N_xS_{3-x} and PO have been elaborated.[59–61] These compounds appear to be very stable—some were able to withstand a glutathione challenge experiment for 24 h.[59] No known ternary complexes of hydrazine/diazo ligands and H_xPO_x have been reported in the literature prior to this report. The ability of H_xPO_x to stabilise intermediate oxidation states and to form hydrolytically stable complexes indicates that the ligand may well be an excellent choice for use in the HYNIC system. To this end, we decided to investigate the reactivity of these ligands with the $[Re(Hhypy)(hypy)]^{2+}$ core.

[Re(Hhypy)(hypyH)Cl_3] reacts with HPO directly in methanolic solution in the presence of base to form a mixture of products. Two products in the mixture were isolated and characterised after purification on a silica gel column. The salt [Re(Hhypy)(hypy)(PO)(HPO)]Cl (**3**) was the major component (64%); all three chlorine atoms were replaced to give an N_3OP_2 coordination sphere. Neutral [ReCl(Hhypy)(hypy)(PO)] (**4**) was isolated as a minor component (24%). A 20 : 1 molar ratio of HPO : Re improved the yield of **3** only slightly and impurities, notably **4**, were still present. There is evidence for the presence of other species in the mixture, but they were present in amounts too small to purify and characterise properly.

Complexes **3** and **4** can also be formed directly from [NH_4][ReO_4] in a "one pot" reaction; reduction/complexation of the perrhenate with 2-hydrazinopyridine in HCl proceeds rapidly in methanol. Addition of excess HPO and sufficient base to neutralise the acid rapidly causes the solution to change colour from purple to red. Purification on silica gel affords the same two complexes isolated by the direct route in only slightly diminished yields. The ability to synthesise complexes in a "one pot" reaction is highly desirable for preparative nuclear

medicine, because the required starting material therein is perrhenate.

Strong IR absorptions at 1580 cm^{-1} and 1550 cm^{-1} are indicative of doubly bonded N=N organodiazo coordination in both complexes. The presence of these two identical bands in **3** and **4** suggests that both hydrazines remain coordinated and retain significant double bond character in both cases. Clearly the complexes do not contain the Re(V) oxo core; there are no bands in the range 850–1050 cm^{-1}. The majority of the spectral features in the infrared spectra are due to the bands arising from the supporting framework of the organic ligands.

The ^{1}H NMR spectrum of **3** consists of a very complex aromatic region (not assigned), the α-nitrogen proton, and the phenolic proton. In CH_2Cl_2 one of the hydrazines retains the doubly bent, α-protonated, diazo mode of the starting material [Re(Hhypy)(hypyH)Cl_3]. The α-nitrogen proton appears as an exchangeable, sharp doublet of doublets at 8.66 ppm. This peak is shifted considerably downfield from that in the starting material, where the protonated pyridyl and α-nitrogen proton appear to be under exchange as a broad peak at 4.22 ppm.[40] There is possibly a weak hydrogen bonding interaction with the free pyridine of the monodentate hypy. This interaction is seen in the crystal structure of the complex (*vide infra*) and is apparently retained in solution. The coupling pattern is consistent with two magnetically inequivalent ^{31}P nuclei. The exchangeable phenolic proton appears as a broad resonance centred at 2.25 ppm in CH_2Cl_2 solution. The ^{1}H NMR spectrum strongly supports a diamagnetic, monocationic Re(III) metal centre.

The ^{31}P NMR spectrum of **3** is consistent with the presence of two magnetically inequivalent, coordinated phosphines. In sharp contrast to the oxo complexes **1** and **2**, the 202 Hz coupling constant of the two AB doublets is a strong indication that the phosphorus nuclei are coordinated *trans* to one another in **3** in CH_2Cl_2. At 25 °C, there is no indication of any fluxional process that exchanges the bidentate and monodentate PO ligands.

Single crystals of **3** for an X-ray structural analysis were obtained by the slow diffusion of cyclohexane into a chlorobenzene/toluene solution of the purified complex (Table 4, Fig. 3). The coordination is best described as distorted octahedral with an N_3OP_2 coordination sphere about Re. Using the formalism of the Re(III) starting material [Re(Hhypy)(hypyH)Cl_3], the complex is an Re(III) cation with a chloride counter anion.

The two diazo groups are *cis* to one another and both bond lengths therein are well within the range for N=N double bonds. One hypy is bidentate; the protonated diazo and pyridyl nitrogens form a 5-membered ring with a bite angle of 72.26(17)°. The other hypy is monodentate and is bound through the diazo group only. The diazo group on the bidentate hypy is best described as a "doubly bent" diazene ligand since the Re–N(1)–N(2) and the N(1)–N(2)–C(19) bond angles are both within 10° of 120°. The monodentate diazo group has a nearly linear Re–N(4)–N(5) bond angle, a bent N(4)–N(5)–C(24) bond angle (*ca.* 120°), and should be regarded as a "singly bent" diazenido ligand. The Re–N(1) bond length of 1.980(4) Å is significantly longer than the Re–N(4) bond length of 1.780(5) Å because of the α-nitrogen proton on N(1). There is a weak 2.870(8) Å hydrogen bond contact between N(1) and the monodentate pyridyl nitrogen N(6), which is deprotonated. This may contribute to the large ^{1}H NMR chemical shift of the α-nitrogen proton that is retained in solution.

As indicated in the ^{31}P NMR spectrum, the two phosphorus nuclei are *trans*, with a P(1)–Re–P(2) bond angle of 166.82(4) Å. One of the PO ligands is bidentate, forming a 5-membered ring with a bite angle of 80.98(9)°. The second PO ligand is bound only through the phosphorus, with the protonated phenolic oxygen pointing away from the metal centre. The two hypy groups are slightly distorted away from P(1) and cause some steric crowding, hence the longer bond to P(2), and the displacement of P(2) towards O(1).

Table 4 Selected bond lengths (Å) and angles (°) in [Re(Hhypy)(hypy)(PO)(HPO)]Cl (**3**)

Re–N(1)	1.980(4)	P(1)–Re–N(1)	94.91(14)
Re–N(3)	2.158(5)	P(1)–Re–N(3)	86.03(13)
Re–N(4)	1.780(5)	P(1)–Re–N(4)	94.83(15)
Re–O(1)	2.032(3)	P(2)–Re–O(1)	86.18(9)
Re–P(1)	2.4137(14)	P(2)–Re–N(1)	98.19(14)
Re–P(2)	2.4666(14)	P(2)–Re–N(3)	96.52(13)
N(1)–N(2)	1.299(7)	P(2)–Re–N(4)	86.66(15)
N(4)–N(5)	1.240(7)	O(1)–Re–N(1)	160.03(16)
O(1)–Re–N(4)	109.65(15)	O(1)–Re–N(3)	87.92(13)
N(1)–Re–N(3)	72.26(17)	Re–N(1)–N(2)	126.3(4)
N(1)–Re–N(4)	90.11(18)	N(1)–N(2)–C(19)	110.7(5)
N(3)–Re–N(4)	162.35(16)	Re–N(4)–N(5)	177.0(4)
P(1)–Re–P(2)	166.82(4)	N(4)–N(5)–C(24)	118.5(5)
P(1)–Re–O(1)	80.98(9)		

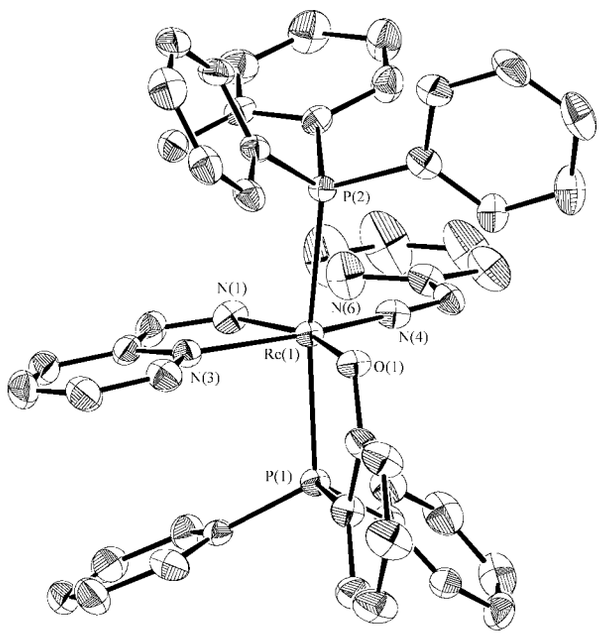


Fig. 3 ORTEP diagram of the cation [Re(Hhypy)(hypy)(PO)(HPO)]$^+$ in **3** (with the solvent molecules, H-atoms and the counter anions omitted); 50% thermal probability ellipsoids.

The ^{1}H NMR spectrum of the minor product [ReCl(Hhypy)(hypy)(PO)] (**4**) shows roughly the same spectral features, with the omission of the free phenolic proton. The α-nitrogen proton appears as a doublet at 8.02 ppm, indicating coupling to only one ^{31}P nucleus in solution. If insufficient base is added to completely deprotonate the pyridine in the starting material, the ^{1}H NMR resonance of the doublet appears at 3.96 ppm. As in the starting material, the protonated pyridyl proton is under exchange with the α-nitrogen proton; however, the peak remains a distinct doublet and does not broaden to a singlet. The ^{31}P NMR spectrum of **4** has the expected singlet at 25.5 ppm. Again, the NMR evidence supports the presence of a diamagnetic Re(III) metal centre.

In most regards, the structure of **4** is very similar to that of **3** (Table 5, Fig. 4). Crystals were obtained by slow evaporation of a CH_2Cl_2/CH_3OH solution of the complex. A distorted octahedral N_3POCl donor set surrounds the formally Re(III) metal centre, resulting in a neutral complex. The arrangement of the two hypy ligands is identical to that in **3**, including the weak pyridine–α-nitrogen contact. The chloride is *trans* to the phosphorus donor of the bidentate PO ligand. The two hypy ligands are pushed away from the bidentate phosphorus donor and distort the Cl sharply towards the oxygen donor resulting in a P(1)–Re–Cl bond angle of 161.77(5)°.

Originally it was hoped that a six-coordinate Re(III) complex

Table 5 Selected bond lengths (Å) and angles (°) in [ReCl(Hhypy)(hypy)(PO)] (**4**)

Re–Cl(1)	2.414(2)	N(4)–Re–O(1)	160.1(2)
Re–N(1)	1.779(5)	N(4)–Re–P(1)	96.14(14)
Re–N(4)	1.942(5)	N(4)–Re–Cl(1)	99.13(14)
Re–N(6)	2.137(5)	N(6)–Re–O(1)	88.3(2)
Re–O(1)	2.035(4)	N(6)–Re–P(1)	88.12(13)
Re–P(1)	2.400(2)	N(6)–Re–Cl(1)	87.20(13)
N(1)–N(2)	1.237(7)	O(1)–Re–P(1)	80.74(11)
N(4)–N(5)	1.312(7)	O(1)–Re–Cl(1)	81.51(11)
N(1)–Re–N(4)	90.7(2)	P(1)–Re–Cl(1)	161.77(5)
N(1)–Re–N(6)	162.4(2)	Re–N(1)–N(2)	174.7(4)
N(1)–Re–O(1)	109.15(18)	N(1)–N(2)–C(1)	118.9(5)
N(1)–Re–P(1)	96.30(15)	Re–N(4)–N(5)	128.7(4)
N(1)–Re–Cl(1)	93.44(15)	N(4)–N(5)–C(6)	108.4(5)
N(4)–Re–N(6)	71.9(2)		

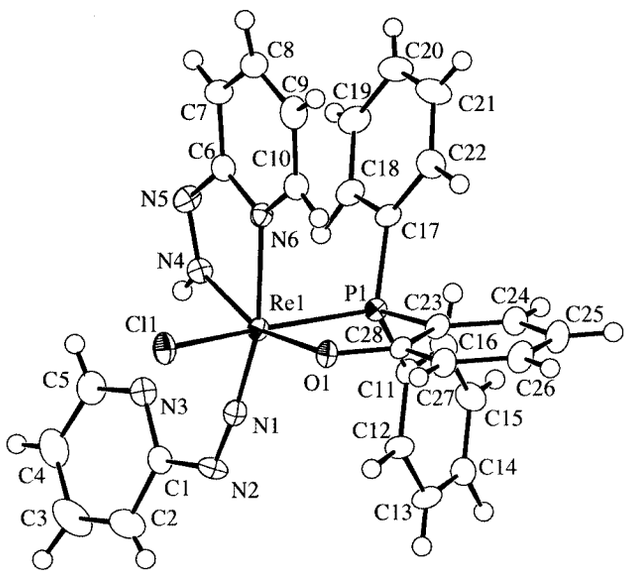


Fig. 4 ORTEP diagram of [ReCl(Hhypy)(hypy)(PO)], **4**; 50% thermal probability ellipsoids.

resembling [Re(hypy)$(PO)_2$] could be synthesised and isolated from the reaction. Since the initiation of our work, a complex of this type has been isolated and characterised from the analogous PS system, [Re(hypy)$(PS)_2$].[39] There appears to be no evidence for the formation of its PO analogue, although in the mixture there are small amounts of other species that cannot be fully characterised. The presence of the H-bonded meridional "belt" of hypy ligands appears to be a stable structural motif in this system. Attempts to displace the second hypy ligand by using a 20 : 1 HPO : Re ratio were unsuccessful. If base is omitted from the synthesis, the starting material remains largely unreacted and is recovered in near quantitative yield.

The phenolic oxygen donor also appears to play a key role in the behaviour of the complexes; the relatively soft Re(III) centre may be unable to accommodate two such hard phenolic donors. In addition to the "belt" effect, the second hypy may also be regarded as a softer donor that is better able to stabilise the Re(III) centre. The remaining coordination site *trans* to the bidentate phosphine displays a distinct preference for soft donors such as Cl^-, the phosphine of PO, or in the case of the analogous PS complex, the thiophenolate donor.[39]

This preference of the metal centre for a relatively soft donor set may explain the inability of **1** and **2** to accept a hydrazine donor and/or reduce the metal centre. Coordination to the sterically-crowded octahedral Re centre would likely have to occur through a dissociative mechanism. The kinetic inertness and thermodynamic stability of the bidentate and tridentate donors in **1** and **2** may be too great for the incoming hydrazine to overcome. Remembering that many diazenido complexes have been synthesised from [$ReOCl_3(PPh_3)$], the chelate effect of the PO_x ligands in **1** and **2** is likely responsible for raising the energy barrier too high for diazenido complex formation to occur.

Complexes of this system have also been made with the PO_2 and Me_2PO_2 ligands; in both cases, octahedral Re(III) complexes with the donor set N_3OP_2 were isolated as the major product. It was hoped that the chelate effect of three free phenolic donors would drive the formation of an $N_2O_2P_2$ coordination sphere, but this was clearly not the case. Crystal structures were not obtained but the NMR data presented in Table 6 are consistent with the structures presented above. The methyl groups *para* to the phenol provided a convenient ^{1}H NMR "handle".

[Re(Hhypy)(hypy)$(HPO_2)(H_2PO_2)$]Cl (**5**) showed a clear *trans*-(P,P) coupling in the ^{31}P NMR spectrum. This complex was extremely difficult to separate from the mixture so only the ^{1}H and ^{31}P NMR data are reported. On the basis of these data, the complex is completely analogous to the structurally characterised PO complex, with three protonated phenols not coordinated to the metal centre.

[Re(Hhypy)(hypy)$(H(Me_2PO_2))(H_2(Me_2PO_2))$]Cl (**6**) also appears to have the same structure as the PO complex. There are four methyl resonances in the ^{1}H NMR spectrum with a 1 : 1 : 1 : 1 integration. This information, combined with a *trans*-(P,P) coupling in the ^{31}P NMR spectrum, strongly suggests that the structural motif remains unchanged. The bidentate $H(Me_2PO_2)$ ligand has one free phenol, and the monodentate P-bound $H_2(Me_2PO_2)$ ligand must have two. Hindered rotation about the Re–P bond results in the two singlets of equal integration for the magnetically equivalent methyl groups of the monodentate $H_2(Me_2PO_2)$ ligand. The retention of both hypy ligands is still clearly favoured over the three phenolic O donors. Clearly, PO_2 ligands are not very suitable to act as ancillary ligands in this system.

Conclusions

New alkylated derivatives of the H_xPO_x system have been synthesised and isolated in pure form. The presence of the methyl groups increased the solubility of the ligands, and of the final complexes, in organic solvents. The methyl groups also provided a convenient ^{1}H NMR probe as the number of peaks provided an estimate of the purity and identity of the resulting complexes.

Compound **1** was obtained by reaction of H(MePO) with *mer*-[$ReOCl_3(PPh_3)_2$] and in a reduction/complexation reaction from [NH_4][ReO_4]. Compound **2** was obtained by direct reaction of $H_2(Me_2PO_2)$ with [NH_4][ReO_4]. An X-ray structural analysis of **1** and **2** demonstrated that both have a *cis*-(P,P)

Table 6 Selected ^{1}H and ^{31}P NMR spectral data for **3**, **4**, **5** and **6**

Complex	Alkyl ^{1}H NMR signals (ppm)	α-nitrogen ^{1}H NMR (ppm) [$^3J_{HP}/^3J_{HP'}$]	^{31}P NMR signals (ppm) [$^2J_{PP}$]
3		8.66 (dd) [1.2/5.1 Hz]	14.1 (d), 33.0 (d) [202 Hz]
4		8.02 (d) [6.1 Hz]	25.5 (s)
5		8.50 (dd) [1.0/4.9 Hz]	13.5 (d), 31.8 (d) [207 Hz]
6	2.17 (s), 2.07 (s), 1.99 (s), 1.80 (s)	8.45 (dd) [1.1/5.0 Hz]	12.8 (d), 32.8 (d) [205 Hz]

arrangement of the ligands. In an attempt to form mixed PO_x/hydrazine complexes, **1** and **2** were reacted with a variety of hydrazines under a wide range of conditions. The PO_x ligands are clearly not suitable for this type of reaction since no products were isolated from these reactions.

The reaction of [Re(Hhypy)(hypyH)Cl_3] with the PO ligand in the presence of base afforded **3** and **4** as a mixture. The major product of the reaction was the cationic **3**. The neutral minor product **4** was easily separated from the cationic **3** on silica gel. Crystal structures were obtained for both complexes. Compound **3** was found to have an N_3OP_2 coordination sphere about a cationic Re(III) centre, **4** had an N_3OPCl donor set about a neutral Re(III) centre. The (+)LSIMS, IR and NMR data are consistent with the crystal structures of each. The same reaction was extended to the H_2PO_2 and $H_2(Me_2PO_2)$ ligands to obtain **5** and **6** respectively as the major products. ^1H and ^{31}P NMR spectral evidence shows these products to have the same structure in solution as the structurally characterised **3**. Three of the four phenolic arms remain protonated and uncoordinated in **6**. Clearly, the mismatched donor sets of PO_2 and Me_2PO_2 would be unfavourable from a clinical standpoint.

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