Rhenium diazenide ternary complexes with dithiocarbamate ligands: towards new rhenium radiopharmaceuticals

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The reaction of the mono-diazenide core, $[ReCl_2(NNC_6H_4\text{-}4\text{-}OCH_3)(NCCH_3)(PPh_3)_2]$, with four equivalents of the sodium or potassium salts of dithiocarbamate (dtc) ligands gives neutral complexes of the formula $[Re(NNC_6H_4\text{-}4\text{-}OCH_3)(dtc)_2(PPh_3)]$. It is possible to use a wide range of dithiocarbamate ligands (S_2CNRR') with a variety of R groups (R = R′ = methyl, phenyl or ethyl; R = methyl, R′ = phenyl and R = R′ = morpholino). Substitution reactions with dtc ligands on the mono-diazenide derived from 2-hydrazinopyridine, $[ReCl_2(NNC_5H_4N)(PPh_3)_2$, give the analogous complexes, $[Re(NNC_6H_5N)(dtc)_2(PPh_3)]$. The new complexes have been characterised by a combination of NMR spectroscopy, mass spectrometry and X-ray crystallography. Cyclic voltammetry measurements in dimethyl formamide show that the rhenium diazenido-dtc complexes undergo a quasi-reversible oxidation tentatively assigned to a Re^{III}/Re^{IV} oxidation. Since the parent complex, $[ReCl_2(NNC_6H_4\text{-}4\text{-}R)(NCCH_3)(PPh_3)_2]$ can be prepared directly from perrhenate and readily derivatised with dtc ligands these complexes have potential relevance to the development of new therapeutic rhenium radiopharmaceuticals.

Introduction

There is currently considerable interest in the development of new radiotherapeutic cancer agents based on rhenium. There are two β-emitting isotopes of Re, ^{186}Re and ^{188}Re, which have suitable nuclear properties for therapeutic applications. ^{188}Re is readily available from a generator by decay of ^{188}W and is obtained as a very dilute solution of $[ReO_4]^-$.[1,2] This can provide a useful source of sterilising β radiation if it can be targeted *in vivo*.[3] Such targeting can be achieved by the incorporation of the metal atom in a coordination complex using a bifunctional ligand. Ideally the ligand must form a highly stable complex and possess a point of further functionalisation that can allow the attachment of biologically active molecules to provide specificity and selectivity *in vivo*.[4]

The use of functionalised diazenide (NNAr, Ar = aryl or 2-pyridyl) ligands for the targeting of radiopharmaceuticals based on technetium is well established,[5,6] particularly for the HYNIC system (where HYNIC = *N*-oxysuccinimidylhydrazino-nicotinamide) which uses the substituted pyridyl group as the bifunctional ligand.[7–11] The activated ester can be used to attach a variety of biologically active targeting molecules whilst the hydrazine fragment is used to form a metal–nitrogen multiple bond with Tc. The synthetic approach involves the reaction of a high oxidation state precursor, $[TcO_4]^-$, with the appropriate hydrazine with reduction of the metal, oxidation of the hydrazine to diazenide and formation of a metal–nitrogen multiple bond. The metal–nitrogen multiple bond is sufficiently stable for *in vivo* imaging applications. HYNIC can occupy one or two coordination sites so further co-ligands are required to occupy the other sites on the five- or six-coordinate metal atom. A well developed technetium system which is undergoing clinical trials utilizes a HYNIC derivatized cyclic peptide to form a metal–nitrogen multiple bond with the metal. The remaining coordination sites are occupied by a combination of tricine and a water soluble phosphine to give a ternary system. The coordinative flexibility of prochiral tricine combined with the ability of pyridylhydrazine-derived ligands to act as either a monodentate or bidentate ligand results in there being a large array of potential isomeric forms.[9]

Similar systems have been investigated with rhenium as its coordination chemistry is superficially similar to technetium, although rhenium is more kinetically inert than technetium and, significantly, it is much harder to reduce $[ReO_4]^-$ than $[TcO_4]^-$.[1] The coordination chemistry of the HYNIC system is shown by the reaction of $[ReO_4]^-$ with 2-hydrazinopyridine which gives systems in which two pyridylhydrazine-derived units are coordinated to the rhenium.[12–15] X-Ray structural characterisation of the compounds formed revealed a complex coordination chemistry due to the ability of the pyridylhydrazine-derived ligands to coordinate as either monodentate or bidentate ligands and the existence of protic equilibria.[15] This results in radiolabelled protein conjugates made using this system consisting of mixtures of complexes which have proved difficult to characterise fully. We have recently reported the reaction of arylhydrazines directly with perrhenate in acetonitrile to give a high yield of a mono-aryl diazenide complex, which has the potential to provide access to a new core for the development of radiotherapeutic agents based on rhenium.[16] We

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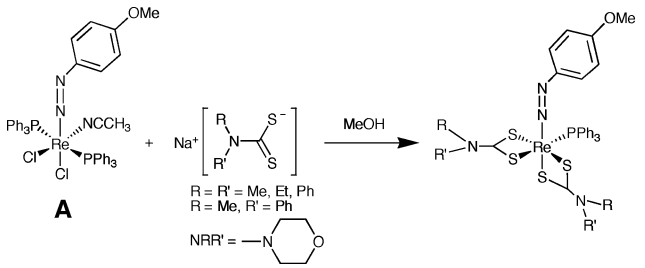
now report that the mono-aryl diazenide core undergoes high yield substitution reactions with substituted dithiocarbamate ligands (dtc) to form stable, well defined ternary complexes, of the type $[Re(NNAr)(dtc)_2(PPh_3)]$.

The use of dithiocarbamate as a co-ligand avoids the isomeric complexity of tricine systems. These complexes have been characterised by X-ray crystallography, NMR, mass spectroscopy and HPLC. The complexes offer potential for the development of well defined ternary systems suitable for the development of rhenium based therapeutic agents.

Results and discussion

We recently reported that the reaction of $[NH_4][ReO_4]$ or $[nBu_4N][ReO_4]$ with substituted phenylhydrazines ($NH_2NHC_6H_4$-4-R; where R = OCH_3, Cl, or CO_2CH_3) in acetonitrile in the presence of aqueous acid results in the rapid formation of a red solution.[16] The electrospray mass spectra of the reaction mixture when R = OCH_3 show that several different rhenium diazenide species are present but by far the biggest peak (in negative ion mode, with appropriate isotope distribution) corresponds to the mono-diazenide species $[ReCl_4(NNC_6H_4\text{-}4\text{-}OCH_3)]^-$ at m/z = 462. Addition of triphenylphosphine results in the formation of a single species by HPLC and a red air-stable solid, $[ReCl_2(NNC_6H_4\text{-}4\text{-}OCH_3)(NCH_3)(PPh_3)_2]$ (**A**) (Scheme 1), in isolated yields of about 70%. It appears that the triphenylphosphine may stabilise the diazenide core and drive the reaction to completion. Similar observations have been made from other species with metal–nitrogen multiple bonds.[17] Interestingly, these compounds are not accessible from the reaction of the well known rhenium precursor, $[ReOCl_3(PPh_3)_2]$, with arylhydrazines in acetonitrile.



Scheme 1 The synthesis of **1–5**.

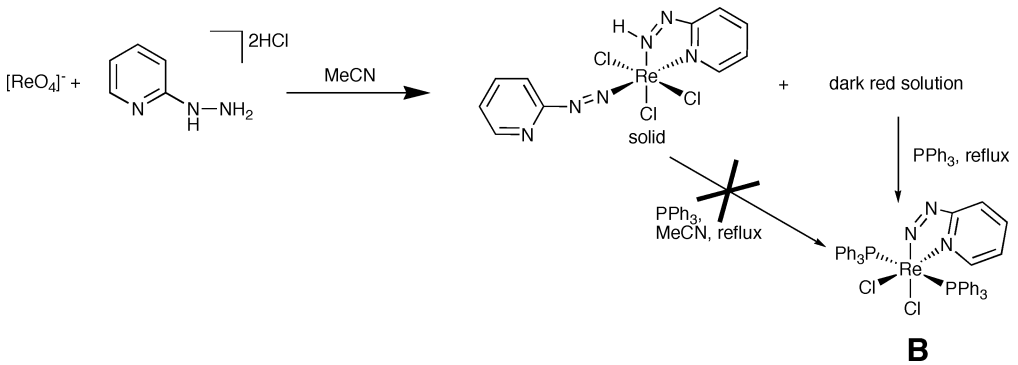
The reaction of 2-hydrazinopyridine hydrochloride with $[ReO_4]^-$ in methanol allows the isolation of $[ReCl_3(N{=}NC_5H_4NH)(HN{=}NC_5H_4N)]$ in high yields (Scheme 2).[15] The structure contains two ligands which originate from the 2-hydrazinopyridine, one acting as a bidentate ligand, coordinating through the pyridine nitrogen atom and a diazene α-nitrogen. The other coordinates as a monodentate ligand with the pyridine nitrogen atom protonated. The reaction of this compound with triphenylphosphine in ethanol in the presence of base results in the formation of $[ReCl_2(PPh_3)(N{=}NC_5H_4N)(HN{=}C_5H_4N)]$. We have found that the reaction of 2-hydrazinopyridine dihydrochloride with perrhenate in acetonitrile also results in the formation of $[ReCl_3(N{=}NC_5H_4NH)(HN{=}NC_5H_4N)]$, which precipitates from the reaction mixture, but the yield of the reaction in acetonitrile is significantly lower than that reported in methanol.[15] The filtrate of the acetonitrile reaction mixture is dark red and addition of triphenylphosphine to this mixture followed by heating at reflux for 4 h allows the isolation of $[Re(NNC_5H_4N)Cl_2(PPh_3)_2]$ (**B**) (Scheme 2). The same compound has been reported as the product of the reaction of 2-hydrazinopyridine with $[ReOCl_3(PPh_3)_2]$.[18] When additional conc. HCl is present, the majority of the solid formed is not $[Re(NNC_5H_4N)Cl_2(PPh_3)_2]$ but the known compound $[ReNCl_2(PPh_3)_2]$, which was identified by X-ray crystallography.[19]

The mono-diazenide complex **A** can be readily and rapidly substituted with a variety of ligands to form kinetically inert species whilst maintaining the mono-diazenide core. The use of co-ligands to complement a particular metal core is particularly attractive in the development of radiopharmaceuticals as it can allow subtle control of factors such as complex stability, lipophilicity, charge and ultimately biodistribution.

The reaction of the mono-diazenide 'core' compound, **A**, with approximately 4 equivalents of the sodium or potassium salts of dithiocarbamate ligands in methanol allows the ready isolation of the neutral complexes $[Re(NNC_6H_4\text{-}4\text{-}R)(dtc)_2(PPh_3)]$ as red-brown solids in high yields (Scheme 1).

It is possible to use a wide variety of dithiocarbamate ligands, (S_2CNRR', where R = Me and R′ = Me or Ph, R = R′ = Ph or Et and finally where RR′ = morpholino (C_4H_8NO)) and in each case the product of the substitution is $[Re(NNC_6H_4\text{-}4\text{-}R)(dtc)_2(PPh_3)]$ (Fig. 1). The electrospray mass spectra of the complexes all show peaks corresponding to the $[M + H^+]$.

Crystals suitable for single crystal X-ray studies were grown of the compounds resulting from the reaction of mono-diazenide **1** with sodium dimethyl dithiocarbamate and sodium methyl phenyl



Scheme 2 The reaction of perrhenate with 2-hydrazinopyrdine dihydrochloride and triphenylphosphine.

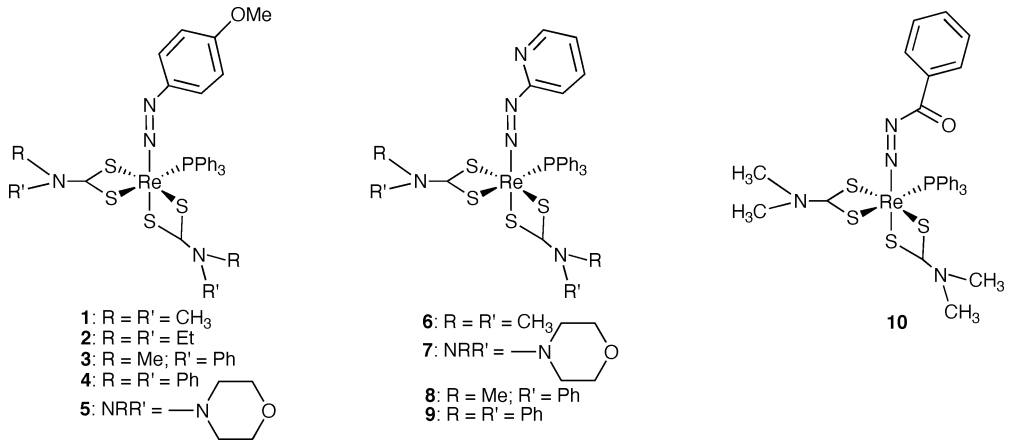


Fig. 1 Rhenium diazenide ternary complexes with dithiocarbamate ligands, complexes **1–10**.

dithiocarbamate (Table 1). Representations of the structures are shown in Fig. 2.

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The site *trans* to the diazenide ligand is occupied by a sulfur atom from one of the dithiocarbamate ligands, with the single phosphine ligand occupying one of the sites *cis* to the diazenide ligand. The Re–N–N system is essentially linear (Re1–N1–N2 = 176.6(3)°) and the Re–N1 and N1–N2 bond distances are characteristically short, consistent with the monodentate diazenide ligand acting as a "type A" monoanionic 3 electron donor.[21] Further evidence of the rhenium–nitrogen multiple bonding is provided by the *trans*-lengthening effect of the $-NNC_6H_4$-4-OCH_3 group; the Re–S bond *trans* to the diazenide is at least 0.051 Å longer than the other Re–S bond lengths. The structures are similar with the rhenium in a distorted octahedral environment and the two dithiocarbamate ligands acting as bidentate ligands, which are disposed *cis* to each other. The mono-diazenide complex derived from 2-hydrazinopyridine (**B**) and $[ReCl_2(\eta^2\text{-}NNCOPh)(PPh_3)_2]$ undergo similar substitutions with sodium salts of dithiocarbamate ligands to give compounds **6–10** (Fig. 1). Representations of the X-ray crystal structures of $[Re(NNPy)(Me_2dtc)_2(PPh_3)]$ (**6**), $[Re(NNPy)(Morphdtc)_2(PPh_3)]$ (**7**) and $[Re(NNCOPh)(Me_2dtc)_2(PPh_3)]$ (**10**) are shown in Fig. 3. A comparison of critical bond lengths and angles relating to the diazenido ligand is shown in Table 2.

Solution NMR

All of the rhenium(III) (d^4) complexes mentioned here are diamagnetic and as such give informative ^1H, ^{31}P and ^{13}C NMR spectra at room temperature in $CDCl_3$ solution, which have been assigned by use of COSY, TOCSY, HMQC, HMBC and DEPT-135 sequences as appropriate.

For $[Re(NNC_6H_4OMe)(Me_2dtc)_2(PPh_3)]$, the ^1H NMR spectrum shows a clear AA′BB′ roofed pair of doublets at 6.80 and 6.69 ppm and a singlet at 3.73 ppm corresponding to the *para*-disubstituted phenyl protons and the methoxy protons of the diazenide ligand respectively. In the ^{13}C spectrum, the two protonated phenyl carbons, with signals at 120.79 and 113.82 ppm, are shown by a HMBC correlation experiment to be linked to signals at 156.17 and 128.51 ppm (quaternary carbons) and the methoxy resonance at 55.5 ppm (Fig. 4).

Identification of the carbon *ortho* to the methoxy-substituted site on the phenyl ring allows the proton doublets to be identified unequivocally, with the proton *ortho* to the methoxy group at 6.69 ppm (consistent with its electron-donating substituent) and

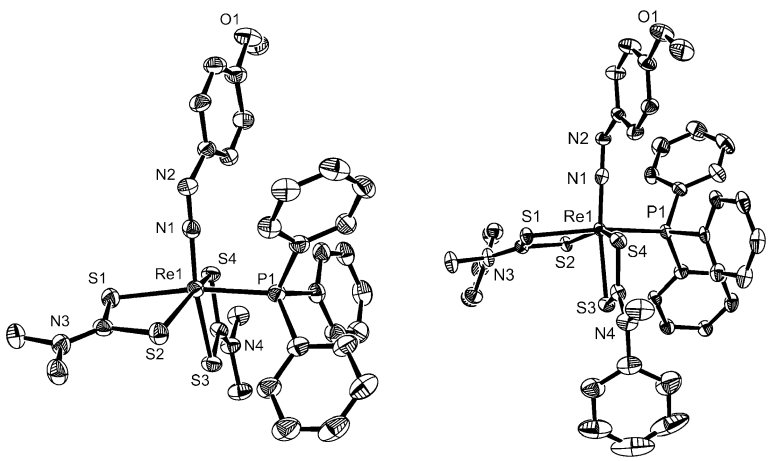

Fig. 2 ORTEP[20] representations of **1** (left) and **3** (right), showing thermal ellipsoids at the 50% probability level.

Table 1 Crystallographic details

Compound	**1** + $x(CH_2Cl_2)$ + 0.5(1 − x)($C_4H_{10}O$) ($x \sim 0.5$)	**3**·$2CHCl_3$	**6**·$2CH_3OH$	**7**·CH_2Cl_2	**10**	[$ReCl_2(\eta^2$-NNPy)(PPh_3)$_2$]·DMF
Empirical formula	$C_{31}H_{34}N_4OPReS_4$ + $x(CH_2Cl_2)$ + 0.5(1 − x)($C_4H_{10}O$) ($x \sim 0.5$)	$C_{35}H_{40}Cl_6N_4OPReS_4$	$C_{30}H_{35}N_5OPReS_4$	$C_{34}H_{37}Cl_2N_5O_2PReS_4$	$C_{31}H_{32}N_4OPReS_4$	$C_{44}H_{41}Cl_2N_4OP_2Re$
M	808.09 + x86.93 + 0.5(1 − x)74.12	1186.95	827.06	964.02	822.06	960.89
T/K	150	150	150	150	150	150
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic	Orthorhombic	Monoclinic
Space group	$C2/c$	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P\,c\,a\,2_1$	$P\,2_1/n$
a/Å	33.1722(4)	13.7100(2)	12.0739(2)	11.4395(3)	16.1725(4)	16.7286(2)
b/Å	11.2208(2)	17.5722(2)	11.4142(2)	12.0609(3)	10.5970(3)	9.6479(2)
c/Å	25.2507(3)	20.1587(3)	25.3935(4)	14.2850(4)	18.8348(5)	24.8790(3)
α/°	90	90	90	78.9889(10)	90	90
β/°	129.7968(6)	93.2214(8)	99.3207(7)	99.3207(7)	90	93.6530(4)
γ/°	90	90	90	86.1885(13)	90	90
V/Å^3	7221.3	4848.9	3453.4	1869.3	3227.91(15)	4007.2
Z	8	4	4	2	4	4
ρ_{calcd}/Mg m^{-3}	1.628	1.626	1.591	1.713	1.691	1.593
μ/mm^{-1}	3.748	3.080	3.838	3.699	4.105	3.286
F(000)	3524.931	2359.180	1643.969	958.528	1632	1915.654
Measured reflns	39920	47019	44526	27572	19830	57704
Unique reflns	8601 [R_{int} = 0.052]	11343 [R_{int} = 0.059]	8255 [R_{int} = 0.069]	8511 [R_{int} = 0.075]	7006 [R_{int} = 0.070]	9635 [R_{int} = 0.050]
Final R indices ($I > 3\sigma(I)$)	R = 0.0337 wR = 0.0418	R = 0.0338 wR = 0.0385	R = 0.0347 wR = 0.0403	R = 0.0365 wR = 0.0382	R = 0.0353 wR = 0.0399	R = 0.0278 wR = 0.0311
Flack Parameter	—	—	—	—	0.346(10)	—

the *meta* at 6.80 ppm. Four singlets corresponding to the four methyl groups on the two dithiocarbamate ligands (A and B) are present at 3.33 (A), 3.27 (A), 3.00 (B), 2.91 ppm (B): for each pair of methyl signals, the related methyl carbons and the quaternary CS_2 carbon for each ligand at 38.35, 39.43, and 225.11 ppm (A) and 38.07, 38.60 and 205.17 ppm (B). The consistent downfield shift for ligand A suggests that this group of resonances may be due to a less shielded site which could be caused by the *trans* effect of the diazenide ligand and so this dithiocarbamate ligand is tentatively assigned as having sulfur donor-atoms in the sites *cis* and *trans* to the diazenide nitrogen. The PPh_3 ligand shows multiplets in the proton NMR at 7.52–7.40 ppm (*ortho*) and at 7.28–7.20 ppm (*meta* and *para*), and singlets in the carbon spectrum at 135.71, 134.07, 129.08 and 127.41 ppm (quaternary, *ortho*, *para* and *meta* respectively), with a singlet in ^{31}P NMR at 14.33 ppm.

The related pyridyl-diazenido compound [Re(NNPy)-(Me_2dtc)$_2$(PPh_3)] has many similarities in its NMR behaviour. The most prominent difference is the resonances due to the pyridyl ring in the ^{1}H spectrum. These were assigned on the basis of their coupling constants by looking at the large 7.0 and 8.0 Hz values characteristic of coupling between the site *para* to the pyridyl nitrogen and one next to it in a substituted pyridine aromatic system.[22] This placed the resonance at 6.81 ppm *ortho* to the diazenide, the carbon *para* to the pyridyl nitrogen (with couplings at both 7.0 and 8.0 Hz) at 7.33 ppm, the one *meta* to the pyridyl N at 6.64 ppm and the last signal *ortho* to the pyridyl N at 8.19 ppm, with a coupling of 5.0 Hz to its *meta* neighbour also typical of such an interaction in a substituted pyridyl ring.

Signals from the triphenylphosphine ligand are shifted downfield (*meta*; 7.54–7.49 ppm ^{1}H) and upfield (*ortho* and *para*; 7.26–7.19 ppm ^{1}H), suggesting a subtle difference in the electronic nature of the complex as a whole, with the *para*-substituted phenyl-diazenido ligand relatively more electron-donating than the pyridyl-diazenido ligand. The ^{31}P singlet is shifted downfield to 14.61 ppm. This effect is also seen in the dithiocarbamate resonances: for the methyl signals for the *cis*, *trans*-ligand A, one signal is almost unchanged at 3.32 ppm (a difference of 0.01 ppm), but the other is moved upfield to 3.27 ppm, a difference of 0.1 ppm. For the symmetrically bound *cis*, *cis*-ligand B both methyl signals are shifted upfield by a similar amount to 2.94 and 2.83 ppm (differences of 0.06 and 0.08 ppm, respectively).

Certain features are common to many of these compounds: phosphorus–carbon coupling causes the signals due to PPh_3 to appear as doublets in ^{13}C NMR, with an increase in the coupling constant on coordination for the quaternary carbon (typically 47 Hz (*c.f.* 20 Hz in free PPh_3). This is presumed to be due to the back-bonding of the phosphine ligand, which reduces shielding on the quaternary carbon. Anomalously, no P–C coupling is observed for [Re(NNAr)(Me_2dtc)$_2$(PPh_3)] (although it is observed for [Re(NNPy)(Me_2dtc)$_2$(PPh_3)]), suggesting that this may be due to a coincidentally negative or zero value coupling constant. ^{31}P NMR shows a singlet at 14.3–16.7 ppm (phenyldiazenido compounds with the anomalous exception of **2**, δ_P −5.17 ppm), 14.2–15.6 ppm (pyridyldiazenido compounds) or 14.2 ppm (benzoyldiazenido compound **10**), although on close inspection a slight "double" nature to this peak can be observed for compounds **2–5** and **6–9** due to the fluxional nature of these structures in solution. The solution fluxionality was resolved for **1**, for which the ^{1}H NMR spectrum of this complex in

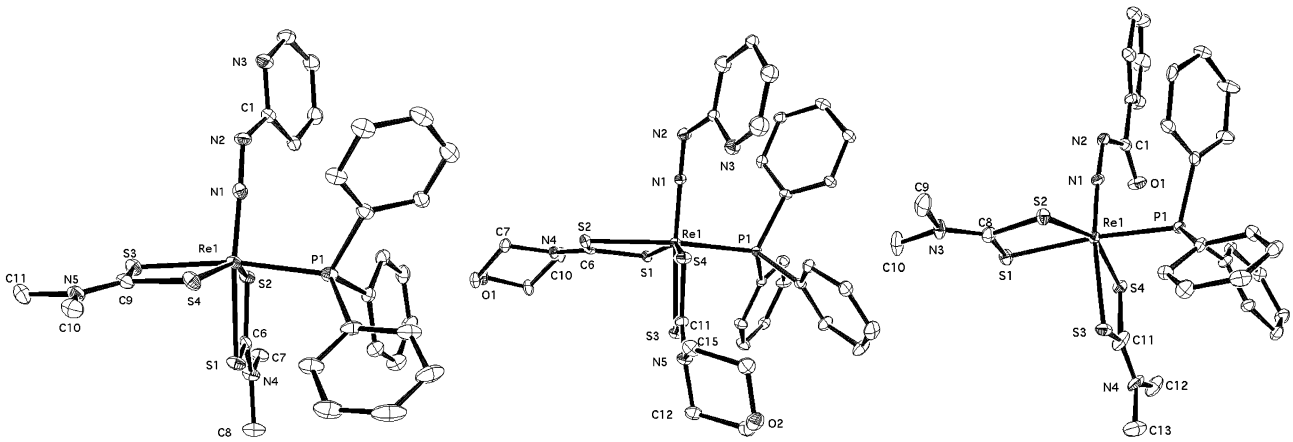

Fig. 3 ORTEP representations of **6** (left), **7** (centre) and **10** (right). Thermal ellipsoids are at the 20% probability level.

Table 2 Selected lengths and angles for the new rhenium diazenido complexes

Complex	M–N/Å	N–N/Å	Re–N–N/°
Category A linear, uninegative, 3e donor	*1.7–1.8*	*1.2–1.3*	*161–173*
[Re(NNC$_6$H$_4$OMe)(Me$_2$dtc)$_2$(PPh$_3$)] (**1**)	1.773(3)	1.248(5)	176.6(3)
[Re(NNC$_6$H$_4$OMe)(PhMedtc)$_2$(PPh$_3$)] (**3**)	1.762(4)	1.261(5)	177.6(3)
[Re(NNPy)(Me$_2$dtc)$_2$(PPh$_3$)] (**6**)	1.747(5)	1.277(7)	176.6(4)
[Re(NNPy)(Morphdtc)$_2$(PPh$_3$)] (**7**)	1.753(5)	1.244(7)	178.7(4)
[Re(NNCOPh)(Me$_2$dtc)$_2$(PPh$_3$)] (**10**)	1.734(7)	1.279(9)	175.7(6)

Entries in italics relate to the categories of hydrazine-derived ligands proposed by Hirsch-Kuchma *et al.*[21]

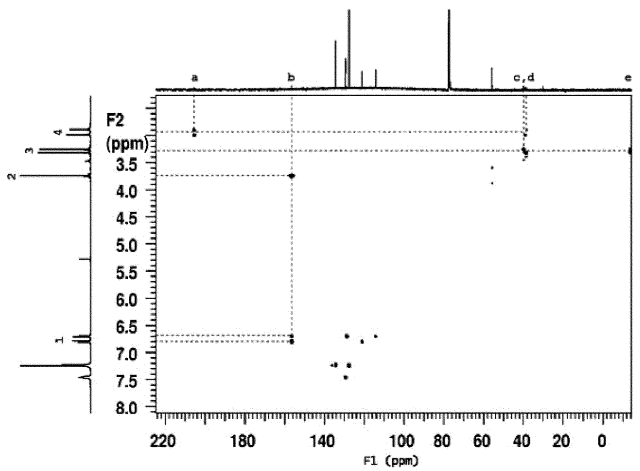

Fig. 4 ^{1}H–^{13}C HMBC spectrum of **1** showing long-range coupling between (1) NNAr aromatic protons, (2) OCH$_3$, (3) dtc A CH$_3$ and (4) dtc B CH$_3$ and (a) dtc B CS$_2$, (b) NNAr *ipso* carbon, (c) and (d) dtc A and B methyl carbon atoms and (e) dtc A CS$_2$ (folded†).

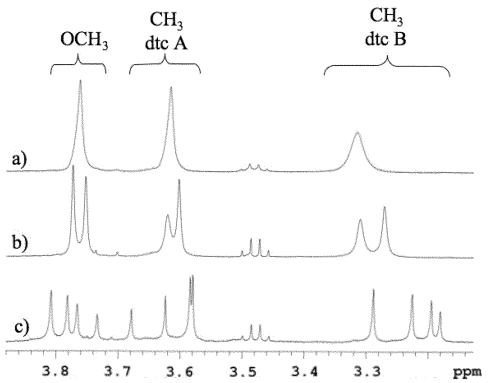

Fig. 5 ^{1}H NMR spectra for **3**, showing methyl protons at (a) 323 K, (b) ambient temperature and (c) 213 K.

CDCl$_3$ at room temperature shows broadened signals for methyl and aromatic protons. Variable temperature NMR studies were undertaken to show that the six broad methyl signals (*i.e.* four due to dimethyldithiocarbamate ligands and two due to the methoxy substituent on the aryldiazenido ligand) observed at ambient temperature (approximately 293 K) coalesce into three signals at 323 K and are resolved into 12 sharp singlets at 213 K (Fig. 5).

Unfortunately the aromatic protons are not completely resolved at 213 K and the freezing point of the solvent prohibits further investigation, but the aromatic region is nevertheless greatly simplified. This behaviour is consistent with a mechanism of C–N bond rotation,[23–28] with the steric bulk of the phosphine ligand and the phenyl N-substituent forming a kinetic barrier to free rotation of the C–N bond of the *cis*, *trans*-dithiocarbamate ligand. However, a mechanism involving change to a monodentate coordination mode and then return to a bidentate mode cannot be ruled out. Variable temperature studies did not improve the spectra for compounds with symmetrical dithiocarbamate ligands relative to those at room temperature.

Cyclic voltammetry

An initial study of the electrochemistry of **1**, **6** and **10** was carried out using cyclic voltammetry to establish the location of key redox processes. Representative voltammograms for the three complexes

Table 3 Electrochemistry of mono-diazenido complexes

Complex	$E_{1/2}$/V	i_{Pa}/i_{Pc}	Peak separation/mV[a]
$[Re(NNC_6H_4OMe)(Me_2dtc)_2(PPh_3)]$ (**1**)	−0.13	0.69	98
$[Re(NNPy)(Me_2dtc)_2(PPh_3)]$ (**6**)	−0.12	0.94	100
$[Re(NNCOPh)(Me_2dtc)_2(PPh_3)]$ (**10**)	+0.08	0.59	83

[a] Under the same conditions, the ferrocene/ferrocenium couple has a peak separation of 100 mV.

with a scan rate of 100 mV s^{-1} are shown in Fig. 6. All three complexes show *quasi*-reversible processes in the range −0.13 to + 0.08 V *versus* the standard calomel electrode, which is interesting as the $[ReCl_2(NNC_6H_4OMe)(NCMe)(PPh_3)_2]$ starting material shows a fully reversible process at 0.56 V; for its *p*-chlorophenyl analogue this occurs at 0.60 V.[16] The shift in the redox process to a more accessible potential, which is tentatively assigned as a Re^{3+}/Re^{4+} couple, indicates that the dithiocarbamate ligands may act to stabilise the rhenium(IV) oxidation state. For the less soluble benzoyldiazenido complex, **10**, the shift of the redox couple to a slightly more positive potential is attributed to the inductive effect of the benzoyl group in comparison to the aromatic substituents of **1** and **6** (Table 3).

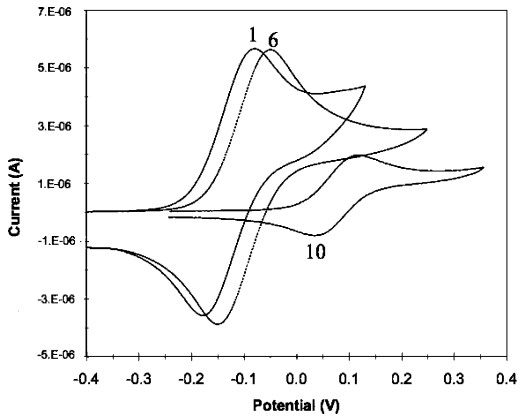

Fig. 6 Cyclic voltammograms of **1**, **6** and **10** in DMF (scan rate 100 mV s^{-1}).

Conclusions

One of the overarching themes of the present work is to add to the present body of knowledge about rhenium and its reactions with organohydrazines. This is of interest not only from the standpoint of developing aryldiazenido-linkers for rhenium radiopharmaceuticals, but also for comparison with the known behaviour of the HYNIC linker system with technetium and the apparent failure of the same technology with rhenium. This could be due to the more extreme conditions needed to overcome the kinetic inertia of rhenium relative to technetium, which could in some way prove damaging to the linker, or it could be that the potentially supportive chelating interaction of the pyridyl nitrogen with the metal ion is more beneficial to technetium than it is to rhenium. In this context it is interesting that all of the new rhenium-diazenido complexes prepared are "linear" (type A)[21] (including those pyridyl- and benzoyldiazenido ligands which could potentially adopt a chelating mode) and that there are no known rhenium or technetium complexes exhibiting a "bent" (type B) diazenido ligand (such that the chelating diazenido ligands have been taken as an approximation of their likely structural properties). Møller and Jørgensen have shown that for the "linear" diazenido complex $[ReCl_2(NNPh)(PPhMe_2)_3]$, the third HOMO includes the π-bond between the diazenido ligand and the $[ReCl_2(PPhMe_2)_3]^+$ fragment and the N_β lone pair, while the antibonding orbital is the LUMO.[29] This is in sharp contrast to the "bent" diazenido complex $[RhCl(NNPh)(PPh_3)_3]^+$ (for which the π* orbital is the HOMO) and similar frontier orbitals are found for rhenium complexes with other types of bent organohydrazine-derived ligands.[21] It is tempting to infer from this that the diazenido complexes for which the Re–N–N bond angle most closely approaches 180° are those which could be most stable and, if this is so, the new family of dithiocarbamate complexes, for which Re–N–N is 175.7–178.7°, is of considerable interest. However it has been found that there is very little change in M–N bond overlap population with M–N–N bond angle over the range of interest.[29] It must be remembered that it is simplistic to assume bond lengths and angles correlate with bond strengths and complex stability and that they may be influenced by extraneous factors such as crystal packing.

We have shown that the parent $[ReCl_2(MeCN)(NNAr)(PPh_3)_2]$ complexes, readily available from perrhenate, can be derivatised with dithiocarbamate ligands in a straightforward manner to give complexes of the type $[Re(NNAr)(dtc)_2(PPh_3)]$. The use of dithiocarbamate as a co-ligand avoids the isomeric complexity of tricine systems that have been investigated in the past. In addition, dithiocarbamate ligands can be prepared with a range of substituents which might allow some control of biodistribution. A recent report demonstrated that the $[ReCl_2(MeCN)(NNAr)(PPh_3)_2]$ can also be derivatised with a crown ether-containing dithiocarbamate ligand and a PNP-type bisphosphine (PNP) to give complexes of the type $[Re(NNAr)(dtc)(PNP)]^+$.[30] These examples demonstrate the potential of arylhydrazine bifunctional chelates for use in rhenium radiopharmaceutical preparations.

Experimental

Syntheses were carried out under a nitrogen atmosphere using standard Schlenk techniques except where otherwise stated. When working under nitrogen, methanol was dried with magnesium turnings and a catalytic amount of iodine under a nitrogen atmosphere and distilled before use. Other solvents, in particular acetonitrile, were used as received and degassed before use. Cyclic voltammetry measurements were carried out in degassed DMF dried over 3 Å molecular sieves.

$[ReCl_2(NNC_6H_4OMe)(NCMe)(PPh_3)_2]$ (**A**) was made according to the published procedure.[16] Unless otherwise specified, other

reagents were purchased from standard commercial suppliers and were used as received. NMR samples were run on either a Varian Mercury 300 (^{1}H: 300.0 MHz, ^{31}P: 121.5 MHz, ^{13}C: 75.5 MHz) or a Varian Unity*plus* (^{1}H: 500.0 MHz, ^{31}P: 202.5 MHz, ^{13}C: 126.0 MHz. NMR data was processed with Varian Solaris software on Sun Microsystems workstations. All NMR spectra were recorded at room temperature unless otherwise stated. ^{31}P NMR was referenced externally with H_3PO_4 taken as 0.0 ppm, and for ^{1}H and ^{13}C NMR residual solvent peaks were used as an internal reference (relative to tetramethylsilane). All ^{13}C and ^{31}P NMR peaks are singlets unless otherwise specified. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer controlled by a personal computer running Grams Analyst software in Microsoft Windows. Samples were prepared as KBr discs. Data was subsequently processed with Perkin–Elmer Spectrum for Windows software. Elemental analyses were performed by the in-house elemental analysis service at the Inorganic Chemistry Laboratory, University of Oxford, on a Elementar Analysensysteme GmbH vario EL machine by oxidative combustion (C, H, N, S, Cl) or with ICP-OES (Na) on a Thermo Jarrell Ash Atom Scan 16. ES-MS samples were run on a Micromass LCT ToF mass spectrometer and samples for positive ion mode were treated with formic acid to encourage ionisation.

X-Ray crystal structures were determined on an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated Mo Kα radiation, $\lambda = 0.71073$ Å) and processed using the DENZO-SMN package,[31] the direct-methods program SIR92[32] and the CRYSTALS program suite.[33]

Cyclic voltammetry experiments were carried out using a BAS Electrochemical Analysis System equipped with BAS Epsilon software (v.1.40.67NT). Sample solutions for cyclic voltammetry were prepared by dissolving a crystalline sample of each complex in degassed, dry DMF, using $[NH_4][BF_4]$ at 0.02 mol dm^{-3} as a supporting electrolyte and the ferrocene/ferrocenium redox couple as an internal reference (+ 0.53 V *vs.* SCE). Data were collected at room temperature using a platinum working electrode and an Ag/Ag$^+$ reference electrode.

Preparation of a family of compounds of the type [Re(NNC$_6$H$_4$OMe)(RR′dtc)$_2$(PPh$_3$)]

[Re(NN(C$_6$H$_4$OMe)(Me$_2$dtc)$_2$(PPh$_3$)] (1). Sodium dimethyldithiocarbamate hydrate (0.09 g, ≤0.63 mmol) was dissolved in MeOH (10 ml) and heated at reflux temperature with [Re(NNC$_6$H$_4$OMe)Cl$_2$(NCMe)(PPh$_3$)$_2$] (0.10 g, 0.11 mmol) for 12 h, then allowed to cool. The brown solid formed was collected by filtration and rinsed with MeOH. Yield 74% (0.07 g, 0.08 mmol). Brown crystals of [Re(NNC$_6$H$_4$OMe)(Me$_2$dtc)$_2$(PPh$_3$)] were grown by diffusion of Et$_2$O into a CH$_2$Cl$_2$ solution. (Found: C, 42.32; N, 6.16; H, 3.76%. $C_{31}H_{34}N_4OPReS_4{\cdot}CH_2Cl_2$ requires C, 42.28; N, 6.16; H, 3.99%); ν_{max}/cm^{-1} (CN) 1557, (N=N) 1493, (PPh) 1433, (COMe) 1245, (*para*-disubst. ring) 824, (mono-subst. Ph) 742 and 693; δ_H ($CDCl_3$) 7.52–7.40 (6H, m, PPh$_3$ *ortho*), 7.28–7.20 (9H, m, PPh$_3$ *meta* and *para*), 6.80 (2H, d, $J_{HH} = 9.0$ Hz, AA′ part of an AA′BB′ spin system, *para*-disubst. Ar–H), 6.69 (2H, d, $J_{HH} = 9.0$ Hz, BB′ part of an AA′BB′ spin system, *para*-disubst. Ar–H), 3.73 (3H, s, OMe), 3.33 (3H, s, Me, dtcA), 3.27 (3H, s, Me, dtcA), 3.00 (3H, s, Me, dtcB), 2.91 (3H, s, Me, dtcB); δ_P($CDCl_3$) 14.33 (s); δ_C($CDCl_3$) 225.1 (CS$_2$, dtcA), 205.2 (CS$_2$, dtcB), 156.2 (Ar–H, *ipso*, NNAr, *ipso* to methoxy), 135.7 (PPh, *ipso*), 134.1 (PPh, *ortho*), 129.1 (PPh, *para*), 128.5 (Ar–H, *ipso*, NNAr, *ipso* to diazenide), 127.4 (PPh, *meta*), 120.8 (NNAr), 113.8 (NNAr), 55.5 (OMe), 39.4 (Me, dtcA), 38.6 (Me, dtcB), 38.4 (Me, dtcA), 38.1 (Me, dtcB); $m/z = 824.9$ (100%) = [M + H$^+$], 603.7 (5%) = [M–PPh$_3$ + K$^+$], 562.6 (70%) = [M–PPh$_3$ + H$^+$]. $E_{1/2} = -0.13$ V, $i_{Pa}/i_{Pc} = 0.69$, peak separation = 98 mV.

[Re(NN(C$_6$H$_4$OMe)(Et$_2$dtc)$_2$(PPh$_3$)] (2). This compound was synthesised following the method used for **1**, with reaction solution evaporated to dryness. Yield (crude solid) 44% (0.04 g, 0.05 mmol). Brown needle-like crystals suitable for elemental analysis were grown by layering CH_2Cl_2 with pentane. (Found C, 46.25; N, 6.14; H, 4.99%. $C_{33}H_{42}N_4OPReS_4$ requires C, 46.25; N, 6.54; H, 4.94%); ν_{max}/cm^{-1} = (CN) 1558, (N=N) 1493, (COMe)124, (Ar, *para*-disubst.) 830, (mono-subst. Ph) 746 and 695; δ_H ($CDCl_3$) 7.49–7.44 (6H, m, PPh$_3$ *ortho*), 7.32–7.17 (9H, m, PPh$_3$ *meta* and *para*), 6.86 (2H, d, $J_{HH} = 9.0$ Hz, AA′ part of an AA′BB′ spin system, *para*-disubst. ring, NNAr), 6.63 (2H, d, $J_{HH} = 9.0$ Hz, BB′ part of an AA′BB′ spin system, *para*-disubst. ring, NNAr), 3.73 (3H, s, o/l, OMe), 3.94–3.08 (8H, m, broad, o/l, CH$_2$, dtc), 1.41–0.84 (12H, m, CH$_3$, dtc); δ_P ($CDCl_3$) −5.17; δ_C ($CDCl_3$) 161.6 (NNAr, *ipso*), 134.6–134.3 (m, PPh$_3$), 134.1–133.9 (m), 132.8–132.1 (m, PPh$_3$, *ipso*), 129.7–129.3 (m, Ph), 129.0–128.9 (m), 128.8–128.6 (m), 128.0–127.8 (m, PPh$_3$), 121.1–120.2 (m, NNAr), 114.3–114.1 (m, NNAr), 55.9–55.7 (OMe), 45.3–41.7 (m, CH$_2$), 15.7–12.5 (m, CH$_3$). NB: Despite several attempts and probably due to complex fluxionality in solution, no CS$_2$ peaks could be observed; $m/z =$ 880 (35%) = [M]$^+$, 618 (8%) = [M–PPh$_3$]$^+$.

[Re(NN(C$_6$H$_4$OMe)(PhMedtc)$_2$(PPh$_3$)] (3). This compound was synthesised following the method used for **1**: **3** is a brown solid produced from [ReCl$_2$(NNC$_6$H$_4$OMe)(NCMe)(PPh$_3$)$_2$] (0.10 g, 0.10 mmol) in 34% yield (0.03 g, 0.04 mmol). Brown crystals of [Re(NNC$_6$H$_4$OMe)(PhMedtc)$_2$(PPh$_3$)] were grown by diffusion of pentane into a $CHCl_3$ solution. ν_{max}/cm^{-1} = (CN) 1553.6, (N=N) 1492.2, (PPh) 1435.0, (COMe) 1241.6, (Ar, *para*-disubst.) 828.0, (mono-subst. Ph) 745.6 and 695.4; δ_H ($CDCl_3$, 213 K) 7.50–7.16 (m, PPh$_3$), 7.00–6.97 (d, aromatic), 6.93–6.80 (m, aromatic), 6.77–6.62 (m, NNAr), 3.78, 3.76, 3.74 and 3.71 (all OMe), 3.65, 3.60, 3.56 (o/l) and 3.56 (o/l; all CH$_3$, dtc A), 3.26, 3.20, 3.17, 3.16 (all CH$_3$, dtc B). NB: As there are four species present in solution no integrals are quoted. Also, at 213 K the CH$_3$ signals are completely resolved but the aromatic signals are not; δ_P ($CDCl_3$, 213 K) 16.76, 16.70, 16.58; δ_P ($CDCl_3$, 293 K) 15.11, 14.93; δ_C ($CDCl_3$, 213 K) ~225.9 (CS$_2$, dtc A), 205.5 (CS$_2$, dtc B), 155.4 (NNAr, *ipso*(OMe)), 155.4–155.3 (m) and 155.3–155.2 (m; both aromatic), 142.2–142.0 (m) and 141.3 (s; both aromatic), 134.6–134.4 (m, aromatic), 134.2–134.0 (m, aromatic), 133.9–133.5 (m, aromatic), 129.5–129.3 (m, aromatic), 129.1–128.9 (m, aromatic), 128.6–128.3 (m, aromatic), 127.7–127.3 (m, aromatic), 126.5–126.4 (m, aromatic), 126.3–126.0 (m, aromatic), 120.4–120.3 (m) and 120.2–120.1 (m; both NNAr), 113.4–113.1 (m, NNAr), 55.3–55.2 (m, OMe), 41.6–41.3 (m, CH$_3$, dtc), 41.0–40.7 (m, CH$_3$, dtc), 40.2–39.9 (m, CH$_3$, dtc) [NB: signals marked ~ are derived from HMBC only]; $m/z =$ 948.3 (100%) = [M + H$^+$], 687.1 (72%) = [M–PPh$_3$ + H$^+$].

[Re(NNC$_6$H$_4$OMe)(Ph$_2$dtc)$_2$(PPh$_3$)] (4). This compound was synthesised following the method used for **1**: the product is a bright

red solid obtained from $[ReCl_2(NNC_6H_4OMe)(NCMe)(PPh_3)_2]$ (0.10 g, 0.10 mmol) in 18% yield (0.02 g, 0.02 mmol). ν_{max}/cm^{-1} = (CN) 1561, (N=N) 1492, (PPh) 1434, (COMe) 1240, (Ar, *para*-disubst.) 827, (mono-subst. Ph) 754 and 692; δ_H ($CDCl_3$) 7.46–7.42 (4.6 H, m, phenyl, dtc), 7.41–7.35 (10H, m, o/l, phenyl dtc and PPh), 7.32–7.19 (16.5 H, m, o/l, phenyl dtc and PPh), 7.02–6.99 (3.9 H, m, phenyl, dtc), 6.79 (2H, dt, J_{HH} = 2.0 and 9.0 Hz, AA′ part of an AA′BB′ spin system, *para*-disubst. ring, NNAr), 6.68 (2H, dt, J_{HH} = 2.0 and 9.0 Hz, BB′ part of an AA′BB′ spin system, *para*-disubst. ring, NNAr), 3.74 (3H, s, OMe); δ_P ($CDCl_3$) 15.53 (s); δ_C ($CDCl_3$) 229.0 (CS_2, dtc), 208.0 (CS_2, dtc), 156.2 (NNAr, *ipso* to OMe), 142.4 (Ph, dtc), 135.8 (d, J_{PC} = 46.0 Hz, PPh, *ipso*), 134.1 (d, J_{PC} = 10.5 Hz, PPh, *ortho*), 129.8 (Ph, dtc), 129.4 (Ph, dtc), 129.1 (PPh, *para*), 128.7 (NNAr, *ipso* to NN), 128.5 (Ph, dtc), 128.4 (Ph, dtc), 128.0 (Ph, dtc), 127.8 (d, J_{PC} = 29.5 Hz, PPh, *meta*), 127.6 (Ph, dtc), 127.4 (Ph, dtc), 126.9 (Ph, dtc), 121.0 (NNAr, *ortho* to OMe), 113.8 (NNAr, *ortho* to NN), 55.5 (OMe); m/z = 1071.81 (60%) = $[M]^+$.

$[Re(NN(C_6H_4OMe)(Morphdtc)_2(PPh_3)]$ (5). This compound was synthesised following the method used for **1**: product is a brown solid formed from $[ReCl_2(NNC_6H_4OMe)(NCMe)(PPh_3)_2]$ (0.10 g, 0.10 mmol) in 73% yield (0.07 g, 0.08 mmol). Crystals of **6** suitable for elemental analysis were obtained by layering a solution of the complex in CH_2Cl_2 with Et_2O. (Found C, 45.81; N, 6.13; H, 4.04%. $C_{35}H_{38}N_4O_3PReS_4$ requires C, 46.25; N 6.17; H, 4.22%); ν_{max}/cm^{-1} = (CN) 1559, (N=N) 1492, (C–O–C) 1235, (Ar, *para*-disubst.) 830, (mono-subst. Ph) 746 and 695; δ_H ($CDCl_3$) 7.46–7.37 (6H, m, PPh_3 *ortho*), 7.27–7.21 (9H, m, PPh_3 *meta* and *para*), 6.80 (2H, d, J_{HH} = 9.0 Hz, AA′ part of an AA′BB′ spin system, NNAr), 6.71 (2H, d, J_{HH} = 9.0 Hz, BB′ part of an AA′BB′ spin system, NNAr), 4.15–4.02 (2H, m, CH_2, dtc), 3.89–3.69 (2.1H, m, o/l, CH_2, dtc), 3.75 (5.9H, s, o/l, OMe), 3.69–3.23 (8H, m, br, CH_2, dtc); δ_P ($CDCl_3$) 15.10 (s); δ_C ($CDCl_3$) 226.0 (CS_2, dtc), 204.9 (CS_2, dtc), 156.4 (NNAr, *ipso* to OMe), 135.4 (d, J_{PC} = 46.5 Hz, PPh_3, ipso), 134.0 (d, J_{PC} = 7.0 Hz, PPh_3, *ortho*), 129.2 (PPh_3, *para*), 128.4 (NNAr, *ipso* to diazenide), 127.6 (d, J_{PC} = 6.5 Hz, PPh_3, *meta*), 120.9 (NNAr), 113.8 (NNAr), 66.0 (CH_2O, dtc), 65.7 (CH_2O, dtc), 55.5 (OMe), 47.4 (CH_2N, dtc), 46.0 (CH_2N, dtc), 45.7 (CH_2N, dtc), 45.1 (CH_2N, dtc); m/z = 908 (100%) = $[M]^+$;

Reaction of pyridylhydrazine dihydrochloride with perrhenate and triphenylphosphine (preparation of B).

Method 1. $[nBu_4N][ReO_4]$ (0.46 g, 0.93 mmol) was dissolved in acetonitrile (15 ml, degasssed) and heated at reflux temperature for 30 min with pyridylhydrazine dihydrochloride (0.71 g, 3.90 mmol) and conc. HCl (0.3 ml, approx. 32%). The red-brown reaction mixture was cooled to room temperature and filtered to remove a fawn solid, presumed to be excess ligand. The filtrate was transferred to another flask containing PPh_3 (1.04 g, 3.97 mmol). After heating at reflux for 2 h, the reaction mixture was allowed to cool. The orange precipitate formed was recovered by filtration and washed with iPrOH (2 × 5 ml) and pentane (2 × 5 ml). 0.45 g of the mixed $[ReNCl_3(PPh_3)_2]$ and $[ReCl_2(NNPy)(PPh_3)_2]$ (**B**) was recovered. Orange crystals were obtained by slow evaporation of a CH_2Cl_2 solution. The crystal structure was found to be $[ReNCl_2(PPh_3)_2]$ (identical to that published by Doedens and Ibers).[19] δ_P (DMSO-d_6) 26.64 ($[ReNCl_3(PPh_3)_2]$), −6.85 ($[ReCl_2(NNPy)(PPh_3)_2]$).

Method 2. $[nBu_4N][ReO_4]$ (0.92 g, 1.87 mmol) was dissolved in acetonitrile (15 ml, degassed) and heated at reflux for 30 min with pyridylhydrazine dihydrochloride (1.38 g, 7.58 mmol). The reaction mixture was cooled to room temperature and filtered to remove dark brown $[ReCl_3(NNPy)(HNNPy)]$, which was rinsed with MeOH and dried. The filtrate was transferred to another flask containing PPh_3 (2.07 g, 7.89 mmol). After heating at reflux for 4 h, the reaction mixture was allowed to cool and the dark red crystalline precipitate formed was recovered by filtration and washed with MeOH and pentane. $[ReCl_3(NNPy)(HNNPy)]$: Yield 12% (0.04 g, 0.07 mmol). $[ReCl_2(NNPy)(PPh_3)_2]$ (**B**): yield 34% (0.27 g, 0.30 mmol). Dark red crystals were grown by layering a frozen solution of the complex in DMF with CH_2Cl_2 and allowing slow mixing as they warmed to room temperature.

Attempted synthesis of $[ReCl_2(NNPy)(PPh_3)_2]$ from $[ReCl_3(NNPy)(HNNPy)]$

$[ReCl_3(NNPy)(HNNPy)]$ (0.15 g, 0.34 mmol) was heated at reflux temperature in acetonitrile (15 ml, degassed) with PPh_3 (0.6 g, 2.28 mmol) for 4.5 h, which gave a reddish-brown solution and metallic dark brown solid. The solid was recovered by filtration, washed with Et_2O and dried. Yield 82% (0.12 g, 0.28 mmol). ^1H NMR (300 MHz, DMSO-d_6): d 8.79 (1H, d, J_{HH} = 5.5 Hz, pyridyl), 8.43 (1H, d, J_{HH} = 5.5 Hz, pyridyl), 8.29 (1H, t, J_{HH} = 7.5 Hz, pyridyl), 7.99 (1H, t, overlapping, J_{HH} = 5.5 Hz, pyridyl), 7.91 (1H, d, J_{HH} = 8.5 Hz, pyridyl), 7.70 (1H, d, J_{HH} = 8.5 Hz, pyridyl), 7.21 (1H, d, J_{HH} = 6.5 Hz, pyridyl), 6.87 (1H, t, J_{HH} = 6.5 Hz, pyridyl), 6.87 (1H, t, J_{HH} = 6.5 Hz, pyridyl).[9]

Synthesis and characterisation of a family of complexes of formula $[Re(NNPy)(dtc)_2(PPh_3)]$ (6–9)

These reactions were carried out using the same methodology as that used for the synthesis of compounds **1–5**; deviations from this method are specified where appropriate.

$[Re(NNPy)(Me_2dtc)_2(PPh_3)]$ (6).

Method 1. The compound was synthesised from a mixture of $[Re(NNPy)Cl_2(NCMe)(PPh_3)_2]$ and $[ReNCl_3(PPh_3)_2]$ (product of $[nBu_4N][ReO_4]$ and pyridylhydrazine dihydrochloride with additional HCl, see above, total mass 0.71 g). The product was formed as dark brown crystals in a suspension of orange solid (thought to be unreacted $[ReNCl_2(PPh_3)_2]$ impurity), which was pipetted off with the solvent. Crystals suitable for X-ray structural determination and elemental analysis were obtained by recrystallisation from a minimum amount of boiling methanol. NMR and ES-MS were also carried out on this sample.

Method 2. The compound was synthesised from pure dark red $[Re(NNPy)Cl_2(PPh_3)_2]$. The product was obtained as a brown amorphous precipitate and its identity confirmed with ES-MS and NMR. Yield 68% (0.05 g, 0.09 mmol) (Found C, 43.69; N, 8.49; H, 4.26%. $C_{29}H_{31}N_5PReS_4$ requires C, 43.81; N, 8.81; H, 3.93%). ν_{max}/cm^{-1} = (CN and N=N, overlapping) 1529, (2-subst. pyridyl, ring str.) 1452, (PPh) 1434, (2-subst. pyridyl, ring str.) 1416, (NC_2, 2-subst. pyridyl, ring str.) 1145, (pyridyl C–H deformation) 772, (mono-subst. Ph) 745 and 693; δ_H ($CDCl_3$) 8.19 (1H, ddd, J_{HH} = 0.5, 2.0 and 5.0 Hz, pyridyl, *ortho* to pyridyl N), 7.54–7.49 (6H, m, PPh_3, *meta*), 7.33 (1H, ddd, J_{HH} = 2.0, 7.0 and 8.0 Hz, pyridyl, *meta* to NN), 7.26–7.19 (9H, m, PPh_3 *ortho* and *para*), 6.81 (1H, dt, J_{HH} = 1.0 and 8.0 Hz, pyridyl, *ortho* to NN), 6.64 (1H, ddd, J_{HH} = 1.0, 5.0 and 7.0 Hz, pyridyl, *meta* to pyridyl N), 3.32 (3H, s,

Me, dtcA), 3.27 (3H, s, Me, dtcA), 2.94 (3H, s, Me, dtcB), 2.83 (3H, s, Me, dtcB); δ_P ($CDCl_3$) 14.61 (s); δ_C ($CDCl_3$) 225.7 (CS_2, dtcA), 205.0 (CS_2, dtcB), 151.6 (pyridyl, *ipso*), 148.4 (pyridyl), 136.5 (pyridyl), 134.7 (d, $J_{PC} = 47.5$ Hz, PPh, *ipso*), 134.3 (d, $J_{PC} = 9.5$ Hz, PPh, *ortho*), 129.2 (d, $J_{PC} = 2.0$ Hz, PPh, *para*), 127.3 (d, $J_{PC} = 10.0$ Hz, PPh, *meta*), 117.6 (pyridyl), 114.8 (pyridyl), 39.6 (Me, dtc), 38.8 (Me, dtc), 38.5 (Me, dtc), 38.1 (Me, dtc); $m/z = 796.2$ (100%) = $[M + H^+]$, 534.1 (95%) = $[M–PPh_3]^+$. $E_{1/2} = -0.12$ V, $i_{Pa}/i_{Pc} = 0.94$, peak separation = 100 mV.

[Re(NNPy)(Morphdtc)$_2$(PPh$_3$)] (7). This compound was synthesised following the method used for **1**, from [$ReCl_2(\eta^2$-NNPy)$(PPh_3)_2$] (0.09 g, 0.10 mmol). Yield 86% (0.07 g, 0.09 mmol). Crystals suitable for elemental analysis and X-ray structural determination were obtained by layering a frozen dichloromethane solution of **7** with methanol and allowing them to mix as they warmed to room temperature. (Found C, 42.39; N, 7.22; H, 3.98%. $C_{33}H_{35}N_5O_2PReS_4.CH_2Cl_2$ requires C, 42.36; N, 7.26; H, 3.87%). ν_{max}/cm^{-1} = (CN) 1516, (N=N) 1493, (2-subst. pyridyl, ring str.) 1455, (PPh) 1432, (2-subst. pyridyl, ring str.) 1412, (NC_2, 2-subst. pyridyl, ring str.) 1147, (pyridyl C–H deformation, weak) 775, (mono-subst. Ph) 747 and 670; δ_H ($CDCl_3$) 8.21 (1H, ddd, $J_{HH} = 1.0$, 2.0 and 5.0 Hz, pyridyl, *ortho* to pyridyl N), 7.54–7.42 (6H, m, PPh_3), 7.32 (1H, ddd, $J_{HH} = 2.0$, 7.0 and 8.0 Hz pyridyl, *meta* to N=N), 7.28–7.20 (9H, m, PPh_3), 6.68 (1H, o/l, dt, $J_{HH} = 1.0$ and 8.0 Hz, pyridyl, *ortho* to N=N, roofing to *meta* to pyridyl N), 6.66 (1H, o/l, ddd, $J_{HH} = 1.0$, 5.0 and 7.0 Hz, pyridyl, *meta* to pyridyl N, roofing to *ortho* to N=N), 4.16–4.05 (2.2H, m, CH_2-fluxional) 3.88–3.69 (6.4H, m, CH_2-fluxional), 3.68–3.43 (4.3H, m, broad, CH_2-fluxional), 3.43–3.30 (2.0H, m, broad, CH_2-fluxional), 3.30–3.17 (1.2H, m, broad, CH_2-fluxional); δ_P ($CDCl_3$) 15.53 (s); δ_C ($CDCl_3$) 225.9 (CS_2, dtcA), 205.1 (CS_2, dtcB), 151.3 (pyridyl, *ipso*), 148.4 (pyridyl, *ortho* to pyridyl N), 136.4 (pyridyl, *meta* to N=N), 134.3 (d, $J_{PC} = 47.5$ Hz, PPh_3, *ipso*), 134.3 (d, $J_{PC} = 10.0$ Hz, PPh_3, *ortho*), 129.3 (d, $J_{PC} = 2.0$ Hz, PPh_3, *para*), 127.5 (d, $J_{PC} = 10.0$ Hz, PPh_3, *meta*), 118.0 (pyridyl, *meta* to pyridyl N), 114.7 (pyridyl, *ortho* to N=N), 66.0 (CH_2, dtc), 65.6 (CH_2, dtc), 47.3 (CH_2, dtc), 46.1 (CH_2, dtc), 45.8 (CH_2, dtc), 45.1 (CH_2, dtc); $m/z = 880$ (55%) = $[M + H]^+$, 618 (8%) = $[M–PPh_3 + H]^+$.

[Re(NNPy)(PhMedtc)$_2$(PPh$_3$)](8). This compound was synthesised following the method used for **1**, using [$ReCl_2(\eta^2$-NNPy)$(PPh_3)_2$] (0.09 g, 0.10 mmol). After refluxing overnight a clear dark red solution was formed, which was evaporated to dryness and extracted with pentane overnight, then filtered off, rinsed with pentane and dried on the frit. This gave a brown solid (mass 0.15 g). δ_H ($CDCl_3$) 8.21–8.14 (1H, m, pyridyl), 7.73–7.68 (1H, m), 7.54–7.48 (4.2H, m, PPh_3), 7.46–7.23 (25.6H, m, o/l solvent, aromatic), 7.21–7.15 (6.2H, m, aromatic), 6.92 (0.8H, d, br, $J = 6.5$ Hz, aromatic), 6.86 (0.8H, d, $J = 6.5$, br, o/l, aromatic), 6.84 (0.8H, d, $J = 8.5$ Hz, o/l, aromatic), 6.76 (0.8H, dd, $J = 8.0$ Hz, aromatic) 6.68 (1.1H, t, $J = 7.5$ Hz, aromatic), 6.66– 6.58 (1.1H, m, aromatic), 3.58 (1.5H, s, o/l, Me), 3.57 (1.5H, s, o/l, Me), 3.24 (1.5H, s, o/l, Me), 3.19 (1.5H, s, o/l, Me) [NB: Based on ^1H NMR integrals for CH_3 peaks, the ratio of rotational isomers at ambient temperature is approx. 1 :1]; δ_P ($CDCl_3$) 15.63 (s) and 15.40 (s) ppm (two rotational isomers); ES-MS (positive ion mode): $m/z = 920.5$ (100%) = $[M + H^+]$, 658.3 (10%) = $[M–PPh_3 + H^+]$.

[Re(NNPy)(Ph$_2$dtc)$_2$(PPh$_3$)] (9). This compound was synthesised following the method used for **1**: the product is a tomato-red solid obtained in 69% yield (0.08 g, 0.07 mmol) from [$ReCl_2(\eta^2$-NNPy)$(PPh_3)_2$] (0.09 g, 0.10 mmol). Crystals suitable for elemental analysis were grown by layering methanol on a dichloromethane solution of the complex. (Found C, 56.13; N, 6.79; H, 3.75%. $C_{49}H_{39}N_5PReS_4$ requires C, 56.41; N, 6.71; H, 3.77%); ν_{max}/cm^{-1} = 1517 (CN), 1490 (N=N), 1450 (2-subst. pyridyl, ring str.), 1434 (PPh, weak), 1416 (2-subst. pyridyl, ring str.), 1142 (NC_2/2-subst. pyridyl, ring str.), 776 (pyridyl C–H deformation), 745, 697 and 691 (Ar, mono-subst.); δ_H ($CDCl_3$) 8.12– 8.10 (1H, m, pyridyl), 7.48–7.43 (12H, m, phenyl), 7.41–7.36 (4.2H, m, phenyl), 7.34–7.20 (approx. 12.9H, m, o/l solvent, pyridyl (1H) and phenyl), 7.00–6.97 (4H, m, phenyl), 6.82–6.79 (1H, m, pyridyl), 6.62–6.59 (1H, m, pyridyl); δ_P ($CDCl_3$) 15.34 (s); δ_C ($CDCl_3$) 229.2 (CS_2), 208.6 (CS_2), 151.4 and 151.4 (o/l, pyridyl), 148.4 (pyridyl), 142.3 (Ph), 142.0 (Ph), 136.5 (pyridyl), 134.8 (d, $J_{PC} = 46.5$ Hz, PPh_3), 134.3–134.2 (m, o/l, phenyl, dtc and PPh_3), 129.3 (d, $J_{PC} = 18.0$ Hz, PPh_3), 129.1 (Ph), 128.1 (Ph), 128.1 (Ph), 127.9 (Ph), 127.8–127.5 (m, o/l, Ph), 127.5 (Ph), 117.7 (pyridyl), 114.8 (pyridyl); $m/z = 1044.6$ (100%) = $[M + H^+]$, 782.5 (1%) = $[M–PPh_3]H^+$.

[Re(η^1-NNCOPh)(Me$_2$dtc)$_2$(PPh$_3$)] (10). This compound was synthesised following the method used for **1**, from [$ReCl_2(\eta^2$-NNCOPh)$(PPh_3)_2$] (0.10 g, 0.10 mmol). Within the first hour of heating at reflux temperature, the reaction mixture changed from a green suspension to a brown one. The dark brown solid formed was recovered by filtration, washed with Et_2O and dried under vacuum. Yield 86% (0.07 g, 0.09 mmol). Crystals suitable for elemental analysis and X-ray structural determination were obtained by diffusion of Et_2O into a CH_2Cl_2 solution of the complex. (Found C, 45.28; N, 6.80; H, 4.03%. $C_{31}H_{32}N_4OPReS_4$ requires C, 45.29; N, 6.82; H, 3.92%); ν_{max}/cm^{-1} = (C=O) 1625, (o/l, incl. CN) 1542–1532, (N=N) 1495, (PPh) 1434, 1234, (monosubst. Ph) 734 and 695; δ_H ($CDCl_3$) 7.75 (2H, d, $J_{HH} = 7.5$ Hz, benzoyl, *ortho*), 7.60–7.52 (6H, m, PPh_3, *ortho*), 7.36 (1H, t, $J_{HH} = 7.5$ Hz, o/l, benzoyl, *para*), 7.34–7.27 (9H, m, o/l, PPh_3, *meta* and *para*), 7.26–7.17 (2H, m, o/l, benzoyl, *meta*), 3.34 (3H, s, methyl, dtc), 3.30 (3H, s, methyl, dtc), 2.89 (3H, s, methyl, dtc), 2.78 (3H, s, methyl, dtc); δ_P ($CDCl_3$) 14.24 (s); δ_C ($CDCl_3$) 205.3 (CS_2), 170.9 (C=O), 135.2 (benzoyl, *ipso*), 134.5 (d, $J_{PC} = 10.0$ Hz, PPh_3, *ortho*), 132.6 (d, $J_{PC} = 48.5$ Hz, PPh_3, *ipso*), 131.1 (benzoyl, *para*), 129.43 (d, $J_{PC} = 2.0$ Hz, PPh_3, *para*), 128.1 (benzoyl, *ortho*), 127.5 (benzoyl, *meta*), 127.4 (d, $J_{PC} = 10.0$ Hz, PPh_3, *meta*), 39.6 (methyl, dtc), 38.9 (methyl, dtc), 38.7 (methyl, dtc), 38.1 (methyl, dtc); $m/z = 823.0856$ (25%) = $[M + H^+]$ ($C_{31}H_{33}N_4OPS_4Re$ requires 823.0833; difference 2.8 ppm). $E_{1/2} = +0.08$ V, $i_{Pa}/i_{Pc} = 0.59$, peak separation = 83 mV.

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References

1 J. R. Dilworth and S. J. Parrott, *Chem. Soc. Rev.*, 1998, **27**, 43.

2 P. J. Blower, J. R. Dilworth, R. I. Maurer, G. D. Mullen, C. A. Reynolds and Y. Zheng, *J. Inorg. Biochem.*, 2001, **85**, 15.
3 W. A. Volkert and T. J. Hoffman, *Chem. Rev.*, 1999, **99**, 2269.
4 L. J. Rader and B. List, *Chem.–Eur. J.*, 2000, **6**, 2091.
5 C. M. Archer, J. R. Dilworth, P. Jobanputra, R. M. Thompson, M. McPartlin and W. Hiller, *J. Chem. Soc., Dalton Trans.*, 1993, 897.
6 J. R. Dilworth, P. Jobanputra, R. M. Thompson, D. C. Povey, C. M. Archer and D. Kelly, *J. Chem. Soc., Dalton Trans.*, 1994, 1251.
7 M. J. Abrams, M. Juweid, C. I. tenKate, D. A. Schwartz, M. M. Hauser, F. E. Gaul, F. A. J., R. H. Rubin, H. W. Strauss and A. J. Fischman, *J. Nucl. Med.*, 1990, **31**, 2022.
8 S. Liu, D. S. Edwards, A. R. Harris, S. J. Heminway and J. A. Barrett, *Inorg. Chem.*, 1998, **38**, 1326.
9 S. Liu and D. S. Edwards, *Chem. Rev.*, 1999, **9**, 2235.
10 S. Liu, D. S. Edwards, A. R. Harris, S. J. Heminway and J. A. Barrett, *Inorg. Chem.*, 1999, **38**, 1326.
11 J.-L. Vanderheyden, K. Verbeke, D. Kieffer, G. Liu, C. J. Dale, C. Liu, R. A. Morgan, D. J. Hnatowich, A. Verbruggen, N. D. Steinmetz and A. M. Green, in *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine 6*, ed. M. Nicolini and U. Mazzi, SGE Ditorali, Padova, 2002, p. 335.
12 T. Nicholson, J. Cook, A. Davison, D. J. Rose, K. P. Maresca, J. Zubieta and A. G. Jones, *Inorg. Chim. Acta*, 1996, **252**, 421.
13 T. Nicholson, J. D. Cook, A. Davison, D. J. Rose, K. P. Maresca, J. Zubieta and A. G. Jones, *Inorg. Chim. Acta*, 1996, **252**, 427.
14 M. Hirsch-Kuchma, T. Nicholson, A. Davison, W. M. Davis and A. G. Jones, *Inorg. Chem.*, 1997, **36**, 3237.
15 D. J. Rose, K. P. Maresca, T. Nicholson, A. Davison, A. G. Jones, J. Babich, A. Fischman, W. Graham, J. R. D. DeBord and J. Zubieta, *Inorg. Chem.*, 1998, **37**, 2701.
16 (*a*) A. R. Cowley, J. R. Dilworth and P. S. Donnelly, *Inorg. Chem.*, 2003, **42**, 929; (*b*) A. R. Cowley, J. R. Dilworth, P. S. Donnelly and S. J. Ross, in *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine 6*, ed. M. Nicolini and U. Mazzi, SGE Ditorali, Padova, 2002, p. 223.
17 A. Boschi, C. Bolzati, E. Benini, E. Malago, L. Uccelli, A. Duatti, A. Piffanelli, F. Refosco and F. Tisato, *Bioconjugate Chem.*, 2001, **12**, 1035.
18 M. Hirsch-Kuchma, T. Nicholson, A. Davison, W. M. Davis and A. G. Jones, *Inorg. Chem.*, 1997, **36**, 3237.
19 R. J. Doedens and J. A. Ibers, *Inorg. Chem.*, 1967, **6**, 204.
20 L. J. J. Farrugia, *Appl. Crystallogr.*, 1997, **30**(5, Part 1), 565.
21 M. Hirsch-Kuchma, T. Nicholson, A. Davison and A. G. Jones, *J. Chem. Soc., Dalton Trans.*, 1997, 3189.
22 E. Pretsch, T. Clerc, J. Seibl and W. Simon, *Tables of Spectral Data for Structure Determination of Organic Compounds*, Springer-Verlag, New York, 1989.
23 R. M. Golding, W. C. Tennant, C. R. Kanekar, R. L. Martin and A. H. White, *J. Chem. Phys.*, 1966, **45**, 2688.
24 R. M. Golding, W. C. Tennant, J. P. M. Bailey and A. Hudson, *J. Chem. Phys.*, 1968, **48**, 764.
25 R. M. Golding, P. Healy, P. Newman, E. Sinn, W. C. Tennant and A. H. White, *J. Chem. Phys.*, 1970, **52**, 3105.
26 R. M. Golding, B. D. Lukeman and E. Sinn, *J. Chem. Phys.*, 1972, **56**, 4147.
27 R. M. Golding, P. C. Healy, P. W. G. Newman, E. Sinn and A. H. White, *Inorg. Chem.*, 1972, **11**, 2435.
28 R. M. Golding, P. C. Healy, P. Colombera, and A. H. White, *Aust. J. Chem.*, 1974, **27**, 2089.
29 E. R. Møller and K. A. Jørgensen, *Acta Chem. Scand.*, 1991, **45**, 68.
30 Y.-S. Kim, Z. He, W.-Y. Hsieh and S. Liu, *Bioconjugate Chem.*, 2006, **17**, 473.
31 Z. Otwinowski and W. Minor, *Methods Enzymol.*, 1997, **276**, 307.
32 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.
33 P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Crystallogr.*, 2003, **36**(6), 1487.

