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Diazenide and hydrazide(2−) derivatives of the $[Re(CO)_3]^+$ core

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Reaction of $[ReBr_3(CO)_3]^{2-}$ with aryldiazonium salts gives the Re(III) diazenide complexes $[ReBr_2(NNC_6H_4R\text{-}4)(CO)_2]^-$. The attachment of a PhNHCS tethering group to pyridyl hydrazine generates a HYNIC related proligand which gives a stable chelated pyridyliumthiocarbazide(2−) derivative of the $[Re(I)(CO)_3]^+$ core.

Certain radioisotopes of rhenium offer potential in the development of targeted radionuclide therapy of cancer. Both rhenium-188 and rhenium-186 are β-emitters with nuclear properties suitable for therapeutic applications.[1–3] The recently developed rhenium-188 generator is clinically convenient and provides an economic source of the radionuclide as a dilute aqueous solution of $[^{188}ReO_4]^-$.[3] For effective treatment, the radionuclide must be selectively delivered to the tumour and this can be achieved by incorporating the radionuclide into a coordination complex using a bifunctional chelate. The chelate should be highly stable and possess a point of further functionalisation to allow the attachment of biologically active molecules that can act as targeting vectors.

The use of functionalised diazenide (NNAr, Ar = aryl or 2-pyridyl) ligands for the targeting of potential radiopharmaceuticals based on technetium[4,5] or rhenium is well established, particularly for the pyridyl (HYNIC) system.[6–10] Although in the latter case there are a number of technetium based systems which are in clinical trials for imaging,[11,12] analogous Re systems are less developed.[13,14]

The $[Tc(CO)_3]^+$ core has been shown to be an extremely versatile precursor for the development of 99m-technetium radiopharmaceuticals, but much less attention has been directed towards the chemistry of the rhenium analogues.[15–18] Despite the wide range of polydentate ligands that have been combined with the $[M(CO)_3]^+$ (M = Tc,Re) cores to provide sites for attachment of appropriate biological targeting agents, the use of diazenide type ligands has not been reported although pyridylhydrazine itself can act as a bidentate ligand.[17]

We here report the use of two different approaches to the introduction of diazenide and related ligands with N–N bonds onto the well established rhenium(I) tricarbonyl core. The first deploys diazonium salts to give the first reported diazenide derivatives of this core. The second uses pyridylhydrazines with pendant soft donors to give dimeric chelated complexes with an unusual zwitterionic bidentate diazene ligand. Both approaches provide the possibility of conjugation to a biological targeting group *via* an amide linkage.

Reaction of $[Et_4N]_2[ReBr_3(CO)_3]$ with diazonium salts $[4\text{-}RC_6H_4N_2][BF_4]$ (R = H, CO_2Et, Cl) in methylene chloride leads to isolation of the complexes $[Et_4N][ReBr_3(NNC_6H_4R\text{-}4)(CO)_2]$ in good yield.† The complex with R = CO_2Et models the way in which a biologically active molecule can in principle be attached to the Re carbonyl core *via* an activated ester. The bromide ligands provide potential sites for introduction of other ligands should manipulation of lipophilicity be required. The diazenides are obtained as pale brown air stable crystalline solids. The formal oxidation state of the rhenium is three but the complexes are diamagnetic showing ^1H NMR resonances for the diazonium aryl protons in the expected region. The IR spectrum for the complex as a nujol mull with R = H shows strong bands due to the C–O stretching vibrations as expected. The ES MS spectra show the mass ions at the expected *m*/*z* value, and the fact that peaks for diazenide species are observed in donor solvents confirms that the diazenide ligand is retained in such solvents. A representation of the crystal and molecular structure of the complex with R = CO_2Et is shown in Fig. 1 together with a summary of selected bond lengths and angles.

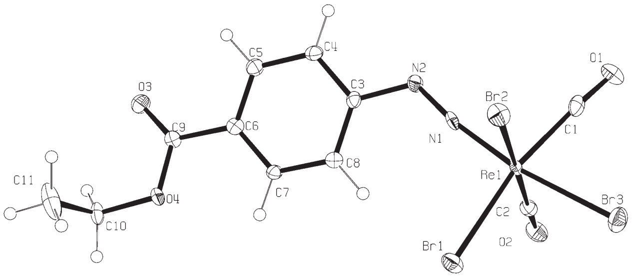

Fig. 1 ORTEP representation of the anion of (**1**) showing the atom labelling scheme. Selected bond lengths (Å) and bond angles (°). Re(1)–Br(1) = 2.5457(7), Re(1)–Br(2) = 2.5991(7), Re(1)–Br(3) = 2.5547(7), Re(1)–C(1) = 1.975(8), Re(1)–C(2) = 1.940(7), Re(1)–N(1) = 1.806(6), N(1)–N(2) = 1.209(8). Br(2)–Re(1)–C(1) = 94.64(19), Br(3)–Re(1)–C(1) = 80.35(19), Br(1)–Re(1)–N(1) = 97.50(17), Re(1)–N(1)–N(2) = 171.3(5), C(2)–Re(1)–N(1) = 96.4(3). Other angles at metal close to 90°.

The geometry about rhenium is essentially octahedral with each of the 2 CO ligands *trans* to bromide. The reaction involves nett oxidative addition of the diazonium salt to the rhenium with elimination of $[Et_4N][BF_4]$. The diazenide ligand is singly bent, consistent with its formally donating three electrons to the metal, and the M–N and N–N distances lie within the range found for other Re(III) diazenides such as $[ReCl_2(NNPh)(MeCN)(PPh_3)_2]$.[19]

Although complexes of the $M(CO)_3^+$ core have been reported with pyridylhydrazine acting as a bidentate ligand,[17] the attachment of one or more soft donor groups could be advantageous in terms of kinetic stability. It would also produce clearly defined complexes and open the possibility of extending the HYNIC methodology to other metals. A number of pyridylhydrazines with tethering groups attached to the NH_2 group of the hydrazine have therefore been prepared, and an example is presented in Fig. 2, together with the abbreviation.

$SHYNICH_3$ rapidly reacts with the carbonyl precursor, $[Et_4N]_2[ReBr_3(CO)_3]$, at room temperature in methanol to give a yellow-green product, **2**, which could be isolated by the addition of water. X-ray quality crystals of **2** were obtained by diffusion of

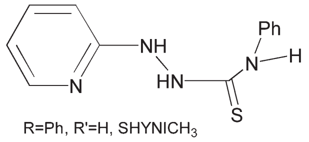

Fig. 2 Structure of a tethered pyridylhydrazine showing abbreviation.

pentane into an acetone solution of the complex. An ORTEP view of the structure of **2** appears in Fig. 3. The structure comprises two pseudooctahedral rhenium carbonyl centres bridged by thione sulfurs. The Re–Re distance of 3.64 Å and the formal valence electron count suggest there is no Re–Re bonding. The bond distances within the doubly deprotonated SHYNICH ligand are consistent with it bearing a dinegative charge. This is partially compensated by the uncoordinated pyridyl nitrogen bearing a proton, with an overall neutral charge on the complex. The delocalized SHYNICH ligand is essentially planar, and this precludes coordination to the three non-carbonyl coordinated facially disposed sites on the $Re(CO)_3$ core. Under the dilute conditions used for radiopharmaceutical synthesis it is likely that a solvated monomeric species will be formed.

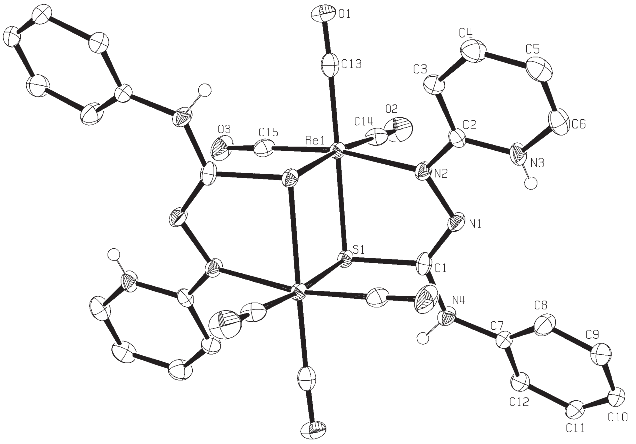

Fig. 3 Structure of complex (**2**) with atom labelling scheme and hydrogen atoms omitted for clarity. Selected bond lengths (Å) and angles (°): Re(1)–S(1) = 2.462(1), Re(1)–S(1)′ = 2.535(1), Re(1)–N(2) = 2.198(3), Re(1)–C(av) = 1.920(5), C(1)–S(1) = 1.790(4), C(1)–N(1) = 1.286(6), N(1)–N(2) =1.424(5). S(1)–Re(1)–S(1)′ = 82.35(1), Re(1)–S(1)–Re(2) = 97.65(4), S(1)–Re(1)–N(2) = 76.6(1), C(13)–Re(1)–C(14) = 91.36(18).

The use of diazonium salts provides access to new anionic diazenide derivatives of the $Re(CO)_3$ core and bifunctionality is available *via* carboxyl substituents on the diazenide aryl group. Pryidylhydrazines with a thioamide tethering group react with the same core to give dimeric thione-bridged complexes with an unusual zwitterionic bidentate bonding mode for the pyridyldiazene ligand. By analogy with the HYNIC system[20,21] it is straightforward to introduce an activated ester group in the pyridyl ring for targeting and this can be done without the use of protecting groups for the hydrazine. This demonstrates that the HYNIC targeting strategy can be adapted to lower oxidation state rhenium cores.

Crystal data for complexes (1) and (2)

For $[Et_4N][ReBr_3(N_2C_6H_4\text{-}4CO_2Et)(CO)_2]$, **1**, $C_{19}H_{29}Br_3N_3O_4Re$, $M = 789.37$, triclinic, $a = 10.3204(3)$, $b = 10.7293(4)$, $c = 11.9771(5)$, $U = 1257.7$ Å^3, $T = 150$ K, space group $P\bar{1}$, $Z = 2$, μ(Mo-Kα) = 9.625 mm^{-1}, 18254 reflections measured, 5492 unique, ($R = 0.0478$). The final wR was 0.0488.

For $[Re_2(C_{12}H_{11}N_4S)_2(CO)_6]\cdot 2CH_3COCH_3$, **2**, $C_{36}H_{34}N_8O_8Re_2S_2$, $M = 1143.24$, triclinic, $a = 10.1017(2)$, $b = 10.1665(2)$, $c = 22.2480(4)$ Å, $U = 1986.27(7)$ Å^3, $T = 150$ K, space group $P\bar{1}$, $Z = 2$, μ(Mo-Kα) = 6.255 mm^{-1}, 27687 reflections measured, 8953 unique ($R_{int} = 0.043$) The final wR was 0.0336. CCDC reference numbers 239543 and 239544. See http://www.rsc.org/suppdata/dt/b4/b407708c/ for crystallographic data in CIF or other electronic format.

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Notes and references

† $[ReBr_3(CO)_3][NEt_4]_2$ (0.05 g, 0.07 mmol) and $[4\text{-}EtCO_2C_6H_4N_2][BF_4]$ (0.02 g, 0.07 mmol) were dissolved CH_2Cl_2 (40 mL). The orange mixture was stirred at reflux under an atmosphere of nitrogen for 4 h. The mixture was allowed to cool to room temperature and the volume was reduced *in vacuo* to about 2 mL. Diethyl ether was added to precipitate $[Et_4N][ReBr_3(N_2C_6H_4\text{-}4CO_2Et)(CO)_2]$ **1** as an orange-brown powder which was collected by filtration and washed with diethyl ether, (0.02 g, 0.02 mmol, 30%). ^{1}H NMR (300 MHz) (d_6-DMSO): δ 8.02, 2H, AA′ BB′ system, ArH; 7.53, 2H, AA′ BB′ system, ArH; 4.29, 2H, q $^3J_{HH} = 7$ Hz, O–CH_2CH$_3$; 3.10, 8H, q, $^3J_{HH} = 7$ Hz, $[N(CH_2CH_3)_4]^+$; 1.29, 3H, t, $^3J_{HH} = 7$ Hz, CH$_2$CH_3; 1.12, 12H, t, $^3J_{HH} = 7$ Hz, $[N(CH_2CH_3)_4]^+$. ESMS (−ve ion mode): $m/z = 658 = [ReBr_3(N_2C_6H_4\text{-}4CO_2Et)(CO)_2]^-$, $m/z = 632$ (100%) = $[ReBr_3(N_2C_6H_4\text{-}4CO_2Et)(CO)]^-$. IR (KBr): $\nu_{N=N} = 1458,1491$, $\nu_{CO} = 1916, 1988, 2066$, $\nu_{Re-N=N} = 1719$.

$[Et_4N]_2[ReBr_3(CO)_3$ (0.100 g, 0.13 mmol) was dissolved in CH_3OH (5 mL). SHYNICH$_3$ (0.032 g, 0.13 mmol) was added and the yellow reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 30 min. Addition of water resulted in the formation of a green-yellow precipitate which was collected by filtration and washed with water to give $[(Re(PhNHCSNNpyH)(CO_3)_3)_2]$ as a green-yellow powder, (0.054 g, 0.05 mmol, 81%). (Found: C, 35.0; H, 2.74; N, 10.52; calc'd for $Re_2C_{30}H_{22}N_8O_6S_2$: C, 35.08; H, 2.16; N, 10.91.) ^{1}H NMR (300 MHz) (d_6-acetone): δ 11.22, 1H, s, *H*NC$_6$H$_5$; 8.4, 1H, s, PhNH; 7.78, 1H, m, ArH; 7.70, 2H, d, $J = 9$ Hz ArH, 7.53–7.25, 4H, m, 4H, 7.02, 1H, m, ArH; 6.39, 1H, m, ArH. ESMS (−ve ion mode): $m/z = 1025$ (10%) = $[Re_2(C_{24}H_{21}N_8S_2)(CO)_6]^-$, $m/z = 513$ (100%) = $[Re(C_{12}H_{10}N_4S)(CO)_3]^-$.

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