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A Mono-Diazenide Complex from Perrhenate: Toward a New Core for Rhenium Radiopharmaceuticals

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A new method for the synthesis of low to intermediate oxidation state rhenium complexes containing a bifunctional ligand has been developed. Reaction of $[ReO_4]^-$ with substituted phenylhydrazines and triphenylphosphine in acetonitrile in the presence of HCl allows the isolation of $[ReCl_2(NNC_6H_4\text{-}4\text{-}R)(NCCH_3)(PPh_3)_2]$ (where R = OCH_3, Cl, or CO_2CH_3). The substituted hydrazine acts as both a reductant and source of a monodentate diazenide ligand. The compounds have all been characterized in the solid state by X-ray crystallography and in the solution state by NMR, electrospray mass spectrometry, and HPLC. Cyclic voltammetry measurements show that the mono-diazenide complexes undergo a reversible oxidation.

There is much 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 sterilizing 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 functionalization that can allow the attachment of biologically active molecules[4] to provide specificity and selectivity in vivo.[1,5−8]

This methodology has been used successfully in the development of ^{99m}Tc imaging agents which use *N*-oxysuccinimidylhydrazinonicotinamide (HYNIC) as the bifunctional ligand.[9,10] Similar systems have been investigated with rhenium, whose 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 it is $[TcO_4]^-$.[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.[11−13] X-ray structural characterization 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.[14] This results in radiolabeled protein conjugates made using this system consisting of mixtures of complexes which have proved difficult to characterize fully.

We have previously reported the reaction of $[ReOCl_3(PPh_3)_2]$ with arylhydrazines ($ArNHNH_2$) in methanol to give the bis(diazenido) complexes $[ReCl(N_2Ar)_2(PPh_3)_2]$.[15] However, the substitution chemistry of these, like the pyridylhydrazine derivatives, is complicated by protic equilibria and somewhat unpredictable loss of diazenide with some ligand systems. We here report the reaction of arylhydrazines directly with perrhenate in acetonitrile to give a high yield of a mono aryl diazenide complex. This undergoes extensive high-yield substitution reactions[16] and has the potential to

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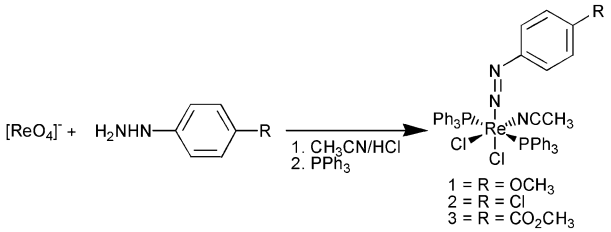
Scheme 1. The Synthesis of **1**−**3**



provide access to a new core for the development of radiotherapeutic agents based on rhenium.

When $[NH_4][ReO_4]$ or $[^nBu_4N][ReO_4]$ is reacted 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, a red color rapidly develops. 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 monodiazenide species $[Re(NNC_6H_4\text{-}4\text{-}OCH_3)Cl_4]^-$ at $m/z = 462$. Other less intense peaks in positive ion mode are assignable to $[Re(NNC_6H_4\text{-}4\text{-}OCH_3)_2(NCCH_3)_2]^+$ and $[Re(NNC_6H_4\text{-}4\text{-}OCH_3)(NCCH_3)_2 + Na^+]^+$. HPLC measurements of the reaction mixture at this stage show a peak due to perrhenate (0.73 min, 90:10 CH_3CN/H_2O) and four other species with retention times (in the case of R = OCH_3) of 1.50, 1.67, 1.87, and 2.33 min in an isocratic eluent mixture of 90:10 CH_3CN/H_2O. The presence of perrhenate may indicate that the reaction does not go to completion or, more likely, that some dissociation of the intermediates occurs under the aerobic aqueous HPLC conditions. Addition of triphenylphosphine results in the formation of a single species by HPLC and red air-stable solids in isolated yields of about 70% (Scheme 1). It appears that the triphenylphosphine may stabilize the diazenide core and drive the reaction in Scheme 1 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.

In this system the arylhydrazine acts both as a reductant, reducing the Re(VII) of the $[ReO_4]^-$ starting material, meaning that no external reducing agents are required, and as a precursor to the diazenide ligand. The complexes are diamagnetic, and ^1H NMR spectra in $CDCl_3$ are well-resolved, showing signals for the AA′BB′ system of the 4-substituted phenyl ring at about δ 6.4 ppm. The signals due to the trans triphenylphosphine ligands come within the expected range, and in the case of compounds **1** and **3** a singlet is observed for the OCH_3 group and the CO_2CH_3 group. The major peak in the electrospray mass spectra (positive ion mode) of the red solids in each case corresponds to $[ReCl_2(NNC_6H_4\text{-}4\text{-}R)(PPh_3)_2 + H^+]$.

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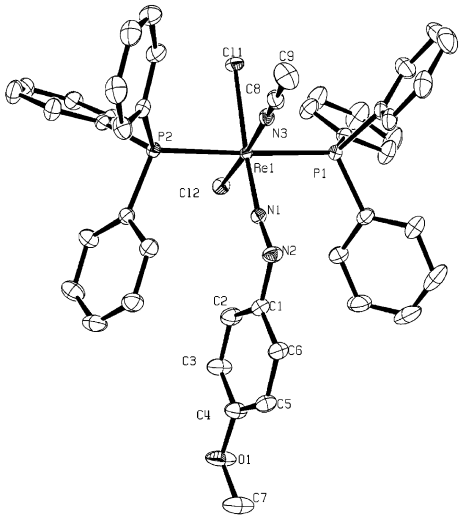

Figure 1. An ORTEP-3 representation of **1**. Hydrogen atoms and solvent molecules have been omitted for clarity.

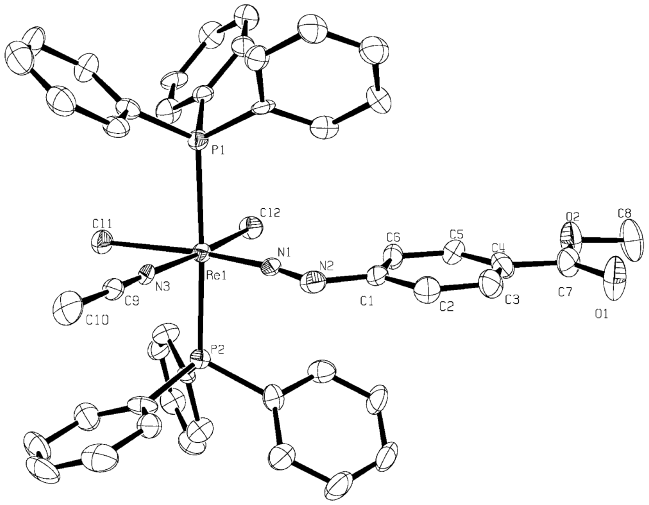

Figure 2. An ORTEP-3 representation of **3**. Hydrogen atoms and solvent molecules have been omitted for clarity.

Table 1. Summary of the Bond Distances for the Re−N−N Fragment

compound	Re1−N1 (Å)	N1−N2 (Å)
1	1.789(2)	1.225(3)
2	1.775(3)	1.240(4)
3	1.786(7)	1.22(1)

Each of the compounds has been structurally characterized by X-ray crystallography, and all have similar structures. ORTEP-3 representations of the X-ray crystal structures of **1** and **3** are shown in Figures 1 and 2.

In all cases the rhenium is in a distorted octahedral environment with the two triphenylphosphine ligands trans to each other, a coordinated chloride trans to the diazenide ligand, another chloride, and a coordinated acetonitrile molecule. In all three compounds the Re−N−N system is essentially linear (Re1−N1−N2 = 167.8(2)° in **1**, 168.5(2)° in **2**, and 168.8(6)° in **3**) and the Re−N and N1−N2 bond distances are characteristically short (see Table 1), consistent with the monodentate diazenide ligand acting as a monoanionic 3 electron donor. The fact that the complexes are isolated in the presence of excess hydrochloric acid suggests that no facile protonation of the diazenide occurs.

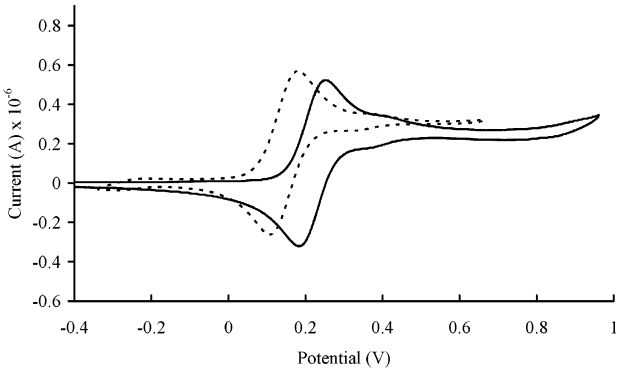

Figure 3. Cyclic voltammograms of **1** (dashed line) and **2** (solid line). Potentials are quoted versus an internal ferrocene reference.

Cyclic voltammetry measurements of **1** and **2** (Figure 3) show that the mono-diazenide species undergo a fully reversible oxidation which is tentatively assigned to a Re(III)/Re(IV) processs.

The 4-chloro-substituted complex (**2**) undergoes a reversible oxidation at +0.18 V versus an internal ferrocene reference (0.60 V versus SCE) while the electronic effects of the methoxy group of **1** are manifested in oxidation at a slightly lower potential, +0.14 V versus an internal ferrocene reference (0.56 V versus SCE). The fully reversible nature of the oxidation process reflects the stability of the Re(IV) cation.

The X-ray crystal structure of **3** shows that the pendant ester substituent lies in an extended position, pointing away from the rest of the complex. This means that it should provide a readily accessible site for further functionalization with a biologically active molecule such as a monoclonal antibody or protein that could provide specificity in vivo. The stability of rhenium diazenide complexes means that any biologically active molecules tethered to the rhenium in this fashion should remain bound in vivo.

These new compounds provide a new "rhenium core" which can be readily substituted with a variety of ligands to form kinetically inert species and to control several important factors such as complex stability, hydrophilicity, charge, and ultimately biodistribution. Importantly, with respect to the potential use of these systems as new radiotherapeutic agents, the synthesis can be readily achieved from $[ReO_4]^-$ in high yields. The fact that this method produces a monodentate mono-diazenido species means that these systems may well provide better defined species than the well-studied Re−HYNIC systems.[14,18]

Supporting Information Available: Crystallographic data (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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