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Metal-Assisted In Situ Formation of a Tridentate Acetylacetone Ligand for Complexation of *fac*-$Re(CO)_3^+$ for Radiopharmaceutical Applications

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Reaction of $[NEt_4]_2[ReBr_3(CO)_3]$ with 2,4-pentanedione (acac) yields a complex of the type *fac*-$Re(acac)(OH_2)(CO)_3$ (**1**) under aqueous conditions. **1** was further reacted with a monodentate ligand (pyridine) to yield a *fac*-$Re(acac)(pyridine)(CO)_3$ complex (**2**). Complex **1** was found to react with primary amines to generate a Schiff base (imine) in aqueous solutions. When a mixed-nitrogen donor bidentate ligand, 2-(2-aminoethyl)pyridine, that has different coordination affinities for *fac*-$Re(acac)(OH_2)(CO)_3$ was utilized, a unique tridentate ligand was formed in situ utilizing a metal-assisted Schiff base formation to yield a complex *fac*-$Re(CO)_3$(3[(2-phenylethyl)imino]-2-pentanone) (**3**). Tridentate ligand formation was found to occur only with the Re-coordinated acac ligand. Reactions of acac with *fac*-$Re(CO)_3Br$(2-(2-aminoethyl)pyridine) (**4**) or a mixture of $[NEt_4]_2[ReBr_3(CO)_3]$, acac, and 2-(2-aminoethyl)pyridine did not yield the formation of complex **3** in water.

Technetium-99m ($t_{1/2}$ = 6.02 h; γ = 140 keV) is the radionuclide of choice in hospitals comprising 90% of all nuclear medicine imaging scans.[1] Development of organometallic technetium complexes, such as *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$, has provided new avenues of complex formation for diagnostic imaging.[2,3] Current labeling strategies include incubation of monodentate, bidentate, tridentate, or combination (2 + 1) ligand systems with the *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ moiety.[4,5] Some of the best ligand systems (histidine, cysteine, and 2,3-diaminopropanoic acid) form tridentate complexes at >90% at 10^{-6} M.[6–9] However, complex formation below 10^{-6} M appears limited by the thermodynamics of ligand substitution of the technetium(I) center.[10]

Interest in developing new modes of complex formation has led us to investigate 2,4-pentanedione or acetylacetone (Acac) as a potential ligand system. acac is a well-established bidentate ligand that coordinates a number of transition metals. Acac can also be synthetically modified to incorporate a linked biotargeting moiety at carbon C1 and/or C3. The Schiff base or imine versions of acac are prepared by reacting a primary amine with the ligand in organic solvents. The stability of the Schiff base ligand in water may be limited by the hydrolytic nature of the imine bond. The mixed-donor (O, N) acac-derived Schiff base ligand provides an excellent ligand for rhenium with improved stability over the acac ligand alone.[11,12]

Acac-based complexes were prepared and characterized with natural rhenium to better understand the chemistry that would be potentially found with radioactive ^{99m}Tc and $^{186/188}Re$ analogues used in nuclear medicine. The reactions reported within were prepared in water to simulate reaction conditions that would be potentially translatable to the analogous radioactive complexes. The rhenium acac complex can be formed by heating $[NEt_4]_2[ReBr_3(CO)_3]$ with acac at 70 °C for 2 h in 10.0 mL of water to yield *fac*-$Re(acac)OH_2(CO)_3$ (**1**; Scheme 1). The product, **1**, remains quite soluble in water but can be isolated as a colorless solid

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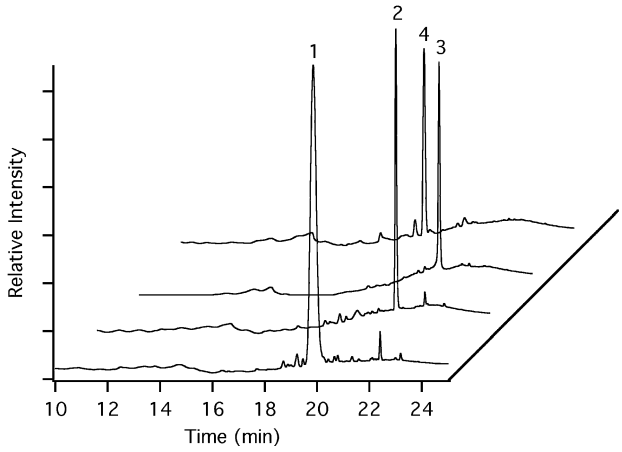
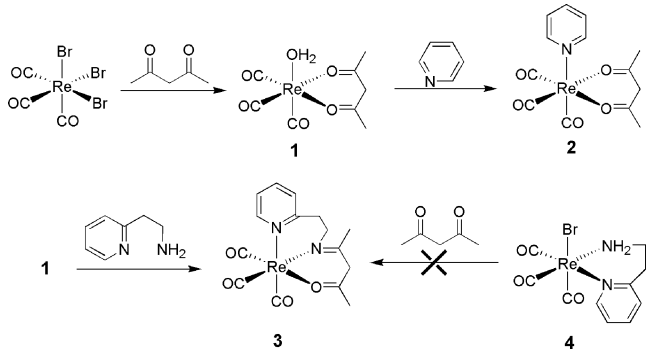


Figure 1. UV−HPLC trace at 220 nm of **1**−**4**.

Scheme 1. Synthetic Route for Preparation of Rhenium acac Complexes and Subsequent Reactions with Mono- and Bidentate Ligands To Yield "2 + 1" and in Situ Formed Tridentate Complexes



in high yield through concentration and cooling of the solution in a refrigerator (∼2 °C) overnight. High-performance liquid chromatography (HPLC) studies of the solution and the isolated solid revealed a single peak of complex **1** at 20.6 min verified by NMR (Figure 1).

Complex **1** is a versatile reagent because it can be isolated as a solid or utilized directly from the reaction mixture. The addition of a second monodentate ligand to **1** generated a "2 + 1" style of complex. When **1** is reacted with pyridine at 70 °C overnight, the complex *fac*-Re(acac)(CO)$_3$py (**2**) can be prepared in high yield. **2** is the only product observed from the solution. Even in the presence of excess pyridine, displacement of the acac ligand was not observed. The formation of **2** can be observed by the appearance of a new peak at 22.3 min in the HPLC (Figure 1). The X-ray structure of **2** was obtained by diffusion of pentane into a dichloromethane solution of **2** (Figure 2).[13] The octahedral complex has comparable Re−CO bonds (1.89–1.92 Å) with an asymmetric axis elongated along the Re−pyr (Re1−N1 2.20 Å) and acac (Re−O1 or Re−O2 2.12 Å) axes. The acac ligands show a minimally constrained bite angle (O1−Re−O2 85.07°). The pyridine N1 is equidistant to the O1/O2 of the acac ligand (O−Re−N1 82.67–83.3°).

(13) **2**, monoclinic space group *P*2(1)/*c* with cell dimensions $a = 14.9940(7)$ Å, $b = 6.8687(3)$ Å, and $c = 14.1746(6)$ Å and $\beta = 104.698(1)°$.

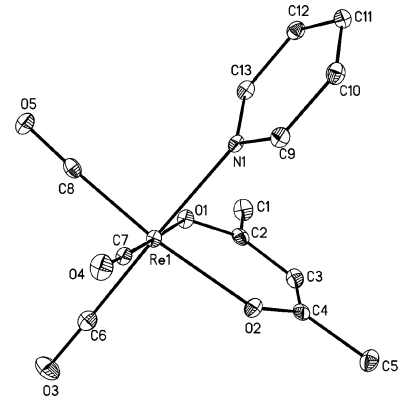


Figure 2. Molecular structure of **2** (thermal displacement 30%). Hydrogen atoms are omitted clarity. Bond distances (Å): Re1−O1 2.1189(19), Re1−O2 2.1226(19), Re1−C6 1.926(3), Re1−C7 1.896(3), Re1−C8 1.903(3), Re1−N1 2.209(2). Bond angles (deg): O1−Re−O2 85.07(8), O1−Re−C6 95.29(10), O1−Re−C7 177.72(10), O1−Re−C8 92.76(10), O2−Re−N1 82.67(8), O2−Re−C6 95.62(11), O2−Re−C7 94.55(10), O2−Re−C8 174.08(10), N1−Re−C6 177.88(10), N1−Re−C7 94.39(10), N1−Re−C8 91.62(11).

Although the "2 + 1" complex **2** is coordinatively saturated, ligand displacement may limit the effectiveness of the complex in vivo. The formation of a tridentate ligand compared to the "2 + 1" complex may have increased stability toward substitution because of the chelate effect. The "2 + 1" complex of **2** can be transformed by an in situ reaction into a tridentate complex utilizing the reactivity of acac in **1** to form an imine from a primary amine. An analogous rhenium pyridine aldehyde complex was previously demonstrated to form a bidentate imine complex system from a primary amine; however, the bidentate complex had limited stability toward ligand substitution.[14,15] *fac*-Re(CO)$_3$(3[(2-phenylethyl)imino]-2-pentanone)] (**3**) was prepared in a two-step process: formation of the acac complex **1** followed by the addition of a second bidentate ligand (Scheme 1). Complex **3** was formed either stepwise or as a single-pot reaction. The formation of the imine bond in **3** was observed by the addition of 2-(2-aminoethyl)pyridine to an aqueous solution of complex **1** followed by heating at 70 °C. The product precipitated as a colorless solid upon cooling to room temperature. The reaction progress was monitored by HPLC, where the disappearance of **1** and the appearance of **3** at 21.4 min were observed in the chromatogram (Figure 1). Crystals of **3** were obtained by slow evaporation of a methanol/water solution at room temperature (Figure 3).

The solid-state structures of the "2 + 1" complex **2** and the tridentate complex **3** have many structural similarities in bond distances (i.e., Re−pyridine ∼2.2 Å, Re−O1 2.13 Å, Re−CO ∼1.9 Å) and angles (O1−Re−N1 82.24(8)° in **3** has a bite angle similar to that of the acac ligand in **2**). However, the methylene carbons (C6 and C7) have larger than typical bond angles (113–115°). C3 of the acac

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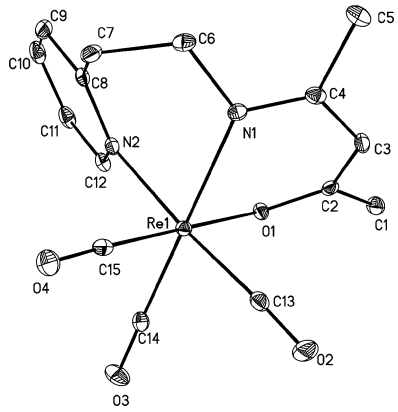

Figure 3. Molecular structure of **3** (30% thermal displacement). Hydrogen atoms are omitted for clarity. Bond distances (Å): Re1−O1 2.1336(18), Re1−N1 2.166(2), Re1−N2 2.197(2) Re1−C13 1.925(3), Re1−C14 1.933(3), Re1−C15 1.901(3). Bond angles (deg): O1−Re−N1 82.24(8), O1−Re−C13 93.27(10), O1−Re−C14 92.46(9), O1−Re−C15 178.39(9), N1−Re−N2 80.36(8), N1−Re−C13 96.05(10), N1−Re−C14 173.77(9), N1−Re−C15 99.16(10), N2−Re1−C13 175.54(10), N2−Re1−C 1495.85(10), N2−Re1−C15 95.76(10).

ligand in **3** is also positioned slightly out of plane because of the steric restraints of the linked pyridine and the imine bond of the tridentate system in **3** compared to **2**.

The Schiff base formation of the tridentate complex utilizes distinct differences in the coordination strength of the bidentate ligand 2-(2-aminoethyl)pyridine, containing a primary amine and an aromatic amine. It is proposed that the pyridine ligand, as opposed to the amine, first coordinates to the rhenium center, replacing the labile aqua ligand. The uncoordinated amine donor is available for nucleophilic attack on the C2 of the coordinated acac ligand. The coordinated oxygen from the acac ligand is converted to water during the Schiff base condensation and probably remains coordinated for a brief moment prior to displacement by the more favorable imine donor from the tridentate ligand. Reactivity of the amine donor with the acac ligand is believed to depend on the effective chelate ring size and steric constraints of the number of methylene carbons between the pyridine and amine.

Displacement of the acac ligand from complex **1** upon introduction of 2-(2-aminoethyl)pyridine was a primary concern. The potential displacement byproduct *fac*-Re(2-(2-aminoethyl)pyridine)Br$(CO)_3$ (**4**) was prepared by refluxing $[NEt_4]_2[ReBr_3(CO)_3]$ with 2-(2-aminoethyl)pyridine in methanol (Scheme 1). HPLC of the reaction yielded a single peak at 20.0 min corresponding to **4**. The complex was characterized and utilized as a reference for HPLC comparison (Figure 1). Single crystals were obtained from a methanol solution of **4** at 0 °C after several days (Figure 4). **4** was further evaluated to determine the dissociation/reactivity of the coordinated 2-(2-aminoethyl)pyridine by introducing excess acac ligand in water (Scheme 1). A second slightly more hydrophilic peak was observed in HPLC over a prolonged period, which may be due to substitution of the coordinated

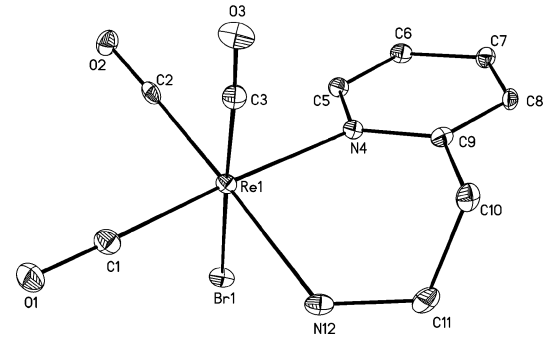

Figure 4. Molecular structure of **4** (thermal displacement 30%). The solvent molecule and hydrogen atoms are omitted for clarity. Bond distances (Å): Re1−Br1 2.1189(19), Re1−O2 2.1226(19), Re1−C6 1.926(3), Re1−C7 1.896(3), Re1−C8 1.903(3), Re1−N1 2.209(2). Bond angles (deg) O1−Re−O2 85.07(8), O1−Re−C6 95.29(10), O1−Re−C7 177.72(10), O1−Re−C8 92.76(10), O2−Re−N1 82.67(8), O2−Re−C6 95.62(11), O2−Re−C7 94.55(10), O2−Re−C8 174.08(10).

bromine in **4** with water. Under the conditions examined, neither the formation of **3** or the displacement of 2-(2-aminoethyl)pyridine by acac yielding **1** was observed, suggesting that 2-(2-aminoethyl)pyridine remains coordinated to the rhenium center in **4** without dissociation or activation of the complex toward Schiff base formation. Although free ligand formation is possible, we examined the possibility that the ligand could be formed in situ by the addition of acac and 2-(2-aminoethyl)pyridine in water followed by the addition of *fac*-$[ReBr_3(CO)_3]^{2-}$. The mixture yielded **4** or the aquo-coordinated complex as observed by HPLC, and no formation of the tridentate ligand complex **3** was observed.

In conclusion, we have demonstrated that acac can be utilized as a bidentate ligand system in a "2 + 1" approach or utilizing coordination differences to generate a tridentate ligand system while coordinated to the rhenium metal center. This new methodology has the potential for linking to targeting molecules, such as small molecules, peptides, and antibodies, for generating in situ tridentate complexes for nuclear medicine applications.

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Supporting Information Available: Full syntheses, characterization of compounds, and X-ray crystallographic bond angles and distances tables (PDF) and X-ray structural information for **2**−**4** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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