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Preparation of Re(I)– and ^{99m}Tc(I)–Metallocarboranes in Water under Weakly Basic Reaction Conditions

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A new method for the preparation of Re– and ^{99m}Tc–metallocarboranes in water under mild reaction conditions was developed. Three *nido*-carborane ligands were reacted with $[Re(CO)_3Br_3]^{2-}$ in the presence of aqueous potassium fluoride to give the corresponding η^5-$Re(CO)_3$–carborane complexes. The use of KF as a base afforded the desired Re–metallocarboranes in good yields while avoiding the formation of Re clusters, which are byproducts commonly observed when reactions are carried out in the presence of strong aqueous bases. The reaction was also performed at the tracer level producing the first ^{99m}Tc–carborane complex, which was isolated in 80% radiochemical yield following a simple Sep-Pak purification process. The resulting organometallic complex was stable to cysteine and histidine challenges for more than 24 h.

Cyclopentadienide (Cp^-) complexes of ^{99m}Tc ($E_\gamma = 141$ keV, $t_{1/2} = 6.02$ h), the most widely used radionuclide in diagnostic medicine,[1] are attractive synthons for the development of organometallic radiopharmaceuticals because of the metal complexes' small size and stability. A number of synthetic approaches to $CpTc(CO)_3$ and related derivatives have been developed;[2] however, because cyclopentadiene (Cp) does not react efficiently with metals in aqueous media and because its conjugate base oligomerizes in water, these methods typically require the use of organic solvents, harsh reagents and reaction conditions, and/or multiple synthetic steps, which limits their applicability for routine clinical use. More recently, Alberto and colleagues showed that introduction of an electron withdrawing carbonyl substituent on the Cp ring stabilizes the conjugate base to the extent that it facilitates the direct synthesis of $RC(O)CpM(CO)_3$ (M = Re, ^{99}Tc, ^{99m}Tc) complexes in water in reasonable yields.[3] Half-sandwich complexes of technetium linked to a serotonergic ligand were prepared using this approach.[4]

As an initial step toward establishing a new class of Tc–organometallic radiopharmaceuticals, we developed a method for preparing ^{99}Tc(I) ($E_{\beta\max} = 294$ keV, $t_{1/2} = 2.13 \times 10^5$ yr) and Re(I)–carborane complexes in water.[5] The carborane ligands, which are prepared by degradation of dicarba-*closo*-dodecaboranes followed by deprotonation of the resulting *nido*-carboranes, are isolobal to Cp^-, but, unlike the quintessential organometallic ligand, they are highly effective at forming metal complexes in water.[6] One further advantage to using carboranes over more traditional ligands is that they can be readily functionalized with a wide range of different groups at select vertices regioselectively.[7] This affords a tremendous amount of flexibility when designing novel radiopharmaceuticals.[8]

Metallocarboranes are typically prepared in the presence of strong bases in order to remove the bridging proton on the *nido*-carborane ligand.[9] The ^{99}Tc–carborane complexes we reported previously were prepared in water in the presence of KOH or Na_2CO_3 and $[^{99}Tc(CO)_3Br_3]^{2-}$. When

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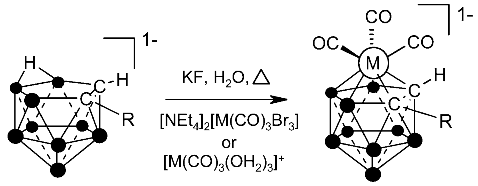
Scheme 1



1a R = H
1b R = $CH_2CH_2CO_2H$
1c R = $CH_2CH_2CH_2NMe_2$

2a R = H, M = Re
2b R = $CH_2CH_2CO_2H$, M = Re
2c R = $CH_2CH_2CH_2NHMe_2$, M = Re
2d R = $CH_2CH_2CO_2H$, M = ^{99m}Tc

the analogous reactions were carried out at the tracer level with $[^{99m}Tc(CO)_3(OH_2)_3]^+$,[10] the yields of the desired products were low (less than 10%) with the major reaction product being $^{99m}TcO_4^-$. Changing the amount of ligand, reaction time, pH, or temperature did not produce yields comparable to those observed for reactions performed at the macroscopic scale with ^{99}Tc or cold Re. The unacceptably low yields obtained at the tracer level are likely due to the highly basic reaction conditions which can cause decomposition of $[^{99m}Tc(CO)_3(OH_2)_3]^+$ prior to complex formation. In light of these results, we began a search for a base that would remove the bridging hydrogen on the carborane, which is needed for efficient complexation, but that would not cause premature decomposition of the Tc starting material.

Fluoride ion ($pK_b \approx 10.8$) is one of the few bases that does not react with the $M(CO)_3^+$ core (M = Re, Tc), making it a plausible candidate for preparing metallocarboranes in aqueous solutions.[11] Bases that are commonly used to prepare metallocarboranes (*n*-BuLi, NaH, TlOEt, and NaOH)[12] are much stronger than fluoride; consequently, the question remained as to whether or not an aqueous fluoride solution would be able to generate sufficient amounts of the deprotonated *nido*-carborane, otherwise referred to as the dicarbollide dianion, to afford good yields of the desired products.

To probe the feasibility of using fluoride as a base, the *nido*-carborane ligands **1a** and **1b** were reacted with $[NEt_4]_2[Re(CO)_3Br_3]$ in the presence of 100 mM KF at 85 °C (Scheme 1). We have previously demonstrated that these particular carborane ligands, under strongly basic conditions, react with the $Re(CO)_3^+$ core to give the corresponding η^5-metal complexes in good yield. After heating, the desired products, **2a** and **2b**, were obtained in 34% and 50% isolated yields, respectively. In the case of the reaction involving **1b**, analysis of the crude reaction mixture by HPLC indicated a yield of greater than 80%; however, difficulties were encountered in separating the different salts of **2b**, which in turn reduced the overall isolated yield. The yield of the unsubstituted carborane was also compromised by our desire to isolate a single salt and by the poor solubility of the ligand in aqueous KF. Nonetheless, the yields of the Re−metallocarboranes are still an improvement over those values reported for the direct synthesis of $CpRe(CO)_3$ type complexes in water.

One major advantage to using fluoride as a base is that it does not promote the formation of polynuclear hydrolysis products. $[Re(CO)_3(OH_2)_3]^+$, which is formed when $[Re(CO)_3Br_3]^{2-}$ is dissolved in dilute aqueous solutions, is stable below pH 6. In the presence of hydroxide ion, deprotonation of the metal bound water molecules occurs, which in turn leads to the formation of Re clusters like $[Re_3(CO)_9(\mu_2\text{-}OH)_3(\mu_3\text{-}OH)]^-$.[13] Until now, the formation of these metal clusters complicated the use of ligands, like carboranes, which require the removal of weakly acidic protons prior to complexation. For example, when compound **1c**, which is a carborane analogue of the monoamine oxidase-B (MAO-B) inhibitor *N*,*N*-dimethyl-3-phenylpropylamine,[14] was reacted with $[NEt_4]_2[Re(CO)_3Br_3]$ in the presence of aqueous NaOH (pH 12), the major products were a series of rhenium clusters. When **1c** and $[NEt_4]_2[Re(CO)_3Br_3]$ were combined in the presence of 100 mM KF and the mixture was heated for 13 h, analysis of the crude reaction mixture by electrospray mass spectrometry showed only the desired product and no evidence of any cluster formation. The pH of the reaction mixture was subsequently adjusted to 5 by the dropwise addition of 1 M HCl, and the product **2c**, as the internal salt, was isolated in good yield (70%).

Compound **2c**, which is a novel metallocarborane derivative, is stable in the solid state and in solution. The IR shows the characteristic B−H stretch at 2526 cm^{-1}, which is not significantly shifted from that of the ligand. The CO peaks appear at 2006 and 1899 cm^{-1} with relative intensities that are consistent with the local symmetry of the metal complex. The electrospray mass spectrum showed the predicted molecular ion having the appropriate isotope distribution while ^{1}H, ^{11}B, and ^{13}C NMR spectra were consistent with the structure of the target compound.

With the success of the reactions involving rhenium, attempts were made to label the bifunctional ligand **1b** with $[^{99m}Tc(CO)_3(OH_2)_3]^+$, which was prepared using commercially available carbonyl labeling kits. $^{99m}TcO_4^-$ (370−740 MBq; 10−20 mCi) was added to the kit and $[^{99m}Tc(CO)_3(OH_2)_3]^+$ prepared according to the commercial protocol. After reacting a ligand/KF mixture with $[^{99m}Tc(CO)_3(OH_2)_3]^+$, to our surprise, only a small quantity of the desired product was obtained (5% radiochemical yield). After 6 h of heating, the main reaction constituents were unreacted starting materials and $^{99m}TcO_4^-$.

Commercially available kits contain sodium tartrate to prevent premature decomposition of $[^{99m}Tc(CO)_3(OH_2)_3]^+$. Thinking that the chelate was interfering with the fluoride mediated complexation reaction, we prepared our own kit

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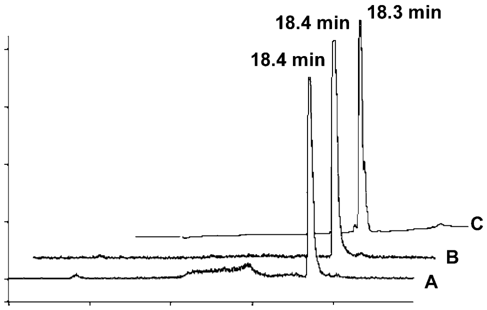

Figure 1. (A) γ-HPLC radiochromatogram of the crude reaction mixture after 3 h at 85 °C. (B) γ-HPLC radiochromatogram of Sep-Pak purified **2d**. (C) UV−HPLC chromatogram of the Re standard **2b**.

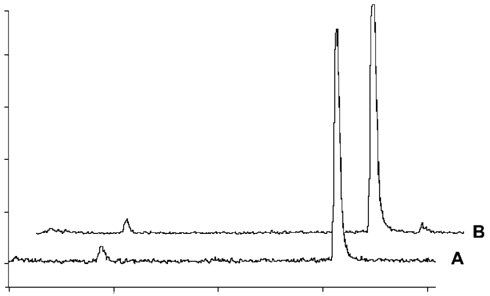

Figure 2. γ-HPLC radiochromatograms of **2d** after 24 h of L-cysteine (A) and L-histidine (B) challenges.

in which KF was substituted for tartrate. $[^{99m}Tc(CO)_3(OH_2)_3]^+$ was successfully prepared using the "KF kit" formulation (see Supporting Information for details) in comparable purity and yield to the product from the commercial kit. It should also be noted that $[^{99m}Tc(CO)_3(OH_2)_3]^+$ prepared in the presence of KF was stable for greater than 6 h, which is comparable to the stability of the product from the tartrate formulation.

Compound **1b**, in the presence of KF, was added to $[^{99m}Tc(CO)_3(OH_2)_3]^+$ and the mixture heated for 3 h. The crude γ-HPLC of the reaction mixture showed an appreciable amount of the desired product and only small amounts of residual starting material and $^{99m}TcO_4^-$. The metallocarborane **2d** was obtained in 80% isolated yield following purification using a C_{18} Sep-Pak. The Sep-Pak procedure was able to separate $^{99m}TcO_4^-$ and the excess carborane ligand used during the labeling reaction from the desired product. The γ-HPLC traces of the crude reaction mixture at 3 h, the purified product **2d**, and the UV trace of the Re standard **2b** are shown in Figure 1.[15] The small difference in retention times between the reference standard and the product is associated with the distance between the UV and γ detectors which are connected in series.

To demonstrate the stability of **2d**, the purified product was incubated separately with a 1000-fold excess of cysteine and histidine. Ligand challenge experiments are routinely used in radiopharmaceutical chemistry to determine the likelihood of a compound remaining intact in vivo where there is an abundance of competing thiol and amine ligands. After incubation at 37 °C in phosphate buffered saline (pH = 7.2) for 24 h, the radiochromatograms from both experiments indicated that greater than 94% of the product remained unchanged (Figure 2). These results strongly suggest that the ^{99m}Tc−metallocarborane complexes are sufficiently robust to be used as synthons for preparing radiopharmaceuticals.

The mechanism of the fluoride mediated reaction, which is currently under investigation in our group, may not necessarily be a simple acid−base reaction given the weak basicity and acidity of KF and the bridging hydrogen on the carborane, respectively. Two plausible alternatives could be (1) initial η^3-coordination of the $M(CO)_3^+$ core to the *nido*-carborane thereby causing a concomitant increase in the acidity of the bridging hydrogen or (2) the presence of KF in solution could generate small quantities of HF, which react with a boron hydride leading to the formation of hydrogen gas and the dicarbollide dianion. The exact details of the mechanism notwithstanding, the reported experiments clearly demonstrate that fluoride, unlike hydroxide ion, does not cause premature decomposition of $[M(CO)_3(OH_2)_3]^+$ (M = ^{99m}Tc, Re) thereby allowing for the preparation of metallocarboranes at both the macroscopic and tracer levels in water.

In summary, a novel strategy for the preparation of Re− and ^{99m}Tc−metallocarboranes in water under mild reaction conditions was developed. The reported Tc complexes are attractive synthons for the preparation of organometallic radiopharmaceuticals because of their inertness, relatively small size, and ease of derivatization. Furthermore, with the KF reaction in hand, it is now possible to use the numerous carborane derivatives that have been designed to target tumors for boron neutron capture therapy as the basis for designing novel ^{99m}Tc radiopharmaceuticals.[16]

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Supporting Information Available: Synthetic procedures for compounds **2a**−**2d** and spectral data for compound **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) HPLC experiments were performed on a Varian Prostar model 230 HPLC using a Varian DYNAMAX (length × i.d. = 250 × 4.6 mm), MicroSorb-MV analytical column (300−5 μm, RP-C18). The mobile phase consisted of solvent A = 0.1% TFA in H_2O, solvent B = 0.1% TFA in CH_3CN. Gradient: 0−3 min, 100% A to 95% A; 3−6 min, 75% A; 6−9 min, 66% A; 9−20 min, 0% A; 20−22 min, 0% A; 22−24 min, 95% A; 24−25 min, 100% A. The flow rate was 1 mL/min.

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