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Microwave-Assisted Synthesis of 3,1,2- and 2,1,8-Re(I) and ^{99m}Tc(I)−Metallocarborane Complexes

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Microwave heating was used to prepare η^5-rhenium carborane complexes in aqueous reaction media. For carboranes bearing sterically demanding substituents, isomerization of the cage from 3,1,2 to 2,1,8 derivatives occurred concomitantly with complexation. Microwave heating was equally effective at the tracer level using technetium-99m, affording access to a new class of synthons for designing novel molecular imaging agents.

Because of their compact size, robustness, and versatile synthetic chemistry, organometallic complexes of ^{99m}Tc(I) and Re(I) are considered highly attractive cores from which to prepare molecular radioimaging and radiotherapy agents.[1] Regrettably, the preparation of organometallic imaging and therapy agents has been hampered by the fact that traditional organometallic ligands are generally incompatible with the reaction conditions routinely used to prepare radiopharmaceuticals. This includes the need to complete labeling reactions in less than one half-life, in aqueous reaction media, while employing only very small amounts (i.e., $10^{-9}-10^{-12}$ mol) of the radioisotope.

With these requirements in mind, we recently developed a methodology that can be used to prepare η^5-carborane complexes of both ^{99m}Tc(I) and Re(I) in water.[2] The approach entails using fluoride ion to prevent the decomposition of the technetium or rhenium starting materials over the prolonged reaction times and elevated temperatures needed to form the desired complexes. However, for certain functionalized carboranes, particularly those with sterically demanding substituents, only modest product yields could be achieved even under optimized reaction conditions. To overcome this limitation, the impact of using microwave radiation as an alternate heat source was investigated with some surprising and rather useful consequences.

As an initial experiment, the carboxylic acid-functionalized *nido-ortho*-carborane **1**[2,4d] (Scheme 1) was heated in a microwave reactor with an excess of $[Re(CO)_3(H_2O)_3]Br$[3] in 0.1 M $KF_{(aq)}$ (Scheme 1) and the progress of the reaction was monitored by HPLC. The desired metallocarborane complex 3,1,2-$[K][Re(CO)_3(RHC_2B_9H_9)]$ ($R = CH_2CH_2CO_2H$) (**2**) was present in >90% yield after 7 min at 180 °C: near-quantitative conversion can be achieved in only 5 min if the reaction is heated at 200 °C. We have observed that **2** can also be formed when the corresponding *closo*-carborane **3** is used in place of **1**. Ultimately, we found that the maximum isolated yields were obtained by heating the carborane with an excess of $[Re(CO)_3(H_2O)_3]Br$, followed by a second heating in the presence of an additional amount of the rhenium reagent. This approach ensures complete consumption of the *nido*-carborane ligand, which often has a similar R_f value to its metal complex, thereby facilitating chromatographic purification.

As stated previously, when rhenacarboranes are prepared in aqueous media using a conventional heat source, the presence of fluoride is required to prevent premature decomposition of the metal(I) starting material.[2] Since these same complexation reactions occur within mere minutes using a microwave reactor, it was of interest to see whether equally good conversion to the desired metallocarboranes could be achieved without fluoride. Indeed, the *nido*-carborane **1** formed the corresponding rhenium complex **2** in the absence of fluoride with no significant decrease in yield. This is somewhat remarkable given the absence of an obvious base, traditionally thought to be needed to afford good yields of this class of metallocarboranes.[4] Reactions

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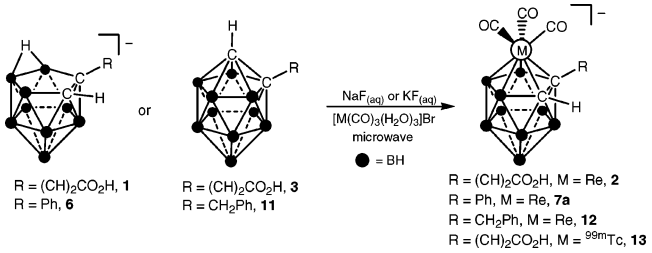
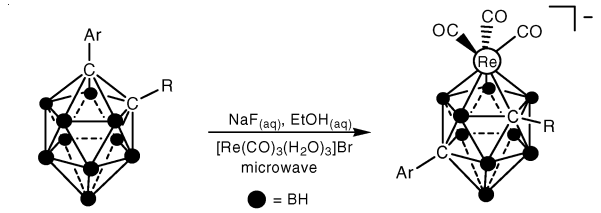
Scheme 1. Microwave-Assisted Synthesis of 3,1,2 Metallocarboranes



Scheme 2. Microwave-Assisted Synthesis of 2,1,8 Metallocarboranes



of other *closo*- and *nido*-carboranes with $[Re(CO)_3(H_2O)_3]$-Br conducted in the absence of fluoride gave varying yields, depending on the substituents present on the ligand. Though a more detailed study of these reactions is currently in progress, to ensure maximum yields all subsequent reactions described here were carried out in the presence of fluoride.

To determine if this microwave methodology were equally effective when using more sterically hindered carborane ligands, the monohydroxyphenyl carborane **4**[5] was combined with $[Re(CO)_3(H_2O)_3]Br$ in aqueous ethanol and the mixture heated at 200 °C for 15 min (Scheme 2). The product was recrystallized from methanol and characterized by multinuclear NMR spectroscopy and single-crystal X-ray diffraction. Curiously, the X-ray structure[6] (Figure 1) revealed that the complex obtained was not the expected 3,1,2 metallocarborane, but rather an isomer, 2,1,8-$[Na][Re(CO)_3(RHC_2B_9H_9)]$ (R = 4-PhOH) (**5a**), where the cage carbon atom linked to the aryl group has migrated out of the bonding face of the η^5-carborane ligand. In simple terms, the observed product can be viewed as a 120° rotation of one of the triangular faces of the carborane. Isomerization of this nature has been noted for other sterically hindered metal−carborane complexes[7] but not for η^5-complexes of rhenium.

To gain some insight into how the microwave-heated reaction of **4** with $[Re(CO)_3(H_2O)_3]Br$ proceeds, a ^1H NMR spectroscopy study of this reaction as a function of temperature was conducted. Using the microwave's autosampler feature to full advantage, a series of 15 min reactions was

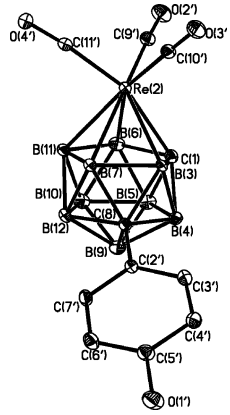


Figure 1. Thermal ellipsoid plot of **5a** (30% probability ellipsoids); Na and H atoms omitted for clarity. Selected bond lengths (Å) and angles (deg): Re2−C1 2.302(4), Re2−B3 2.277(5), C1−B3 1.699(6), B3−B7 1.783(6), B3−Re2−B7 45.3(2), B3−C1−B6 110.0(5).

carried out at 10 °C increments between 100 and 200 °C. The ^1H NMR spectra of the reaction mixtures indicated that the first step of this process consists of the conversion of the *closo*-carborane **4** to the corresponding *nido*-cage with concomitant formation of BF_4^-, as indicated by ^{11}B NMR spectroscopy. This is followed by η^5-coordination of the carborane to the $[Re(CO)_3]^+$ core and simultaneous isomerization to yield **5a**: no evidence for either the isomerization of the free *nido*-carborane ligand or for the initial formation of the 3,1,2 isomer was found. At a reaction temperature of 200 °C, 95% of the product is associated with migration of the C-aryl group (**5a**) while 5% involves migration of the CH group (**5b**) out of the bonding face.

To determine if a similar isomerization process could take place from a 3,1,2 isomer, 3,1,2-$[Re(CO)_3(RHC_2B_9H_9)]^-$ (R = Ph) (**7a**, Scheme 1) was prepared from the corresponding *nido*-carborane using a conventional approach involving anhydrous reaction conditions and a strong base (*n*BuLi).[4] The identity of the product was confirmed by X-ray crystallography and multinuclear NMR spectroscopy. A sample of **7a** was then heated at 200 °C in aqueous ethanol in the microwave reactor for 15 min; subsequent spectroscopic characterization revealed quantitative conversion to the 2,1,8 complex **7b**.

Proton nuclear Overhauser effect (nOe) experiments were carried out on the *closo*-carborane **8**[8] and both isomers **7a** and **7b**, wherein the resonance due to the carborane CH unit was irradiated: in the case of **8** and **7a**, significant enhancement of the resonances associated with the protons of the phenyl ring was evident. No such enhancement was observed for the 2,1,8 isomer **7b** due to the greater distance between the two cage carbon atoms. Similar experiments provide a convenient means of assessing whether isomerization of a given carborane ligand has occurred in systems where X-ray quality crystals cannot be obtained.

A major driving force behind the isomerization of these carborane ligands is likely relief of the steric interactions between the aromatic ring and the CO groups on the metal.[7]

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(6) Crystal data for **5a**: $C_{12}H_{17}B_9NaO_8Re$, $M_r = 595.74$, monoclinic, space group $P2(1)/c$, $a = 11.7890(5)$ Å, $b = 24.5236(9)$ Å, $c = 7.1903(3)$ Å, $\beta = 94.935(2)°$, $V = 2071.07(14)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.911$ g cm^{-3}, $\mu = 5.926$ mm^{-1}, R1 = 0.0669, wR2 = 0.0757.

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This is supported by the fact that when the more sterically encumbered bis-substituted carborane **9**[9] was reacted with $[Re(CO)_3(H_2O)_3]Br$ at 200 °C (Scheme 2), the observed product was exclusively the 2,1,8 isomer **10**. Conversely, when a methylene spacer was incorporated as in the monofunctionalized benzyl carborane **11** (Scheme 1), microwave reactions with $[Re(CO)_3(H_2O)_3]Br$ yielded exclusively the 3,1,2-isomer **12**, even after prolonged (35 min) heating at 200 °C. The unexpected complexity of the NMR spectra of **10** and related compounds were initially attributed to multiple conformational states of the aryl rings;[2b] however, the observed ^1H, ^{13}C, and ^{11}B NMR spectra can now be readily assigned to the isomerized product **10**, which lacks the symmetry possessed by the initially anticipated 3,1,2 isomer. A more detailed study is in progress to examine both electronic and steric substituent effects on the barrier to isomerization. This information will be compared to data reported for the isomerization of other metallocarborane complexes which include both C_2B_9 derivatives and smaller heteroboranes.[10]

The subsequent step in our in investigation was to determine whether microwave heating could be used to perform analogous metal−carborane complexation reactions at the tracer level using ^{99m}Tc in place of rhenium. The microwave reactor vials are similar to reaction vessels typically employed in radiochemistry experiments. A further convenience is that the commercial microwave system employed is equipped with a pressure monitoring system and rapid cooling capabilities. Thus, if proven successful, this methodology should be readily adaptable to the preparation of radiopharmaceuticals. For ease of comparison with our previous radiolabeling work,[2c] the *nido*-carborane **1** was used and combined with $[^{99m}Tc(CO)_3(H_2O)_3]^+$ prepared[11] in the presence of fluoride. The desired product 3,1,2-[Na][$Tc(CO)_3(RHC_2B_9H_9)$] (R = $CH_2CH_2CO_2H$) (**13**) was obtained in 64% isolated yield. The only byproduct, TcO_4^-, was readily separated from the product by a convenient and easily automated solid-phase extraction procedure. This yield is lower than that obtained using a conventional heat source;[2c] however, the reaction was complete in 15 min and the product obtained in high effective specific activity and >99% radiochemical purity. Efforts to further optimize the reaction yield, by means including minimizing the amount of dissolved oxygen present in the reaction mixture, are currently in progress.

It is clear that microwave heating greatly increases the rate and, in certain cases, the yield of the reactions used to prepare Re(I) and Tc(I) carborane complexes compared to conventional heating methods. Although microwave-assisted synthesis has been used elsewhere in carborane chemistry,[7b] this is the first report of such a reaction for preparing metallocarboranes in water at the tracer level. In light of the success of this work, we have begun exploring the general utility of microwave-assisted synthesis for preparing organometallic complexes of other radiometals including the therapeutic isotopes ^{186}Re and ^{188}Re, which undergo substitution reactions much more slowly than with ^{99m}Tc.

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Supporting Information Available: Details of the syntheses of compounds **2**, **5a/b**, **10**, **12**, and **13**; characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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