

## Carboranes as Ligands for the Preparation of Organometallic Tc and Re Radiopharmaceuticals. Synthesis of $[\text{M}(\text{CO})_3(\eta^5\text{-}2,3\text{-C}_2\text{B}_9\text{H}_{11})]^-$ and $\text{rac-}[\text{M}(\text{CO})_3(\eta^5\text{-}2\text{-R-}2,3\text{-C}_2\text{B}_9\text{H}_{10})]^-$ ( $\text{M} = \text{Re}, {}^{99}\text{Tc}$ ; $\text{R} = \text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ) from $[\text{M}(\text{CO})_3\text{Br}_3]^{2-}$

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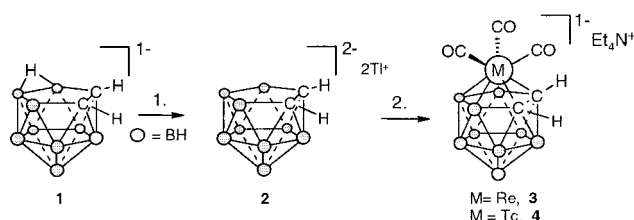
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A new and high yielding method for the synthesis of  $[\text{M}(\text{CO})_3(\eta^5\text{-}2,3\text{-C}_2\text{B}_9\text{H}_{11})]^-$  and the bifunctional metal complexes,  $\text{rac-}[\text{M}(\text{CO})_3(\eta^5\text{-}2\text{-R-}2,3\text{-C}_2\text{B}_9\text{H}_{10})]^-$  ( $\text{R} = \text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ), from  $[\text{M}(\text{CO})_3\text{Br}_3]^{2-}$  ( $\text{M} = \text{Re}, {}^{99}\text{Tc}$ ) was developed. The general approach entailed the addition of *nido*- $[(\text{C}_2\text{B}_9\text{H}_{12})^-]$ , or the acid substituted analogue, to  $[\text{M}(\text{CO})_3\text{Br}_3]^{2-}$  ( $\text{M} = \text{Re}, {}^{99}\text{Tc}$ ) in the presence of TIOEt in THF. It was also possible to prepare the reported products in water using sodium carbonate in place of TIOEt. The reported approach led to the preparation, and X-ray crystallographic structure determination, of the first Tc–carborane complex reported to date ( $a = 13.606(17) \text{ \AA}$ ,  $b = 10.685(13) \text{ \AA}$ ,  $c = 15.534(16) \text{ \AA}$ ,  $\alpha = \gamma = 90^\circ$ ,  $\beta = 111.84(2)^\circ$ ). Because of the stabilities of the metal complexes, and the fact that the compounds can be prepared in water, the bifunctional derivatives can be considered as novel synthons for the preparation of organometallic  ${}^{99\text{m}}\text{Tc}$  and  ${}^{186/188}\text{Re}$  radiopharmaceuticals.

Bifunctional carboranes have been used successfully as carriers of a variety of different radionuclides<sup>1</sup> including some radiometals. This is typified by the report by Hawthorne et al. describing the synthesis of a pyrazole-bridged dicarbollide compound known as the “Venus Flytrap ligand”, which was used to prepare bifunctional complexes of  ${}^{57}\text{Co}$  ( $\gamma$ ,  $t_{1/2} = 271 \text{ d}$ ).<sup>2</sup> To our surprise, however, the syntheses of technetium–carborane complexes have thus far not been reported, despite the fact that  ${}^{99\text{m}}\text{Tc}$  ( $\gamma$ ,  $t_{1/2} = 6.02 \text{ h}$ ) is the most widely used radionuclide in diagnostic medicine.<sup>3</sup>

We investigated the feasibility of using carborane [*nido*-7,8-( $\text{C}_2\text{B}_9\text{H}_{11}$ ) $^{2-}$ , **2** (Scheme 1), which is formally isolobal to ( $\text{C}_5\text{H}_5$ ) $^-$ , as an  $\eta^5$ -ligand for Re(I) and Tc(I) in an attempt to circumvent the synthetic challenges encountered when attempting to prepare  $\text{CpM}(\text{CO})_3$  ( $\text{M} = \text{Tc}$  and Re)-based

Scheme 1<sup>a</sup>



<sup>a</sup> 1. TIOEt 2.  $[\text{NEt}_4][\text{M}(\text{CO})_3\text{Br}_3]$ , THF.

radiopharmaceuticals.<sup>4</sup> One of the advantages in using this particular carborane, also known as the dicarbollide dianion, is that it can be conveniently generated from the stable, and readily accessible, ( $\text{C}_2\text{B}_9\text{H}_{12}$ ) $^-$  ion in alkaline solutions. Dicarbollide dianions can be prepared having a broad range of different functional groups, which expands the number of possible strategies that can be used to incorporate the proposed radiometal complexes into biomolecules.

$\eta^5$ -Carborane complexes with a variety of metals have been reported, two of the earliest being  $[\text{Re}(\text{CO})_3(\eta^5\text{-}2,3\text{-C}_2\text{B}_9\text{H}_{11})]^-$ , **3**, and its manganese analogue.<sup>5</sup> The original preparation of **3** (as its  $\text{Cs}^+$  salt) involved reacting the dicarbollide dianion with  $\text{Re}(\text{CO})_5\text{Br}$ ,<sup>6</sup> a precursor which is not available at the tracer level. Consequently, a new method for the synthesis of  ${}^{99}\text{Tc}$  and Re carborane complexes from  $[\text{M}(\text{CO})_3]^{2+}$  synthons, which are now widely accessible at the tracer level,<sup>7</sup> was developed.

The *nido*-carborane, **1**<sup>8</sup> (Scheme 1), was deprotonated with TIOEt yielding the thallium salt of the dicarbollide dianion, **2**, as a yellowish precipitate. The addition of  $[\text{M}(\text{CO})_3\text{Br}_3]^{2-}$

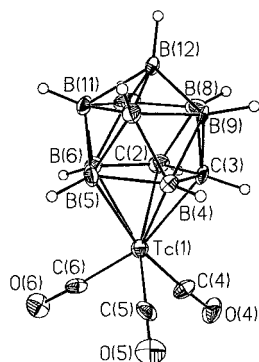
- (4) (a) Wenzel, M. J. *Labelled Compd. Radiopharm.* **1992**, *31*, 641. (b) Top, S.; Kaloun, E. B.; Jaouen, G. *J. Am. Chem. Soc.* **2000**, *122*, 736. (c) Cesati, R. R., III; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 4093. (d) Alberto, R.; Wald, J.; Ortner, K.; Candrea, L.; Pietzsch, H.-J. *J. Labelled. Compd. Radiopharm.* **2001**, *44*, Suppl. 1, S54.
- (5) Hawthorne, M. F.; Andrews, T. D. *J. Am. Chem. Soc.* **1965**, *87*, 2496.
- (6) An improved procedure starting with  $[\text{ReBr}(\text{CO})_5(\text{THF})_2]$  prepared in situ from  $\text{ReBr}(\text{CO})_5$  under anhydrous conditions was reported later. See Ellis, D. D.; Jelliss, P. A.; Stone, F. G. A. *Organometallics* **1999**, *18*, 4982.
- (7) Alberto, R.; Schibli, R.; Egli, A.; Schubiger, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 7987.

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(1) Hawthorne, M. F.; Maderna, A. *Chem. Rev.* **1999**, *99*, 3421.

(2) Hawthorne, M. F.; Varadarajan, A.; Knobler, C. B.; Chakrabarti, S. *J. Am. Chem. Soc.* **1990**, *112*, 5365.

(3) Dilworth, J. R.; Parrott, S. J. *Chem. Soc. Rev.* **1998**, *27*, 43.



**Figure 1.** ORTEP drawing of **4** showing 30% thermal probability ellipsoids. The  $[\text{NEt}_4]^+$  counterion was omitted for clarity.

( $M = {}^{99}\text{Tc}, \text{Re}$ )<sup>9</sup> in THF resulted in the solubilization of **2**, followed by rapid precipitation of  $\text{TlBr}$ . After gentle reflux overnight, the desired products were isolated by preparative TLC in 80% (Tc) and 93% yields (Re). Negative ion ESMS indicated the presence of the two target compounds, each exhibiting the expected isotopic distributions. The  $\nu(\text{CO})$  absorptions for the Re–carborane complex were 2009, 1896, and 1865  $\text{cm}^{-1}$ , which are comparable to those values previously reported for **3**.<sup>10</sup> Compound **4** exhibited  $\nu(\text{CO})$  absorbances at 2016, 1918, and 1908  $\text{cm}^{-1}$ . The B–H stretching frequencies were broad ( $\nu(\mathbf{3}) = 2556 \text{ cm}^{-1}$ ,  $\nu(\mathbf{4}) = 2523 \text{ cm}^{-1}$ ) and within the expected range for related metalcarboranes including  $[\text{Re}(\text{CO})_3(\eta^5\text{-7-CB}_{10}\text{H}_{11})]^{2-}$  reported by Blandford et al.<sup>11</sup> The <sup>11</sup>B NMR of **3** exhibited peaks ranging from  $-24.16$  to  $-7.99$  ppm, while the corresponding resonances in the <sup>11</sup>B spectrum of **4** were only slightly shifted from those of **3**, ranging from  $-22.42$  to  $-7.52$  ppm.

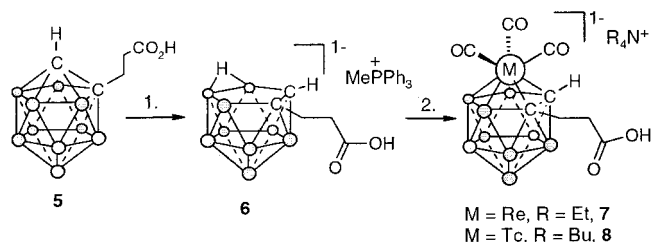
The X-ray structure of **4** (Figure 1) was obtained and is the first reported structure of a technetium–carborane complex. Compound **4** is, as expected, nearly isostructural to the Re complex, which was reported nearly 35 years ago.<sup>12</sup> The average distance at which the atoms composing the bonding face of the carborane reside from the metal center is 2.32 Å, which is nearly identical to the corresponding distance reported for the Re complex. The carborane cage itself appears to be a slightly irregular icosahedron with the average B–B, B–C, and C–C bond distances being 1.76, 1.71, and 1.60 Å, respectively.

The unit cell dimensions of **4** are, as expected, different from those of the reported Re complex owing to the presence of a different counterion. It is interesting to note that despite the obvious similarities between the Re and Tc complexes, the relative orientation of the CO tripod to the atoms of the bonding face of the carborane is significantly different in

each structure. In the Re complex, one of the CO ligands eclipses a carborane carbon atom while the remaining ligands bisect a C–B and a B–B bond. In compound **4**, one of the CO ligands bisects the C–C bond, while the remaining ligands nearly eclipse two boron atoms.

To be useful as a radiopharmaceutical ligand, a means to conjugate the carborane– $\text{M}(\text{CO})_3$  unit to targeting agents must be available. To this end, the *nido*-acid **6** was prepared (Scheme 2) and its ability to complex Re and Tc evaluated.

#### Scheme 2<sup>a</sup>



<sup>a</sup> 1. (a) KOH, EtOH; (b)  $[\text{MePPh}_3]\text{Br}$ . 2. (a)  $\text{TlOEt}$ ; (b)  $[\text{NEt}_4]_2\text{-}[\text{M}(\text{CO})_3\text{Br}_3]$ , THF; (c) HCl; (d)  $\text{Na}^+$  resin; (e)  $\text{R}_4\text{NBr}$  aq.

Compound **5** was prepared in three steps from 4-pentynoic acid and converted to the desired *nido*-anion, **6**, as a racemic mixture. Compound **6** was treated with 2 equiv of  $\text{TlOEt}$  followed by the addition of the limiting reagents,  $[\text{M}(\text{CO})_3\text{Br}_3]^{2-}$  ( $M = {}^{99}\text{Tc}, \text{Re}$ ). The  $\text{TlBr}$  precipitate was removed by filtration, and the products, **7** and **8**, were isolated in quantitative yields as the  $(\text{MePPh}_3)^+$  salts by preparative TLC. We found, however, that the phosphonium salt of **7** and **8** did not have convenient solubility properties and, in the case of the Tc complex, showed signs of slow degradation when exposed to light for long periods of time. Using cation exchange, we prepared the sodium salts (which were water soluble and therefore facilitated analysis by HPLC) and the  $[\text{R}_4\text{N}]^+$  salts, both of which demonstrated improved stability and exhibited no signs of degradation upon prolonged exposure to light.

The various salts of compounds **7** and **8** were characterized by MS, <sup>1</sup>H, <sup>13</sup>C, and <sup>11</sup>B NMR, IR, and, in the case of the sodium salts, HPLC. All results were in agreement with the proposed structures. The IR of **7** and **8** (as the  $[\text{Et}_4\text{N}]^+$  and  $[\text{Bu}_4\text{N}]^+$  salts, respectively) exhibited B–H stretches at similar frequencies (2527 and 2526  $\text{cm}^{-1}$ ). The <sup>11</sup>B NMR for **7** and **8** showed substantial overlap of signals and, because of the loss of symmetry, increased complexity compared to that for compounds **3** and **4**. The electrospray mass spectra for **7** and **8** contained the molecular ion and two other fragment ions corresponding to the loss of one and then two CO groups. The parent peaks in both spectra exhibited the expected isotopic distribution patterns.

The resistance of the complexes to substitution by biological ligands was evaluated by using a cysteine challenge experiment.<sup>13</sup> Compound **3**, for example, was incubated with a 1000-fold excess of L-cysteine in a 1:1 (v/v) phosphate buffer (pH = 7.4)–ethanol mixture at 37 °C over 24 h. HPLC, FTIR, and ESMS experiments indicated that the

(8) Hawthorne, M. F.; Young, D. C.; Garrett, P. M.; Owen, D. A.; Schwerin, S. G.; Tebbe, F. N.; Wegner, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 862.

(9) Alberto, R.; Schibli, R.; Egli, A.; Schubiger, P. A.; Herrmann, W. A.; Artus, G.; Abram, U.; Kaden, T. A. *J. Organomet. Chem.* **1995**, *492*, 217.

(10) Hawthorne, M. F.; Young, D. C.; Andrews, T. D.; Howe, D. V.; Pilling, R. L.; Pitts, A. D.; Reintjes, M.; Warren, L. F., Jr.; Wegner, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 879.

(11) Blandford, I.; Jeffery, J. C.; Jelliss, P. A.; Stone, F. G. A. *Organometallics* **1998**, *17*, 1402.

(12) Zalkin, A.; Hopkins, T. E.; Templeton, D. H. *Inorg. Chem.* **1966**, *5*, 1189.

(13) Stalteri, M. A.; Bansal, S.; Hider, R.; Mather, S. J. *Bioconjugate Chem.* **1999**, *10*, 130.

## COMMUNICATION

complex showed no signs of decomposition over the entire duration of the experiment. This stability, which is essential if carboranes are to be used as carriers of radionuclides, was expected because the 18 e<sup>-</sup> system exhibits electron delocalization between the transition metal and carborane orbitals of appropriate symmetry.<sup>14</sup>

To validate the use of compounds **7** and **8** as ligands for the preparation of radiopharmaceuticals, it was important to determine if the metal complexes could be prepared in aqueous solution. As a preliminary investigation, an attempt was made to prepare compound **7** under conditions that are similar to those used to label compounds at the tracer level. Initially, an excess of the potassium salt of *nido*-carborane **6** was dissolved in deionized water and the mixture basified with KOH (in place of TIOEt) prior to the addition of [Re(CO)<sub>3</sub>Br<sub>3</sub>]<sup>2-</sup>. After heating the mixture to reflux, formation of the product, **7**, was readily observed by HPLC. LCMS studies further confirmed that the product had in fact formed in absence of any other compounds with the exception of the excess ligand. After these experiments, we determined that compound **7** could in fact be prepared in sodium carbonate buffer (pH = 9), heated to around 80 °C for just over an hour, using a 1:1 ligand-to-metal ratio.

(14) Varadarajan, A.; Johnson, S. E.; Gomez, F. A.; Chakrabarti, S.; Knobler, C. B.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1992**, *114*, 9003.

In summary, a convenient method for the preparation of [M(CO)<sub>3</sub>(η<sup>5</sup>-2,3-C<sub>2</sub>B<sub>9</sub>H<sub>11</sub>)]<sup>-</sup> and *rac*-[M(CO)<sub>3</sub>(η<sup>5</sup>-2-R-2,3-C<sub>2</sub>B<sub>9</sub>H<sub>10</sub>)]<sup>-</sup> (M = Re, <sup>99</sup>Tc; R = CH<sub>2</sub>CH<sub>2</sub>COOH) from *fac*-[M(CO)<sub>3</sub>Br<sub>3</sub>]<sup>2-</sup> in both organic solvents and water has been developed. The stabilities of the reported compounds, which include the first two examples of Tc-carborane complexes, to cysteine challenge along with the high yields of synthesis warrant further investigation into the use of carboranes as ligands for the preparation of Re(I) and Tc(I) organometallic radiopharmaceuticals. Adaptation of our synthetic methodology for carrying out labeling at the tracer level, using the products of this research as well characterized standards, remains work in progress.

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**Supporting Information Available:** Complete experimental procedures, X-ray data for compound **4**, and relevant spectral data for compounds **3**, **4**, **7**, and **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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