Re and Tc Complexes Containing B−H···M Agostic Interactions as Building Blocks for the Design of Radiopharmaceuticals

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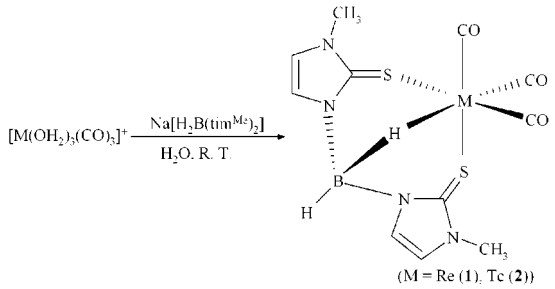
Recent studies on the basic coordination chemistry of Tc(I) and Re(I) compounds containing the *fac*-$[M(CO)_3]^+$ moiety highlighted the potential relevance of these complexes in the development of radiopharmaceuticals for diagnostic (^{99m}Tc) and therapeutic ($^{186/188}$Re) nuclear medical applications.[1] In fact, based on synthons $[M(OH_2)_3(CO)_3]^+$ (M = ^{99m}Tc, $^{186/188}$Re), which can be easily obtained under the conditions as required for routine preparation of radiopharmaceuticals, a number of targeting vectors could be labeled in good yields with high specific activity and retention of bioactivity.[2] Since closed-shell d^6 compounds reveal a distinct kinetic stability, charge, size, and lipophilicity can easily be influenced by an appropriate choice of the tridentate ligand without considering thermodynamic stability. These unique and favorable features of Tc(I) or Re(I) tricarbonyl complexes make them superior in terms of ligand flexibility over the more classical labeling procedures based on Tc(V)═O or Re(V)═O complexes.[3] The electron-withdrawing properties of the three CO ligands enhance the hardness of the *fac*-$[M(CO)_3]^+$ moiety significantly (p*K*s ≈ 8). Thus, much of the coordination chemistry developed so far involved medium hard ligands containing nitrogen (i.e., pyridines, imidazoles) and oxygen donor atoms (i.e., carboxylates).

To extend the range of potential radiopharmaceuticals labeled with *fac*-$[M(CO)_3]^+$, we describe the synthesis and characterization of the novel complexes $[M\{\kappa^3\text{-}H(\mu\text{-}H)B(tim^{Me})_2\}(CO)_3]$ (M = Re (**1**), ^{99}Tc (**2**), ^{99m}Tc (**2a**)), including an agostic B−H−Tc bond and prepared directly from aqueous solution by reacting $[M(OH_2)_3(CO)_3]^+$ (M = Re, Tc) with $Na[H_2B(tim^{Me})_2]$ (Scheme 1). (**Caution**: ^{99m}Tc is a γ emitter (140 keV) with a half−life of 6.0 h and special precautions should be taken to minimize radiation exposure. ^{99}Tc is a weak β^- emitter with a half−life of 2.12×10^5 years. Bremsstrahlung is not a significant problem due to the low energy of the β^- emission, but normal safety procedures must be used when ^{99}Tc is handled to prevent contamination). The high stability and lipophilicity of the corresponding ^{99m}Tc compound might open the way to new classes of radiopharmaceuticals as required for ^{99m}Tc-labeled CNS-receptor ligands.

Dihydrobis(2-mercapto-1-methylimidazolyl)borate ($[H_2B(tim^{Me})_2]^-$ **3**) (we use the abbreviation tim^{Me}, from the term "thioimidazolyl", to represent the 2−mercapto-1-methylimidazolyl fragment) can provide a bidentate or tridentate facial coordination geometry, including the two thione sulfurs and one agostic hydrogen.[4] The ligand **3** can be considered as the soft congener of dihydrobis(pyrazolyl)borate, ($H_2B(pz)_2^-$), which has been largely used in organometallic and coordination chemistry.[5−7] Contrastingly, the coordination chemistry described for poly(thioimidazolyl)borates such as **3** is quite limited and is restricted, to our knowledge, to a few complexes of late transition metals.[4] $Na[H_2B(tim^{Me})_2]$ features inherent requirements for developing novel radiopharmaceuticals. It is water soluble, stable toward hydrolysis or aerobic oxidation, and can be attached with minimal difficulties at a targeting molecule, for example, by the imidazole moiety.

Scheme 1



Complex **1** can be prepared classically by reacting $[ReBr(CO)_5]$ with the stoichiometric amount of **3**. Alternatively, treatment of $[M(OH_2)_3(CO)_3]^+$ with **3** in water led, immediately, to the precipitation of $[M\{\kappa^3\text{-}H(\mu\text{-}H)B(tim^{Me})_2\}(CO)_3]$ (M = Re (**1**), Tc (**2**)), as white microcrystalline solids in high yields (**1**, 85%; **2**; 75%) (Scheme 1).

Complexes **1** and **2** represent unique examples of structurally characterized Re or Tc carbonyl complexes exhibiting B−H··· M agostic interactions. The presence of these agostic interactions was confirmed by spectroscopy[8] (IR: **1**, $\nu(B-H)_{term}$, 2440 cm^{-1}; $\nu(B-H)\cdots Re$, 2060, 2140 cm^{-1}; ^{1}H NMR: **1**, 4.50 ppm ($B-H)_{term}$; −6.40 ppm ($B-H)\cdots Re$; ^{11}B NMR: 33.98 ppm (*m*)) and by X-ray diffraction analysis.[9] Although not isomorphous, **1** and **2** are isostructural. An ORTEP presentation of $[Tc\{\kappa^3\text{-}H(\mu\text{-}H)B(tim^{Me})_2\}(CO)_3]$ is given in Figure 1.

Coordination of **3** takes place through the thione sulfur atoms and one of the hydrogen atoms attached to the boron atom,

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(8) Complex **1**: IR (cm^{-1}) 1900 and 2000 (ν(CO)), 2060 and 2140 ($\nu(BH\cdots Re)$), 2440 ($\nu(BH)_{term.}$); ^{1}H NMR (300 MHz, CD_3CN, δ (ppm)) −6.40 (1H, br, BH), 3.50 (s, 6H, Me), 4.50 (1H, br, BH), 6.90 (d, 2H, CH), 7.08 (d, 2H, CH); ^{11}B NMR (96 MHz, CD_3CN, δ (ppm)) 33.98 (m).
(9) Crystal data: complex **1**, $C_{11}H_{12}BN_4O_3ReS_2$, MW = 509.38, light yellow plates, orthorhombic, *Pnnm*, a = 17.372(2) Å, b = 6.8151(7) Å, c = 15.170(3) Å, V = 1796.0(5) Å^3, Z = 4, D_{calc} = 1.884 Mg/m^3, μ (Mo Kα) = 7.011 mm^{-1}, 2598 reflections, R_1 = 0.0416, wR_2 = 0.0812 for 1660 with $I > 2\sigma(I)$; complex **2**, $C_{11}H_{11}BN_4O_3S_2Tc.0.5CHCl_3$, MW = 480.86, colorless blocks, triclinic, *P*1, a = 7.1363(5) Å, b = 11.5834(9) Å, c = 22.942(2) Å, α = 83.739(9)°, β = 82.477(9)°, γ = 87.616(9)°, V = 1868.2(2) Å^3, Z = 4, D_{calc} = 1.710 Mg/m^3, μ (Mo Kα) = 1.225 mm^{-1}, 6691 reflections, R_1 = 0.0375, wR_2 = 0.1025 for 5669 with $I > 2\sigma(I)$; Complex **4**, $C_{14}H_{16}BN_6O_3ReS_2{\cdot}OC_4H_8$, MW = 649.56, white plates, triclinic, *P*1, a = 10.244(3) Å, b = 11.045(3) Å, c = 11.770(2) Å, V = 1214.4(5) Å^3, Z = 2, D_{calc} = 1.776 Mg/m^3, μ (Mo Kα) = 5.211 mm^{-1}, 3598 reflections, R_1 = 0.0677, wR_2 = 0.1243 for 2376 $I > 2\sigma(I)$. The data were collected with Mo Kα radiation (λ = 0.71073 Å) on Enraf Nonius CAD4 in the case of **1** and **4** and with STOE IPDS diffractometer in case of **2**.

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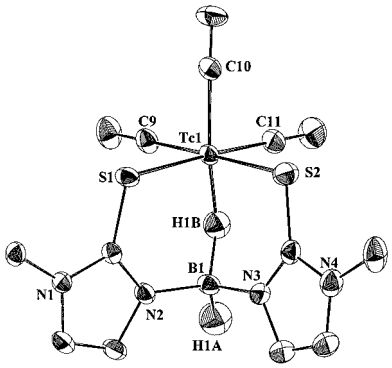


Figure 1. ORTEP view of molecule 1 of $[Tc\{\kappa^3\text{-}H(\mu\text{-}H)B(tim^{Me})_2\}(CO)_3]$ (**2**) with ellipsoids drawn at the 40% probability level. Selected bond distances (Å) and angles (deg): Tc(1)−C(9) 1.928(5), Tc(1)−C(10) 1.916(5), Tc(1)−C(11) 1.926(5), Tc(1)−S(1) 2.5190(11), Tc(1)−S(2) 2.4931(12), Tc(1)−H(1B) 1.65(6), Tc(1)−B(1) 2.834(5), S(1)−Tc(1)−S(2) 88.34(4), C(9)−Tc(1)−S(2) 177.32(13), C(11)−Tc(1)−S(1) 177.2 (2), H(1B)−Tc(1)−C(10) 168(2).

defining two six-membered and one eight-membered chelates. In case of **2**, the hydride could be localized from the X-ray structural analysis. For **1,** the B···Re distance is 2.832 (12) Å, and for **2** the B···Tc distance is 2.834 (5) Å. These distances are consistent with the formation of strong B−H···M agostic interactions, as already predicted from IR and ^{1}H NMR data.[8] The coordination behavior of $[H_2B(tim^{Me})_2]^-$ contrasts markedly with the one previously described for the harder congener $[H_2B(pz)_2]^-$. In fact, when $[ReBr(CO)_5]$ was treated with $Na[H_2B(pz)_2]$, no compound containing an B−H···Re agostic interaction was detected.[7]

Compounds **1** and **2** are remarkably stable toward aerobic oxidation and hydrolysis. These features prompted us to attempt the preparation of the corresponding ^{99m}Tc complex **2a**. In saline, $[^{99m}Tc(OH_2)_3(CO)_3]^+$ ($\sim 10^{-6}$ M) reacted readily at room temperature with an almost stoichiometric amount of **3**, giving after 30min $[^{99m}Tc\{\kappa^3\text{-}H(\mu\text{-}H)B(tim^{Me})_2\}(CO)_3]$ (**2a**) as the only ^{99m}Tc complex formed. Its identity was confirmed by HPLC comparison with the analogous ^{99}Tc complex (**2**). The formation of **2a** is surprising in several respects. Although preorganized for facial tridentate coordination, **3** can easily adopt a conformation to favor bidentate coordination as well. The $\sim 10^5$ fold excess of Cl^- present in solution does not compete agostic M−H bond formation at all. Even when assuming that intramolecular tridentate complex formation is much faster than the complexation by an incoming Cl^-, one could expect subsequent substitution of the agostic hydride, resulting in bidentate coordination of **3** only. Neither of these two reactions could be observed, even when complexation was run at an elevated temperature. This underlines the excellent properties of ligand **3** to stabilize the $[^{99m}Tc(CO)_3]^+$ moiety in biological media. It is in agreement with this observation that **2a** can be kept in phosphate buffer at 37 °C for at least 48 h without detectable decomposition.

Obviously, σ- or π-donating ligands like coordinating solvents such as water or monoanions such as Cl^- are not able to compete with the agostic hydride. It is likely that this lack of reactivity is coupled to the electronic properties of the incoming ligand for mechanistic reasons. We therefore evaluated the reactivity of **1** and **2** toward good or medium π acceptors such as *tert*-butylisonitrile or imidazole, triphenylphosphine, and 4-(dimethylamino)pyridine since these functionalities could easily be introduced into a variety of biomolecules and be used as monodentate coupling groups for ^{99m}Tc.

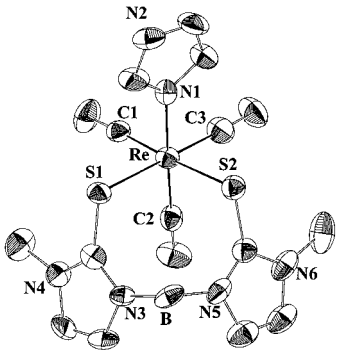
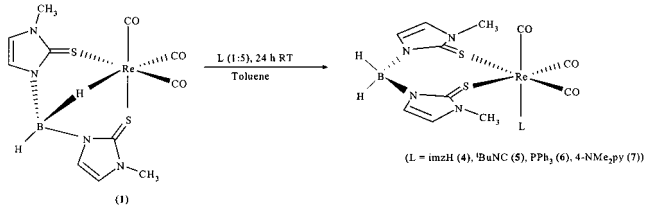


Figure 2. ORTEP view of $[Re\{H_2B(tim^{Me})_2\}(CO)_3(imzH)]$ (**4**) with ellipsoids drawn at the 40% probability level. Selected bond distances (Å) and angles (deg): Re−C(1) 1.88(2), Re−C(2) 1.89(2), Re−C(3) 1.89(2), Re−S(1) 2.532(4), Re−S(2) 2.535(5), Re−N(1) 2.178(13), S(1)−Re−S(2) 88.4(2), C(1)−Re−S(2) 176.0(5), C(3)−Re−S(1) 177.2 (6), C(2)−Re−N(1) 174.1 (7).

Scheme 2



In contrast to the pure σ- or π-donating ligands, preliminary studies have shown that **1** or **2** can be substituted with any of these ligands (Scheme 2). The complexes with general composition $[Re\{H_2B(tim^{Me})_2\}(CO)_3(L)]$ (L = imzH (**4**), ^{t}BuNC (**5**), PPh_3 (**6**), 4-NMe_2py (**7**)) formed, but all of the reactions are kinetically unfavorable, and the cleavage of the B−H···M agostic interaction needs a large excess of substrates. Besides, compounds **6** and **7** slowly transformed into the starting compound **1**, attesting to the robustness of the B−H···M agostic interaction. In compounds **4**−**7** the bidentate coordination of the ligand **3** was confirmed by spectroscopic data and by X-ray structural analysis in the case of **4** (Figure 2).[9]

In conclusion, we have shown that $[H_2B(tim^{Me})_2]^-$ is a very powerful ligand for the $[fac\text{-}M(CO)_3]^+$ (M = Re, ^{99}Tc, ^{99m}Tc) moieties, acting as tridentate chelator through the two sulfur atoms and through a remarkably robust B−H···M agostic interaction. Noticeably, this unprecedented donor set of atoms coordinates at very low ligand concentration and stays coordinated even under aqueous aerobic conditions. This allows the labeling of biomolecules with very high specific activity. Thus, ligands based on **3** open the way to a novel class of small and highly lipophilic ^{99m}Tc radiopharmaceuticals, particularly useful for the labeling of CNS-receptor ligands. A selective in vivo reactivity of the agostic interaction, namely toward biomolecules containing imidazolyl residues, is expected to play a crucial role in the brain retention of the complexes.

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Supporting Information Available: ORTEP drawings, atomic coordinates and displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, and tables of crystallographic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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