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Very Small and Soft Scorpionates: Water Stable Technetium Tricarbonyl Complexes Combining a Bis-agostic (k^3-H, H, S) Binding Motif with Pendant and Integrated Bioactive Molecules

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Abstract: The novel trihydro(mercaptoazolyl)borates Na[$H_3B(tim^{Me})$] (**L**[1]) (tim^{Me} = 2-mercapto-1-methylimidazolyl), Na[$H_3B(tim^{Bupip})$] (**L**[2]) (tim^{Bupip} = 1-[4-((2-methoxyphenyl)-1-piperazinyl)butyl]-2-mercaptoimidazolyl), and Na[H_3B(bzt)] (**L**[3]) (bzt = 2-mercaptobenzothiazolyl) were synthesized by reaction of $NaBH_4$ with the corresponding azole. Ligands **L**[1]−**L**[3] represent a new class of light and soft scorpionates that stabilizes the $[M(CO)_3]^+$ core (M = ^{99}Tc, Re) by formation of the complexes *fac*-[M{κ^3-H(μ-H)$_2$B(tim^{Me})}$(CO)_3$] (M = ^{99}Tc (**1**), Re (**2**)), *fac*-[Re{κ^3-H(μ-H)$_2$B(tim^{Bupip})}$(CO)_3$] (**3**), and *fac*-[Re{κ^3-H(μ-H)$_2$B(bzt)}$(CO)_3$] (**4**), respectively. The soft scorpionates are coordinated to the metal in unique (κ^3-H, H′, S) fashion, as confirmed by X-ray crystallography of **1**, **2**, and **4**. These complexes with bis-agostic hydride coordination are formed in aqueous solution with the two hydrides replacing two coordinating aquo ligands. The agostic hydrogen atoms were located directly, confirming an unprecedented donor atom set combining one sulfur and two hydrogen atoms. Preliminary studies have shown the possibility of preparing some of these complexes at the no carrier added level (^{99m}Tc), under conditions as required in radiopharmaceutical preparation. Due to their lipophilicity, small-size, and easy functionalization with adequate biomolecules, the trihydro(mercaptoazolyl)borate technetium tricarbonyl complexes are suitable for the design of CNS receptor ligand radiopharmaceuticals as exemplified with **3**, comprising a pendant serotonergic 5-HT_{1A} ligand. The integrated design of radiopharmaceuticals involving a bis-agostic scorpionate ligand is demonstrated by the synthesis of **4**, with an integrated benzothiazolyl fragment for the recognition of β-amyloid plaques.

Introduction

Poly(azolyl)borates are a class of tripodal ligands, combining a central and tetrahedral boron atom with a variable number (n = 2−4) of azolyl rings. They play an important role in coordination and organometallic chemistry for various purposes.[1−6] Among this class of ligands, poly(mercaptoimidazolyl)borates and their complexes have received considerable attention in recent years, namely as biomimetics of metalloenzymes.[7,8]

Despite the impressive chemistry based on poly(azolyl)borates, their complexes have not assumed great relevance in biomedical applications probably due to their relatively large size and reduced stability under biological conditions.[9,10] For radiopharmaceuticals in particular, in which ^{99m}Tc is complexed with a receptor-targeting molecule, topology, size, and molecular weight of the ligands are of utmost importance. Coordinating agostic hydrides are very attractive because they represent a ligand with the smallest possible molecular weight (MW = 1). However, this sort of coordination is found more commonly in organometallic chemistry than in aqueous biological chemistry. Recently, we have shown that poly(mercaptoimidazolyl)borates have potential as bifunctional chelators in the design of target-specific drugs containing ^{99m}Tc, the radionuclide of choice in diagnostic nuclear medicine. On the basis of studies with dihydrobis(mercaptoimidazolyl)borates, we were able to demonstrate that one agostic hydride, the smallest possible donor atom in coordination and organometallic chemistry, binds very efficiently to the *fac*-$[M(CO)_3]^+$ (M = Re, ^{99}Tc, ^{99m}Tc) moiety in aqueous media along with the two sulfur donors from the

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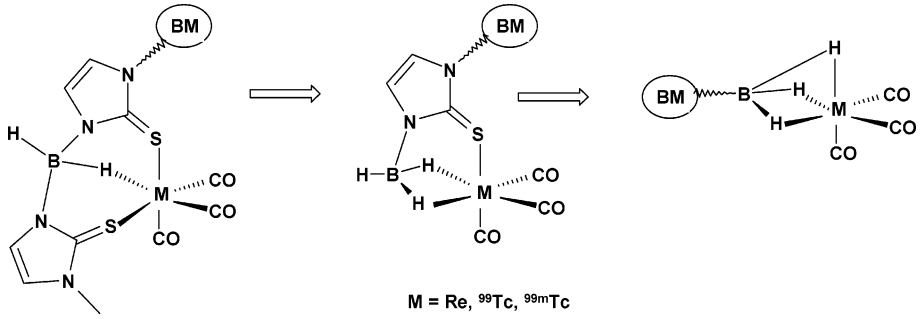
Scheme 1



mercaptoimidazolyl groups.[11−14] Coupling of bioactive fragments to these ligands led to *biocomplexes* exhibiting excellent affinity and selectivity for central nervous system (CNS) receptors of the 5-HT_{1A} serotonergic type.[14]

There is some impetus to replace one or even two mercaptoimidazolyl groups by further agostic hydrides in order to reduce size and to ascertain retention of biospecificity upon introduction of the metal complex (Scheme 1). The favorable features of the complexes *fac*-[M{κ^3-R(μ-H)B(tim^{Me})$_2$}(CO)$_3$] (M = Re, ^{99}Tc, ^{99m}Tc; R=H, Me, Ph) prompted us to study the introduction of two agostic hydrides while retaining the option of further functionalization with targeting biomolecules (BM). We evaluated the possibility of preparing trihydro(mercaptoazolyl)borates with 2-mercapto-1-methylimidazole (tim^{Me}H) and 2-mercaptobenzothiazole (bztH). This novel class of soft scorpionates, if acting as (κ^3-H, H′, S) chelators, will allow for the synthesis of complexes with the *fac*-[M(CO)$_3$]$^+$ metal center, an interesting synthon for the development of target-specific drugs. To our knowledge, only a limited number of complexes exhibiting the general (κ^3-H, H′, E) coordinating feature are known (exclusively with E = P), but all of them are based on borane ligands, not on borohydride derivatives. Moreover, most of these complexes stem from classical organometallic chemistry but not from aqueous chemistry.[15−18]

In this paper, we report the first examples of trihydro(mercaptoazolyl)borates coordinating through two hydrides and one sulfur in scorpionate fashion (κ^3-H, H′, S) to the *fac*-[M(CO)$_3$]$^+$ moiety (M = Re, ^{99}Tc, ^{99m}Tc) in and from aqueous media. We emphasize that the replacement of two water ligands by two agostic hydrides in aqueous solution is very uncommon. The versatility of these chelators are further explored by the preparation of target-specific radiopharmaceuticals, using pendant and integrated approaches.

Experimental Section

General Methods and Materials. All chemicals and solvents were of reagent grade and were used without purification unless stated otherwise. The synthesis and purification of the (mercaptoazolyl)-trihydroborate ligands were carried out under a N_2 atmosphere, using solvents that had been dried and distilled prior to use according to described procedures, whereas the synthesis and manipulation of the Tc and Re complexes were performed in air. The starting materials $(NEt_4)_2[TcCl_3(CO)_3]$[19] and $(NEt_4)_2[ReBr_3(CO)_3]$[20] were prepared as described elsewhere. The compound 1-[4-((2-methoxyphenyl)-1-piperazinyl)butyl]-2-mercaptoimidazole (tim^{Bupip}H) was synthesized by described methods.[21] ^{1}H, ^{11}C, ^{11}B, and ^{99}Tc NMR spectra were recorded on a Varian Unity 300 MHz spectrometer; ^{1}H and ^{11}C chemical shifts (ppm) were referenced with the residual solvent resonances relative to tetramethylsilane. The ^{11}B and ^{99}Tc NMR spectra were recorded in ppm relative to $BF_3{\cdot}Et_2O$ and $NH_4{}^{99}TcO_4$ as external references, respectively. IR spectra were recorded on a Perkin-Elmer 577 spectrometer in Nujol or as KBr pellets. The Raman spectra were obtained using samples in the form of microcrystalline powders, contained in glass capillaries. C, H, and N analyses were performed on an EA 110 CE Instruments automatic analyzer. Electrospray mass spectrometry measurements (ESI-MS) were performed at the ITQB (Oeiras, Portugal) on a ThermoFinnigan LCQ mass spectrometer in negative ion mode. Na[$^{99m}TcO_4$] was eluted from a Mallinckrodt Med. Inc. generator, using 0.9% saline. HPLC analysis was performed on a Merck Hitachi LaChrom D-7000 instrument coupled to a EG&G Berthold LB 508 radioflow detector. Separations were achieved on a Nucleosil column (5 μm, 250 mm × 4 mm), using a flow rate of 0.5 mL/min; UV detection, 254 nm; eluents, A − aqueous 0.1% CF_3COOH solution, B− methanol: 0−3 min, 100% A; 3−9 min 75% A; 9−9.1 min, 75%−66% A; 9.1−20 min 66%−0% A; 20−25 min, 0% A; 25.0−25.1, 0%-100% A; 25.1−30 min, 100% A.

Caution! *^{99}Tc is a weak β^- emitter ($t_{1/2} = 2.13 \times 10^5$ yrs, $\beta^- = 294$ keV). Therefore, all manipulations were carried out in specially equipped (C-type) laboratories to avoid contamination or ingestion.*

Synthesis of Na[$H_3B(tim^{Me})$] (L^1). To a stirred suspension of $NaBH_4$ (1.990 g, 52.6 mmol) in THF (100 mL), at 50 °C, was added dropwise a solution of 2-mercapto-1-methyl imidazole (3 g, 26.3 mmol) in the same solvent (50 mL). After complete addition, the mixture was stirred at 50 °C for 3 h. $\mathbf{L}_1$ was purified by successive recrystallizations from THF/*n*-hexane to remove unreacted $NaBH_4$ and some Na[$H_2B(tim^{Me})_2$] formed. $\mathbf{L}^1$ precipitates as a microcrystalline white solid, upon addition of increasing amounts of *n*-hexane. Yield: 34% (1.330 g, 8.9 mmol). Analysis calculated for $C_4H_8N_2SBNa$: C, 32.03%; H, 5.38%; N, 18.68%. Found: C, 32.03%; H, 4.74%; N, 18.23%. IR (Nujol, ν/cm^{-1}): 2395, 2359 and 2279 ν(B−H). ^{1}H NMR (CD_3CN): δ 3.43 (3H, s, CH_3−N), 6.61 (1H, d, J_{H-H} = 2.1 Hz, CH), 6.64 (1H, d, J_{H-H}= 2.1 Hz, CH). ^{13}C NMR (CD_3CN): δ 34.9, 117.1, 124.0, 162.4. ^{11}B NMR (CD_3CN): δ −19.0 (q, J_{B-H} = 91 Hz). ESI-MS (CH_3CN) *m*/*z*: calcd for $[C_4H_8N_2SB]^-$ (found), 127.0 (127.1).

Synthesis of Na[$H_3B(tim^{Bupip})$] (L^2). To a mixture of $NaBH_4$ (109 mg, 2.89 mmol) and 1-[4-((2-methoxyphenyl)-1-piperazinyl)butyl]-2-

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mercaptoimidazole (500 mg, 1.44 mmol) was added 20 mL of THF, and the resulting suspension was stirred at 50 °C. After several hours, ^{11}B and ^{1}H NMR analysis of the mixture showed that an intermediate borane adduct, $\mathbf{I}_1$, was formed. This intermediate is slowly converted to the trihydroborate $\mathbf{L}^2$, this conversion being almost complete after 5 days of heating at 50 °C. Compound $\mathbf{L}^2$ was purified by successive recrystallizations from THF/*n*-hexane, as previously described for $\mathbf{L}^1$. Yield: 60% (330 mg, 0.86 mmol).

$\mathbf{I}_1$ − ^{1}H NMR (CD_3CN): 1.45 (2H, q, CH_2), 1.69 (2H, q, CH_2), 2.36 (2H, t, CH_2), 2.85−3.28 (8H, m, CH_2−N, pip), 3.80 (3H, s, CH_3−O), 3.95 (3H, tr, J_{H-H} = 6.8 Hz, CH_2−N), 6.62 (1H, br, CH), 6.78 (1H, br, CH), 6.87−7.01 (4H, m, Ph). ^{11}B NMR (CD_3CN): δ −11.6 ppm (br).

$\mathbf{L}^2$ − Analysis calculated for $C_{18}H_{28}N_4OBSNa$: C, 56.65%; H, 7.38%; N, 14.65%. Found: C, 55.84%; H, 7.05%; N, 14.35%. IR (Nujol, ν/cm^{-1}): 2288, 2250 ν(B−H). ^{1}H NMR (CD_3CN): δ 1.45 (2H, tr, J_{H-H} = 7.5 Hz, CH_2), 1.67 (2H, tr, J_{H-H} = 7.5 Hz, CH_2), 2.35 (2H, tr, J_{H-H} = 7.5 Hz, CH_2−N), 2.49 (4H, br, CH_2−N, pip), 2.97 (4H, br, CH_2−N, pip), 3.78 (3H, s, CH_3−O), 3.92 (2H, tr, J_{H-H} = 7.5 Hz, CH_2−N), 6.61 (1H, d, J_{H-H} = 2.1 Hz, CH), 6.65 (1H, br, CH), 6.86−6.97 (4H, m, Ph). ^{13}C NMR (CD_3CN): δ 24.5, 28.0, 47.5, 51.4, 54.2, 55.8, 112.6, 116.1, 119.0, 121.8, 123.4, 124.2, 142.7, 153.3, 161.6. ^{11}B NMR (CD_3CN): δ −19.3 ppm (br). ESI-MS (CH_3CN) *m*/*z*: calcd for $[C_{18}H_{28}N_4OSB]^-$ (found), 359.2 (359.3).

Synthesis of Na[H_3B(bzt)] ($\mathbf{L}^3$). To a mixture of sodium borohydride (250 mg, 6.6 mmol) and 2-mercaptobenzothiazole (1.12 g, 6.7 mmol) was added 20 mL of THF, and the resulting suspension was stirred at room temperature. Release of H_2 was observed immediately after addition of the solvent. After 4 h of stirring at room temperature, ^{1}H and ^{11}B NMR analysis of one aliquot of the reaction mixture showed the complete consumption of the benzothiazole and the nearly quantitative formation of $\mathbf{L}^3$. Compound $\mathbf{L}^3$ was purified and recovered as described for $\mathbf{L}^2$. Yield: 83% (1.123 g, 5.5 mmol). Analysis calculated for $C_7H_7NS_2BNa$: C, 41.37%; H, 3.47%; N, 6.89%. Found: C, 42.44%; H, 4.40%; N, 6.40%. IR (Nujol, ν/cm^{-1}): 2361, 2308, 2259 ν(B−H). ^{1}H NMR (DMSO-d_6): δ 7.09 (1H, d, J_{H-H} = 8.1, 1.5 Hz, CH), 7.24 (1H, d, J_{H-H} = 8.1, 1.5 Hz, CH), 7.44 (1H, d, J_{H-H} = 8.4, 1.2 Hz, CH), 7.57 (1H, d, J_{H-H} = 8.4 Hz, CH). ^{13}C NMR (DMSO-d_6): δ 117.5, 119.3, 122.4, 125.2, 130.2, 148.8, 188.3. ^{11}B NMR (CD_3CN): δ −20.3 (q, J_{B-H} = 100 Hz). ESI-MS (CH_3CN) *m*/*z*: calcd for $[C_7H_7NS_2B]^-$ (found), 180.0 (180.0).

Synthesis of *fac*-[^{99}Tc{κ^3-H(μ-H)$_2$B(tim^{Me})}(CO)$_3$] (1). $(NEt_4)_2[Tc(CO)_3Cl_3]$ (42 mg, 0.078 mmol) was dissolved in 4 mL of distilled water, and Na[H_3B(tim^{Me})] ($\mathbf{L}^2$) (20 mg, 0.134 mmol) was added to the resulting solution. Immediately after addition of the ligand, complex **1** precipitates in the form of a microcrystalline yellow solid. After stirring at room temperature for 1 h, complex **1** was collected by filtration, purified by washing with small portions of distilled water, and dried under vacuum. Yield: 79% (19 mg, 0.061 mmol). Raman (ν/cm^{-1}): 2483 ν(B−H); 2042, 1946 and 1925 ν(CO). ^{1}H NMR ($CDCl_3$): δ − 6.04 (2H, br, B−H···Tc), 3.71 (3H, s, CH_3−N), 4.63 (1H, br, B−H), 6.97 (1H, d, J_{H-H} = 2.1 Hz, CH), 7.04 (1H, d, J_{H-H} = 2.1 Hz, CH). ^{11}B NMR ($CDCl_3$): δ 8.2 ppm (m). ^{99}Tc NMR ($CDCl_3$): δ −1312 (br, $w_{1/2}$ = 1175 Hz).

Synthesis of *fac*-[Re{κ^3-H(μ-H)$_2$B(tim^{Me})}(CO)$_3$] (2). Solid Na[H_3B(tim^{Me})$_3$] (30 mg, 0.20 mmol) was added to a solution of $(NEt_4)_2[Re(CO)_3Br_3]$ (100 mg, 0.13 mmol) in distilled water and the mixture was stirred for 2 h at room temperature. The mixture was then centrifuged to recover a pale-yellow precipitate that was washed twice with 5 mL of distilled water. The solid was purified by silica gel flash chromatography using CH_2Cl_2/*n*-hexane (50/50) as eluent. After removal of the solvent from the collected fractions, complex **2** was obtained as a microcrystalline yellow solid. Yield: 62% (32 mg, 0.08 mmol). Analysis calculated for $C_7H_8N_2SO_3BRe$: C, 21.11%; H, 2.03%; N, 7.04%. Found: C, 21.69%; H, 1.82%; N, 6.87%. IR (KBr, ν/cm^{-1}): 2506 (w) ν(B−H); 2043 (s) and 1931 (vs) ν(CO). Raman (ν/cm^{-1}): 2495 ν(B−H); 2034, 1926 and 1914 ν(CO). ^{1}H NMR ($CDCl_3$): δ − 5.48 (2H, br, J_{B-H} = 80 Hz, B−H···Re), 3.73 (3H, s, CH_3−N), 6.20 (1H, br, B−H), 7.08 (1H, d, J_{H-H} = 2.1 Hz, CH), 7.17 (1H, d, J_{H-H} = 1.8 Hz, CH). ^{13}C NMR ($CDCl_3$): δ 34.8, 122.2, 123.2, 164.1, 190.3, 193.5. ^{11}B NMR ($CDCl_3$): δ 11.9 ppm (m).

Synthesis of *fac*-[Re{κ^3-H(μ-H)$_2$B(tim^{Bupip})}(CO)$_3$] (3). Compound **3** was prepared as described above for **2**, starting from 100 mg (0.13 mmol) of $(NEt_4)_2[Re(CO)_3Br_3]$ and 75 mg (0.20 mmol) of Na[H_3B(tim^{Bupip})] ($\mathbf{L}^2$). Compound **3** was purified by silica gel flash chromatography using a CH_2Cl_2/CH_3CN gradient, from 0 to 80% of CH_3CN. Yield: 27% (22 mg, 0.035 mmol). IR (KBr, ν/cm^{-1}): 2512 (w) ν(B−H); 2038 (s) and 1937 (vs) ν(CO). ^{1}H NMR ($CDCl_3$): δ −5.49 (2H, br, B−H···Re), 1.56 (2H, m, CH_2), 1.88 (2H, m, CH_2), 2.47 (2H, tr, CH_2), 2,65 (4H, br, N−CH_2), 3.09 (2H, br, N−CH_2), 3.84 (3H, s, CH_3−O), 4.10 (2H, tr, CH_2), 6.83−6.89 (4H, br, Ph), 7.09 (1H, d, J_{H-H} = 2.1 Hz, CH), 7.20 (^{1}H, d, J_{H-H} = 2.1 Hz, CH). ^{13}C NMR ($CDCl_3$): δ 23.6, 26.9, 48.1, 50.5, 53.4, 55.3, 57.7, 111.0, 118.1, 121.0, 122.1, 122.4, 123.0, 141.0, 152.2, 163.8, 193.6.^{11}B NMR ($CDCl_3$): δ 11.1 ppm (br). FT/ICR-MS (+) (*m*/*z*): 630 $[M]^+$.

Synthesis of *fac*-[Re{κ^3-H(μ-H)$_2$B(bzt)}(CO)$_3$] (4). Compound **4** was synthesized and purified as described for **2**, starting from 108 mg (0.14 mmol) of $(NEt_4)_2[Re(CO)_3Br_3]$ and 45 mg (0.22 mmol) of Na[H_3B(bzt)] ($\mathbf{L}^3$). Yield: 55% (35 mg, 0.078 mmol). Analysis calculated for $C_{10}H_7NS_2O_3BRe$: C, 26.67%; H, 1.57%; N, 3.11%. Found: C, 26.41%; H, 1.43%; N, 3.04%. IR (KBr, ν/cm^{-1}): 2514 (w) (B−H); 2040 (s) and 1930 (vs). ^{1}H NMR ($CDCl_3$) δ −5.67 (2H, br, J_{B-H} = 88 Hz, B−H···Re), 6.60 (1H, br, B−H), 7.45 (1H, m, CH), 7.55 (1H, m, CH), 7.64 (1H, d, J_{H-H} = 7.8 Hz, CH), 7.95 (1H, d, J_{H-H} = 8.1 Hz, CH). ^{13}C NMR ($CDCl_3$): δ 116.8, 122.9, 125.9, 127.7, 134.3, 144.0, 190.2, 192.3, 193.7. ^{11}B NMR ($CDCl_3$): δ 12.1 ppm (m).

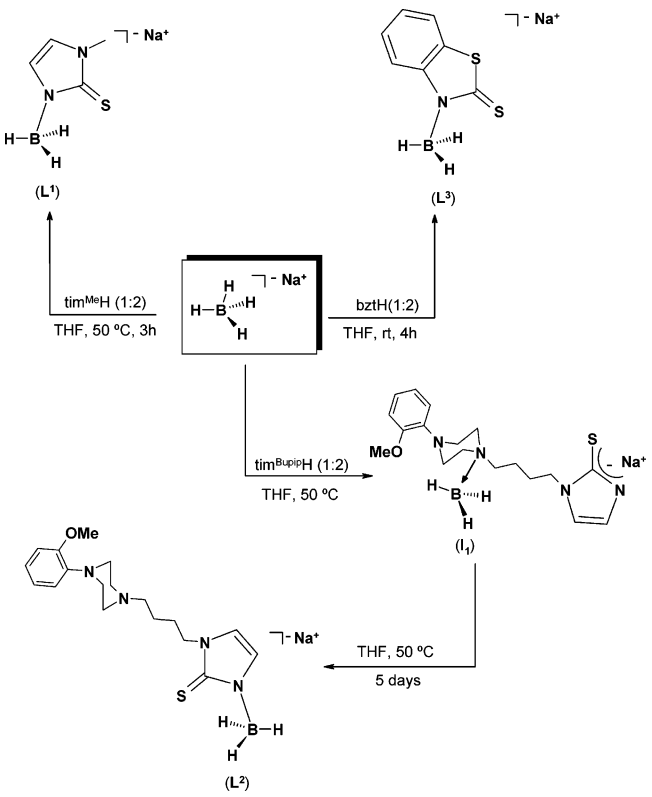
Synthesis of *fac*-[^{99m}Tc{κ^3-H(μ-H)$_2$B(tim^{Me})}(CO)$_3$] (1a). In a nitrogen-purged glass vial, 100 μL of a 2.5×10^{-2} M aqueous solution of ligand $\mathbf{L}^1$ was added to 400 μL (7.5 mCi) of the organometallic precursor *fac*-[^{99m}Tc$(OH_2)_3(CO)_3]^+$, and the mixture was incubated at room temperature for 30 min. After this time, complex **1a** has been obtained in 90% yield, as checked by gradient HPLC analysis. The chemical identity of **1a** was confirmed by comparing its HPLC chromatogram with the HPLC profile of the analogous ^{99}Tc complex **1** (retention time: **1**, 25.4 min; **1a**, 25.9 min).

X-ray Crystallography. Crystal data and experimental details are listed in Table 1. Suitable crystals of complexes **1** and **2** were covered with Paratone N oil, mounted on top of a glass fiber, and measured in a Stoe IPDS diffractometer. Crystal data for a yellow crystal of **4**,

Table 1. Crystallographic Data for Complexes **1**, **2**, and **4**

	1	2	4
lattice	monoclinic	monoclinic	triclinic
formula	$C_7H_8BN_2O_3STc$	$C_7H_8BN_2O_3SRe$	$C_{10}H_7BNO_3S_2Re$
F_w	309.02	397.22	450.30
space group	*P*21/*n*	*P*21/*n*	$P\bar{1}$
a/Å	13.3060(10)	13.1996(9)	7.306(1)
b/Å	7.0523(3)	7.1101(3)	11.841(1)
c/Å	13.6754(11)	13.5641(8)	16.476(3)
α/deg	90	90	71.669(10)
β/deg	118.449(8)	118.135(7)	77.421(13)
γ/deg	90	90	87.599(11)
Z	4	4	2
T/K	183(2)	183(2)	293(2)
ρ(calcd)/ g cm^{-3}	1.819	2.350	2.266
μ (Mo Kα)/ mm^{-1}	1.447	10.996	9.517
θmax/deg	30.5	30.5	27.0
n° of data	3406	3306	5718
n° of params	146	146	349
*R*1	0.0431	0.0663	0.0746
wR_2	0.0679	0.1324	0.1101
GOF	0.855	0.996	0.994

Scheme 2



mounted in a thin-wall capillary, were collected on an Enraf Nonius CAD4 diffractometer. Data were collected at 183(2) K (**1** and **2**) or at 293(2) K (**4**) using graphite-monochromated Mo Kα radiation. Data were corrected for Lorentz and polarization effects as well as for absorption (numerical). Structures were solved with direct methods using SIR97[22] and were refined by full-matrix least-squares methods on F^2 with SHELXL-97.[23] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms linked to the boron atoms were located in difference Fourier map and refined isotropically. The remaining hydrogen atoms were placed in calculated positions.

Results

Synthesis of trihydro(mercaptoazolyl)borates. Slow addition of $tim^{Me}H$ to a suspension of $NaBH_4$ in THF at 50 °C, in a 1:2 molar ratio, followed by heating at 50 °C for 3 h led to the trihydro(mercaptoimidazolyl)borate $Na[H_3B(tim^{Me})]$ (**L**^{1}) (Scheme 2). **L**^{1} was purified by recrystallization from THF/*n*-hexane and obtained in 34% isolated yield. The successful synthesis of **L**^{1} prompted us to further explore the preparation of a related ligand with 2-mercaptoimidazole, functionalized with a small biomolecule. 1-[4-((2-methoxyphenyl)-1-piperazinyl)butyl]-2-mercaptoimidazole ($tim^{Bupip}H$) was selected because of its high affinity and selectivity for serotonin 5-HT_{1A} receptors, as previously reported by our group.[21] By reacting $tim^{Bupip}H$ with $NaBH_4$ under conditions as described for **L**^{1} (Scheme 2), we found that after several hours, at 50 °C, an intermediate compound, which was not the desired trihydro(mercaptoazolyl)-borate **L**^{2}, was formed. The ^{11}B NMR spectrum of the reaction mixture displayed a broad resonance at −11.6 ppm, considerably downfield shifted from the ^{11}B frequency of $Na[H_3B(tim^{Me})]$ (**L**^{1}) (δ (^{11}B) = −19.0 ppm). Keeping the reaction mixture at 50 °C for an extended period of time promoted a slow decrease of the ^{11}B resonance at −11.6 ppm and, concomitantly, the increase of a new ^{11}B signal at −19.3 ppm. This signal corresponds to **L**^{2} as was confirmed by ^{1}H, ^{13}C, NMR, IR, elemental analysis and mass spectrometry. Thus, the synthesis of **L**^{2} takes place through an intermediate **I**$_{1}$ which is almost quantitatively converted to **L**^{2} after 5 days at 50 °C. **L**^{2} was purified by successive recrystallizations from THF/*n*-hexane, and finally obtained in 60% yield.

The synthesis of **L**^{3} was straightforward. For example, the reaction of $NaBH_4$ with a slight excess of bztH in THF, at room temperature, yielded **L**^{3} in high yield. The authenticity of **L**^{3} was confirmed by ^{1}H and ^{11}B NMR analysis (**L**^{3}, δ(^{11}B) = −20.3 ppm) and by ESI-MS.

The novel ligands **L**^{1}-**L**^{3} are white, hygroscopic, microcrystalline solids, soluble in common organic solvents and in water. Importantly, all of them can be kept in aqueous solution without significant hydrolysis to boronic acids. Hydrolytic stability is essential for the use of these scorpionate ligands in the development of radiopharmaceuticals.

Synthesis of the ^{99}Tc and Re Complexes. The reaction of an aqueous solution of $(NEt_4)_2[^{99}TcCl_3(CO)_3]$ or $(NEt_4)_2[ReBr_3(CO)_3]$ with stoichiometric amounts of **L**^{1} affords the complexes *fac*-$[M\{\kappa^3\text{-}H(\mu\text{-}H)_2B(tim^{Me})\}(CO)_3]$ (M = ^{99}Tc (**1**), Re (**2**)). They precipitate from the reaction mixtures as pale-yellow microcrystalline solids. Similarly, the complexes *fac*-$[Re\{\kappa^3\text{-}H(\mu\text{-}H)_2B(tim^{Bupip})\}(CO)_3]$ (**3**) and *fac*-$[Re\{\kappa^3\text{-}H(\mu\text{-}H)_2B(bzt)\}(CO)_3]$ (**4**) were obtained from water (Scheme 3).

The reactions in Scheme 3 occur very quickly, with compounds **1**−**4** beginning to form almost immediately after addition of the corresponding ligands. The purification of the ^{99}Tc complex **1** involved successive washings with distilled water, whereas for the Re complexes (**2**−**4**), silica gel column chromatography was needed to obtain analytically pure compounds.

Spectroscopic Characterization of the ^{99}Tc and Re Complexes. The most interesting feature of the ^{1}H NMR spectra of **1**−**4** are high-field shifted resonances between −6.04 and −5.48 ppm, integrating for two protons each. Due to their chemical shifts, these signals were assigned to the two bridging hydrides involved in the three center-two electrons (3c-2e) B−H···M (M = Re, Tc) bonds. These resonances appear in a quite narrow range for the Re complexes (**2**−**4**: −5.48 to −5.67 ppm) but are more high field shifted for the Tc complex **1** (−6.04 ppm). The chemical shifts of the B−H···M resonances of **1**−**4** are relatively close to the values previously found for related Re(I) tricarbonyl complexes anchored by (κ^3-H,S,S′) dihydrobis(mercaptoimidazolyl)borate ligands (−5.20 to −6.71 ppm).[11−14] The B−H···Tc resonance in complex **1** ($w_{1/2}$ = 600 Hz) is considerably broader than the B−H···Re resonances in **2**−**4** ($w_{1/2}$ = 150−200 Hz), reflecting the effect of the quadrupolar ^{99}Tc nucleus (Figure 1). The scalar coupling J_{B-H} between the boron and the bridging hydrides in **2** and **4** are 80 and 88 Hz, respectively. A smaller scalar coupling constant would be expected for complexes containing σ-boryl and hydride ligands.[24]

The terminal B−H protons for **2** and **4** are broad quartets at 6.20 and 6.60 ppm, respectively. For **1**, this resonance is at 4.63 ppm and is much broader. The presence of distinct resonances

(22) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115−119.
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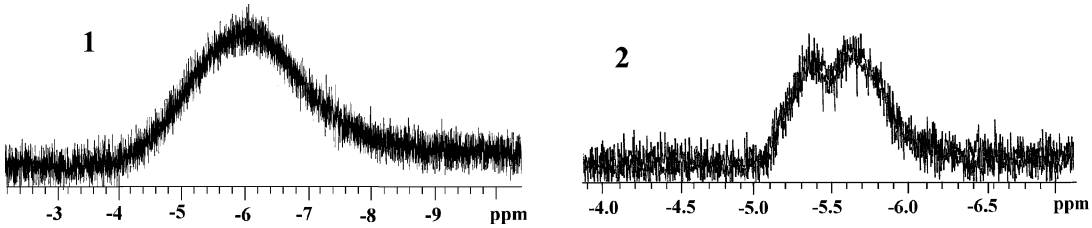
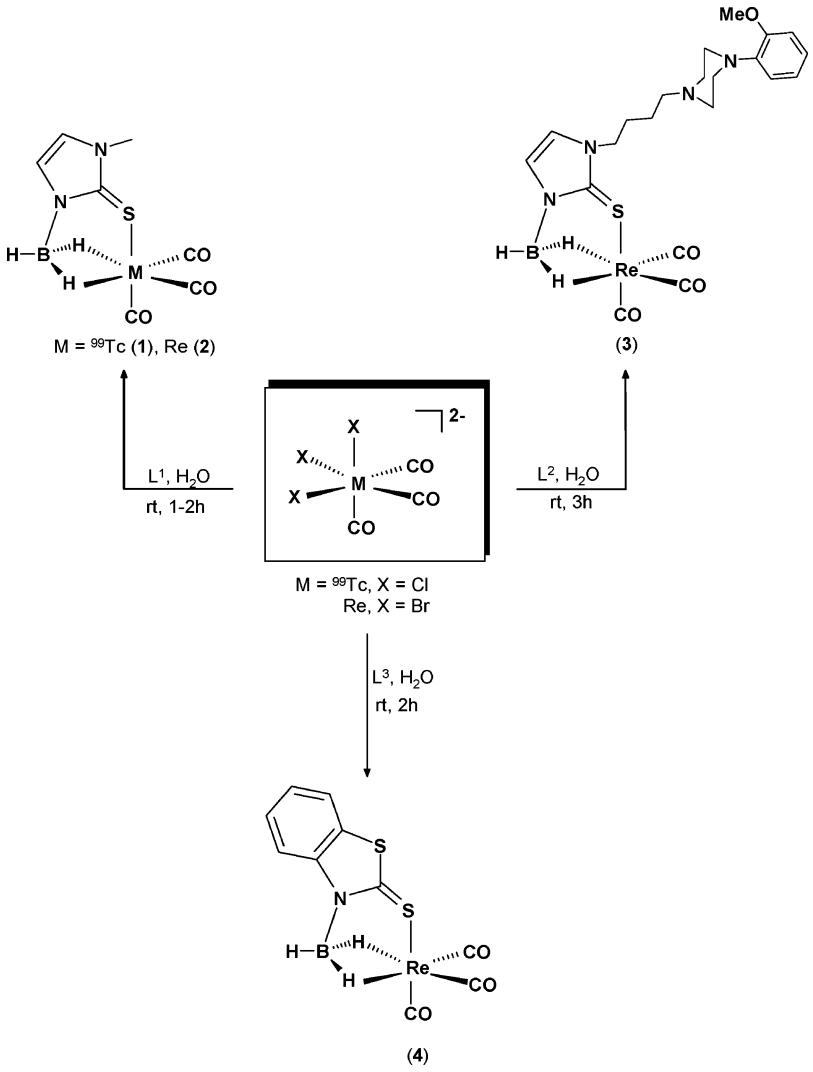


Figure 1. ^{1}H NMR spectra of complexes **1** and **2** in the hydride region.

Scheme 3



for the terminal B−H and bridging B−H···M hydrides clearly implies no fluxional process in solution, as often observed for complexes bound to borohydrides.[24]

The ^{11}B NMR resonances appear as broad multiplets (**1**, **2** and **4**) or broad singlets (**3**), in the range 8.2−12.1 ppm, consistent with the presence of B−H···M bonds (M = Re, ^{99}Tc). Due to broadness, the multiplicity could not be ascertained accurately, but the profile of some of the signals showed that the ^{11}B nuclei are coupled to magnetically different ^{1}H nuclei, i.e., to the terminal and bridging hydrides (Figure 2). Due to the quadrupolar moment of the ^{99}Tc nucleus ($I = 9/2$), the ^{99}Tc signal of **1** appears as a broad singlet at −1312 ppm ($w_{1/2}$ = 1175 Hz) without any resolved coupling to the coordinated hydrides (Figure 2). The ^{11}B resonances for **1**−**4** are strongly downfield shifted as compared to the free ligands. The shifts span between $\Delta\delta$ = 27.2 ppm and $\Delta\delta$ = 32.4 ppm. This behavior markedly contrasts with the one for complexes *fac*-[Re{κ^3-R(μ-H)B(tim^{Me})$_2$}(CO)$_3$] in which ^{11}B chemical shifts are almost identical to the respective free ligands.[11−14] These differences reflect the formation of two B−H···M bonds in **1**−**4** and the consequent increasing of electronic deficiency at boron.

The IR spectra of **2**−**4** show ν(B−H) stretching bands in the range 2506−2514 cm^{-1}. The ν(B−H···Re) bands could not be identified in the spectra due to overlap with the two strong CO bands between 1930 and 2040 cm^{-1}.

Complexes *fac*-[M{κ^3-H(μ-H)$_2$B(tim^{Me})}(CO)$_3$] (M = ^{99}Tc (**1**), Re (**2**)) were also studied by Raman spectroscopy, and the

(24) Marks, T. J.; Kolb, J. R. *Chem. Rev.* **1977**, *77*, 263−293.

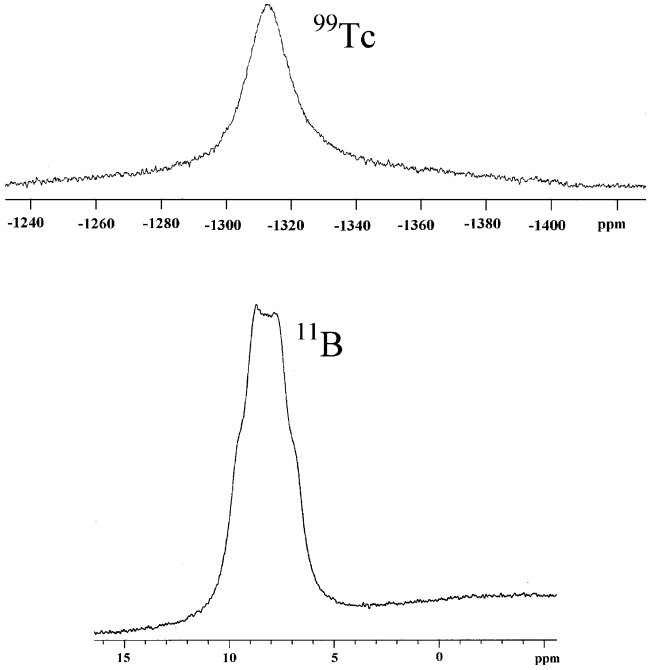


Figure 2. $^{99}Tc\{^1H\}$ and $^{11}B\{^1H\}$ NMR spectra of complex **1**.

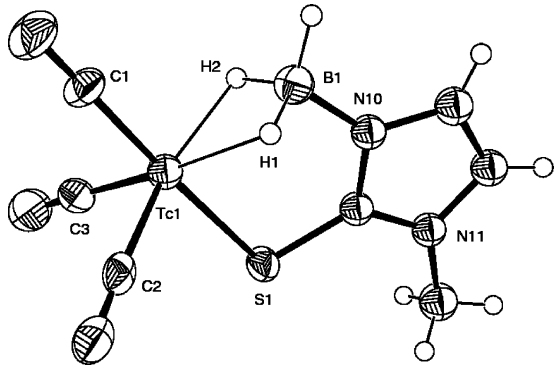


Figure 3. ORTEP view of *fac*-[^{99}Tc{κ^3-H(μ-H)$_2$B(tim^{Me})}(CO)$_3$] (**1**) with ellipsoids drawn at the 40% probability level. Selected bond distances (Å) and angles (deg): Tc−C(1) 1.940(3), Tc−C(2) 1.905(3), Tc−C(3) 1.938-(2), Tc−H(1) 1.89(3), Tc−H(2) 1.94(3), Tc−S(1) 2.4739(6), Tc−B 2.329-(3), H(2)−Tc−H(1) 61.5(12), H(2)−Tc−S(1) 84.5(8), H(1)−Tc−S(1) 86.7(8), C(2)−Tc-B 132.51(11), C(3)−Tc−B 138.53(11).

vibrational spectra obtained had well-defined and sharp peaks. The bridging ν(B−H···M) bands could not be assigned and the terminal ν(B−H) vibration peaks appear at 2483 and 2495 cm^{-1} for **1** and **2**, respectively. As expected for complexes with a C_s symmetry and a facial arrangement of the three carbonyl ligands, **1** and **2** present three peaks in the ν(CO) stretching region (**1:** 2042, 1946, 1925 cm^{-1}; **2**: 2034, 1926, 1914 cm^{-1}), corresponding to the A_1 and to the resolved *E* vibration modes.[25]

Structural Characterization of Complexes 1, 2, and 4. Single crystals of **1**, **2**, and **4** were grown by cooling saturated hexane solutions. Complexes **1** and **2** are isomorphous and isostructural. An ORTEP presentation of complex **1** is given in Figure 3. For **4**, two crystallographically independent but chemically equivalent molecules per asymmetric unit are present. One of the two independent molecules of **4** is depicted in Figure 4.

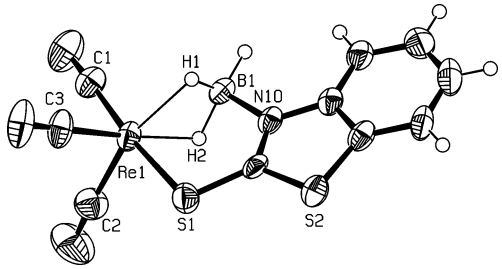


Figure 4. ORTEP view of molecule 1 of *fac*-[Re{κ^3-H(μ-H)$_2$B(bzt)$_2$}-(CO)$_3$] (**4**) with ellipsoids drawn at the 40% probability level. Selected bond distances (Å) and angles (deg): Re(1)−C(1) 1.921(9), Re(1)−C(2) 1.927-(10), Re(1)−C(3) 1.928(10), Re(1)−H(1) 1.93(7), Re(1)−H(2) 1.63(16), Re(1)−S(1) 2.447(2), Re(1)−B(1) 2.282(10), H(2)−Re(1)−H(1) 55(6), H(2)−Re(1)−S(1) 73(5), H(1)−Re(1)−S(1) 80(2), C(2)−Re(1)−B(1) 133.7 (4), C(3)−Re(1)−B(1) 135.2(4).

The coordination geometries around the central atoms in **1**, **2**, and **4** are distorted octahedral. One face of the coordination polyhedron is defined by the carbonyl ligands, whereas the three remaining positions are occupied by two hydrides and the sulfur atoms from $\mathbf{L^1}$ and $\mathbf{L^3}$, respectively. For all of the structures, the boron-linked hydrogens have been located in the difference Fourier map and refined isotropically.

Coordination of the BH_2 motif in **1**, **2**, and **4** to the metal is relatively symmetrical, as shown by the similar C(2)−M−B and C(3)−M−B bond angles. For **1** and **2**, respectively, the two Tc−H (1.89(3) and 1.94(3) Å) and Re−H (1.93(10) and 1.98(10) Å) bond distances vary in a relatively narrow range, whereas larger differences were found for the two Re−H bond distances in complex **4** (molecule 1: 1.62(16) and 1.93(7) Å; molecule 2: 1.77(7) and 1.87(10) Å). These results may be due to the different temperature used in the measurement of the crystals (**1**, **2**, 183(2) K); **4** (293(2) K).

The Tc−H bond distances in **1** are significantly larger than the corresponding bond distance in *fac*-[Tc{κ^3-H(μ-H)B(tim^{Me})$_2$}-(CO)$_3$] (1.65 (6) Å).[11] Unfavorable repulsive interactions between the metal and the central boron atom by the shortening of both Tc−H bonds in **1** is likely to account for this observation. The Re−H distances in **2** are comparable to the values reported by Berke et al. for the bridging hydrides in [Re-(CO)$_2$(PMe$_3$)(κ^2-BH$_4$)] (1.80(6) and 1.93(6) Å),[26] a relatively rare example of an organometallic Re(I) complex containing a bidentate borohydride ligand.

In complexes **1**, **2**, and **4**, the chelation of the two bridging hydrogen atoms causes small H−M−H bite angles (55(6)−63-(4) Å) and relatively short M−B distances (2.282(10)−2.329 Å). Nevertheless, the M−B (M = Tc, Re) distances are larger than the sum (2.10 Å) of the covalent radii of Tc or Re and boron, being comparable to the Re−B distance (2.329(9) Å) found in the aforementioned Re(I) complex with κ^2-BH$_4$.[26] As expected, the Re−B distances in all **1**, **2**, and **4** are considerably shorter than the values (2.79(2)−2.92 Å) previously described for bis(mercaptoimidazolyl)borate chelators coordinated in (κ^3-S, S′, H) fashion.[11−13]

In **1**, **2**, and **4**, the intraligand bond distances and angles are normal and the M−S (M = Tc, Re) bond distances (**1**, 2.4739-(6); **2**, 2.470(2) Å; **4**, 2.447 (2) Å) are comparable (**1** and **2**) or slightly shorter (**4**) than the Tc−S or Re−S distances (2.462-

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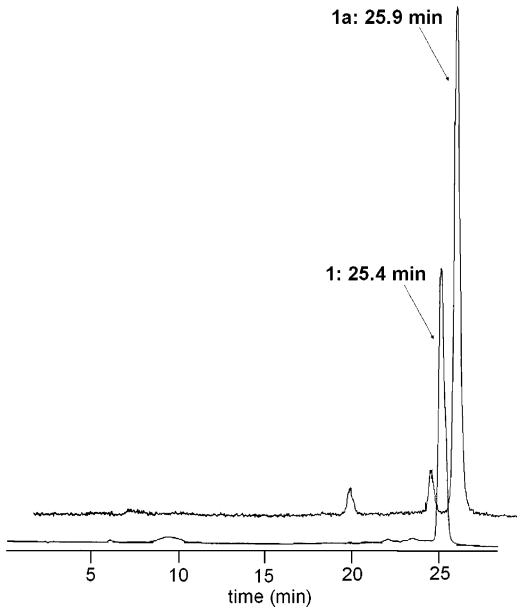

Figure 5. HPLC chromatograms for complexes *fac*-[M(k^3 − $\mathbf{L^1}$)$(CO)_3]^+$ (M = ^{99}Tc (**1**), ^{99m}Tc (**1a**))

(6)−2.5190(11) Å) previously reported for *fac*-[M{κ^3-R(μ-H)B-$(tim^{Me})_2$}$(CO)_3$] (M=Tc, Re).[11−13]

Labeling Studies. The results on the macroscopic level demonstrated the feasibility of preparing trihydro(azolyl)borate *fac*-$[M(CO)_3]^+$ complexes with (κ^3-H, H′, S) coordination mode in water and motivated further studies at the no carrier added level with ^{99m}Tc. Macroscopically, one might argue that these bis-agostic complexes can only be isolated due to their insolubility in water. This does not necessarily hold true for highly diluted (1−100 nM) solutions of ^{99m}Tc, in which the complexes are completely dissolved in aqueous solutions. Insight into the preparation for compounds of this type with ^{99m}Tc was received from the reaction of the aqua-ion precursor *fac*-[^{99m}-$Tc(H_2O)_3(CO)_3]^+$ with $\mathbf{L^1}$. In aqueous solution and at room temperature, $\mathbf{L^1}$ coordinates readily at mM concentrations and affords the complex *fac*-[^{99m}Tc{κ^3-H(μ-H)$_2$B(tim^{Me})}$(CO)_3$] (**1a**) in 90% radiochemical yield (Figure 5). The chemical identity of **1a** (retention time = 25.4 min) was confirmed by comparing its HPLC profile with the one of the fully characterized ^{99}Tc complex (**1**, retention time = 25.9 min). The long retention times of complexes **1**/**1a** are among the highest values ever observed for $[Tc(CO)_3]^+$-based complexes and indicate highly lipophilic properties, which is in agreement with the solubility of **1** in apolar organic solvents and even in *n*-hexane. Stability studies with **1a** in phosphate buffer at 37 °C, as checked by HPLC at different intervals of time, did not show any cleavage of the ligand or oxidation to $[^{99m}TcO_4]^-$ over at least 6 h. Despite having an uncommon set of donors, rate of formation and stabilities imply that trihydro(2-mercaptoimidazolyl)borates are good ligands, even at the no-carrier added level (^{99m}Tc), and compare well with dihydrobis(mercaptoimidazolyl)borates.[11,14]

Discussion

The pyrazolyl derivatives of poly(azolyl)borates are the most thoroughly studied scorpionates since their introduction by Trofimenko in the 1960s.[1−3] More recently, their soft congeners, the poly(mercaptoimidazolyl)borates, have received considerable attention.[7,8] For both families a wide variety of complexes with d- and f-transition metals has been reported.[1−9] Surprisingly, chemistry with these tripods has been based exclusively on bis-, tris-, or tetrakis(azolyl)borates and the chemistry of trihydro(azolyl)borates is essentially unexplored. Until recently, none of these ligands has been considered for medicinal or biological purposes. Following our work on bifunctional poly(mercaptoimidazolyl)borates for the development of target-specific radiopharmaceuticals, we extended the investigations to trihydro(mercaptoazolyl)borates, the smallest member of this family of soft scorpionates. As outlined in the Introduction, bifunctional, low molecular weight, and small-sized chelators are crucial for retaining receptor affinity and specificity of ^{99m}Tc labeled targeting vectors. Complexes with the lowest molecular weight investigated for medicinal applications are, so far, piano stool-like $[CpTc(CO)_3]$ compounds.[27] Cyclopentadienyl is an attractive but difficult ligand in water due to its high basicity and instability. Other tripods, such as histidine, are more bulky.[28] Reducing molecular weight of donors is limited in classical coordination chemistry but is feasible in organometallic chemistry where agostic hydride binding (a donor of MW = 1!) is not uncommon. The ligands presented herein act in the same way, two classical Werner type donors are replaced by two agostic hydrides resulting in small complexes of low molecular weight. These novel ligands were explored as model chelators only, as well as in the so-called pendant and integrated approach for designing bio specific organometallic complexes of Re and Tc.

As a model, we synthesized Na$[H_3B(tim^{Me})]$ ($\mathbf{L^1}$). During the synthesis of $\mathbf{L^1}$, the previously described compound Na-$[H_2B(tim^{Me})_2]$ (δ (^{11}B) = −2.8 ppm) also formed. Experimental parameters such as molar ratio of reagents, temperature, and reaction time have been varied to optimize the yield of $\mathbf{L^1}$ to approximately 75%.

For a pendant approach, we prepared a trihydro(mercaptoazolyl)borate conjugated to an arylpiperazine pharmacophore between one of the nitrogen atoms of the azole ring and the secondary N of the piperazine ring by using $(tim^{Bupip}H)$.[21] For the integrated approach in which part of the biomolecule backbone is replaced by a metal chelate,[29] we focused on 2-mercaptobenzothiazole. The benzothiazole fragment is present in a series of amyloid-binding organic molecules, namely in the compound *N*-methyl-[^{11}C]-2-(4′-methyl aminophenyl)-6-hydroxybenzothiazole, commonly designated as the Pittsburgh Compound-B (PIB). PIB has recently been approved for clinical use as a positron emission tomography (PET) tracer for imaging β-amyloid deposition in the brain of Alzheimer's patients.[30,31] Hence, we expect that (benzothiazolyl)trihydroborates ($\mathbf{L^3}$) could lead to small and lipophilic organometallic ^{99m}Tc complexes, potentially useful for targeting β-amyloid plaques.

The preparation of $\mathbf{L^1}$−$\mathbf{L^3}$ is very different in terms of reactivity and pathway. Whereas the reaction of $tim^{Me}H$ with

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(31) Klunk, W. E.; Engler, H.; Nordberg, A.; Wang, Y.; Blomqvist, G.; Holt, D. P.; Bergstrom, M.; Savitcheva, I.; Huang, G. F.; Estrada, S.; Ausen, B.; Debnath, M. L.; Barletta, J.; Price, J. C.; Sandell, J.; Lopresti, B. J.; Wall, A.; Koivisto, P.; Antoni, G.; Mathis, C. A.; Langstrom, B. *Ann. Neurol.* **2004**, *55*, 306−319.

$NaBH_4$ is fast, the functionalized 2-mercaptoimidazole ($tim^{Bupip}H$) reacted much slower and through an intermediate $\mathbf{I_1}$. After several hours at 50 °C an intermediate compound could be identified. The ^{11}B NMR spectrum of the reaction mixture displayed a broad boron resonance at −11.6 ppm, considerably downfield shifted from the ^{11}B frequency of $\mathbf{L^1}$ (δ (^{11}B) = −19.0 ppm). Keeping the reaction mixture at 50 °C promoted a decrease of the ^{11}B resonance at −11.6 ppm and a concomitant appearance of a new ^{11}B signal at −19.3 ppm, due to the desired product ($\mathbf{L^2}$). The authenticity of the intermediate $\mathbf{I_1}$ (Scheme 2), a kinetic product, was based on the ^1H and ^{11}B NMR spectroscopy of the reaction mixture. The ^1H NMR spectra of $\mathbf{I_1}$ in CD_3CN displayed a complex set of multiplets, between 2.8 and 3.3 ppm, due to the methylenic protons of the piperazinyl ring. The pattern obtained for these protons contrasts with the one displayed by the same protons in compounds $tim^{Bupip}H$ and $\mathbf{L^2}$, which originate two well-defined resonances of equal intensity at 2.49 and 2.97 ppm. The splitting and the low field shift of the piperazinyl N−CH_2 protons of $\mathbf{I_1}$ suggest an interaction between the piperazinyl nitrogen and the electron deficient boron atom (Scheme 2).[32] Most probably, a borane adduct of the type "H_3B.$timBu^{pip}$" is formed rationalizing the ^{11}B NMR chemical shift of $\mathbf{I_1}$ (−11.6 ppm), a range where BH_3-amine adducts typically appear.[33] Finally, the chemical shift of the methine protons from the mercaptoimidazolyl moiety of $tim^{Bupip}H$ (6.83 and 6.70 ppm) and $\mathbf{I_1}$ (6.78 and 6.62 ppm) are relatively close, showing that the azole ring is not directly involved in the interaction with boron.

The formation of $\mathbf{I_1}$ indicates that sodium borohydride is acting as a source of BH_3 in the presence of $tim^{Bupip}H$. In this process, the mercaptoimidazole group must behave as a hydride acceptor, whereas the piperazinyl fragment traps the released borane. The adduct $\mathbf{I_1}$ seems to be a kinetically favored species, being converted to Na[$H_3B(tim^{Bupip})$] ($\mathbf{L^2}$), upon prolonged heating at 50 °C. The synthesis of amine-boranes by reaction of borohydrides with hydride acceptors is a well-known process.[34]

Due to the high acidity of benzothiazole, $NaBH_4$ reacts with bztH (pK_a = 4.2) considerably faster than with $tim^{Me}H$ (pK_a = 4.7) or $tim^{Bupip}H$, leading exclusively to $\mathbf{L^3}$.[35]

The novel ligands $\mathbf{L^1}$−$\mathbf{L^3}$ have different possibilities for coordination to a metal center. Monodentate sulfur coordination only would not be versatile for biomedical application because two coordinating sites remain occupied with water and are available for binding to competing sites in serum such as sulfur or nitrogen from serum proteins.[36] Coordination of one sulfur and one hydride entails the same problem. Occupation of all three sites by one sulfur and two hydrides results in a complex with the three coordinating sites occupied by one single ligand. This type of coordination has not been observed to date since agostic interactions are usually weak and easily replaced by other two electron donors such as water. Still, the three ligands ($\mathbf{L^1}$−$\mathbf{L^3}$) reacted promptly in water with the aquo-carbonyl precursors $[M(OH_2)_3(CO)_3]^+$, affording *fac*-[M{κ^3-H(μ-H)$_2$B-(tim^{Me})}$(CO)_3$] (M = ^{99}Tc (**1**), Re (**2**)), *fac*-[Re{κ^3-H(μ-H)$_2$B-(tim^{Bupip})}$(CO)_3$] (**3**), and *fac*-[Re{κ^3-H(μ-H)$_2$B(bzt)}$(CO)_3$] (**4**), respectively, in which the two hydrides replaced one water ligand each. The structural analysis of **1**, **2**, and **4** confirmed the presence of two bridging B−H···M hydrides, which are maintained in solution, as shown by ^1H, ^{13}C, and ^{11}B NMR data.

We want to emphasize at this point that the ability of $\mathbf{L^1}$−$\mathbf{L^3}$ to coordinate with two of its hydrides to a metal center paves the avenue for a completely new set of ligands in inorganic medicinal chemistry in general, and for radiopharmacy in particular. It might be anticipated that the agostic ligands are readily replaced by coordinating solvents and that complexes **1**−**4** are stable in noncoordinating solvents only. To prove the concept for the versatility of these ligands, we switched to labeling experiments with ^{99m}Tc, the metastable radionuclide used in nuclear medicine. Because concentrations are very low, solubility is not an issue and even very lipophilic complexes remain in solution, thus maintaining a homogeneous solution. Labeling occurred at low ligand concentration and at ambient conditions. The yield of the ^{99m}Tc complexes was close to quantitative as verified with HPLC analysis of the reaction solutions. Trihydro(mercaptoazolyl)borates are, thus, able to compete with water or chloride ligands and replace them irreversibly. Once formed, the complexes are also stable for hours in PBS (phosphate buffer 0.9% NaCl) without reoxidation or hydrolysis of the ligand taking place. The complexes are especially suited for the labeling of small biomolecules, namely CNS receptor ligands for which small sized metal fragments are of utmost importance. Currently, we are investigating the in vivo behavior of these complexes as well as the replacement of the mercaptoimidazolyl group by other, even smaller coordinating functionalities.

Conclusions

Despite strong competition from other imaging techniques such as PET, the importance of ^{99m}Tc in nuclear medicine is well recognized. One great challenge is to find specific radiopharmaceuticals, for diagnostic and/or therapy of cancer, central nervous system (CNS) diseases, or metabolic disorders. The incorporation of a *d*-transition metal into a biomolecule for molecular imaging is a challenge, because the metabolic fate and biophysical properties must not be affected. For CNS receptor ligands, low molecular weight and lipophilicity of the radiopharmaceuticals is crucial for crossing the blood brain barrier (BBB). Many traditional chelators have been investigated for that purpose, with little success so far. Soft scorpionates have rarely been considered as bifunctional chelators, and we have been exploring this family of compounds for medical applications.[9] In this work, we described a general approach for the synthesis and characterization of a novel class of ligands, trihydro(azolyl)borates (azolyl= mercaptoazolyl and benzothiazolyl), which are the smallest soft scorpionates described so far. By this strategy, it is possible to introduce the "BH_3" moiety into biomolecules for later labeling with the [^{99m}Tc$(CO)_3$]$^+$ core. We have shown, for the first time, that is possible to stabilize Re and Tc tricarbonyl complexes with trihydro(azolyl)borates which coordinate through two B−H···M agostic interactions and one sulfur atom of the azolyl ring. The resulting building

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blocks can be used to incorporate small biomolecules, using the so-called pendant or integrated approaches. We have also shown that these complexes can be prepared at the no carrier added level (^{99m}Tc). The final complexes are stable in aqueous solution, even in the presence of high NaCl concentrations. Thus, the unprecedented *fac*-[Tc{κ^3-H(μ-H)$_2$B(azolyl)}(CO)$_3$] maintains its (κ^3-H, H′, S) coordination motif even in water.

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Supporting Information Available: Crystallographic data for complexes **1**, **2**, and **4** and ORTEP diagram for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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