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The synthesis and X-ray crystallographic structure determination of 3-isocyano-1,2-dicarba-*closo*-dodecaborane-Re(I) complexes

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Abstract

3-Isocyano-1,2-dicarba-*closo*-dodecaborane, otherwise referred to as 3-isonitrilecarborane (L), reacts with $[NEt_4]_2[Re(CO)_3Br_3]$ and $[Re(CO)_3(solv.)_3]^+$ in a manner similar to that of aliphatic isonitriles resulting in the formation of compounds of the general formulae $[Re(CO)_3L_2Br]$, $[Re(CO)_3L_3]^+$ and $[Re(CO)_3L_2L']$, where L′ denotes a nido-carborane isonitrile ligand. The latter compound, whose structure was determined crystallographically, has an overall neutral charge as a result of a deboronation reaction which takes place upon recrystalization of the complex. We also observed that the ligand L has the ability to displace CO ligands from $[Re(CO)_3(solv.)_3]^+$, which led to the formation of $[Re(CO)_2L_4]^+$.

Keywords: Carboranes; Isonitriles; Rhenium; BNCT; BNCS; X-ray

1. Introduction

Boron neutron capture therapy (BNCT) is a binary approach to cancer treatment originally proposed by Locher in 1936 [1] that entails exposing cells enriched with ^{10}B with thermal neutrons. One of the allures of BNCT is its potential for achieving selective cell killing [2,3]. This feature is a consequence of the fact that the daughters of the boron neutron capture reaction, an alpha particle and lithium ion, traverse a distance which is similar to the diameter of a typical cell [4], thereby depositing highly ionizing radiation within a confined area. A related technique, boron neutron capture synovectomy (BNCS) [5,6], has been recently proposed as a way of treating severe cases of rheumatoid arthritis that do not respond to conventional therapies and as a potentially safer and more selective alternative to radiation synovectomy.

Because pharmacokinetics, in addition to the selectivity, plays an important role in achieving successful therapeutic outcomes, a number of researchers have begun using clinical imaging modalities such as magnetic resonance imaging (MRI) [7,8] and positron emission tomography (PET) [9] to evaluate new BNCT/BNCS agents in both animal models and in human subjects. The latter technique, along with single photon emission computed tomography (SPECT) [10], is a particularly attractive means of rapidly evaluating compounds in animals, as opposed to the arduous and expensive method of measuring boron concentrations in excised animal tissue samples. The opportunity for using imaging modalities for this type of research is greatly enhanced with the advent of dedicated small animal PET and SPECT scanners [11,12].

We are interested in developing a highly flexible class of targeted BNCT/BNCS agents that will allow for the inclusion of diagnostic radionuclides without changing the overall structure of the parent compound. Our proposed strategy (Fig. 1) involves the preparation of transition metal-derived BNCT agents in which a bifunctional carborane, linked to a targeting agent, is coordinated to a metal (M) through a donor group (X). By increasing the coordination number, through the judicious choice of M and X, the number of boron

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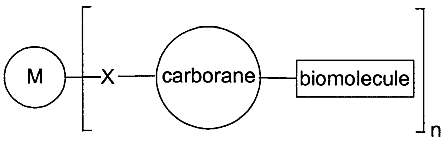


Fig. 1. Metal complexes as BNCT/BNCS agents.

atoms in a given molecule can be increased and furthermore, the metal can be conveniently interchanged with a radioactive isotope of M, without altering the structure of the complex. Having multiple biomolecules in one complex (i.e. for values of $n > 1$) also presents the opportunity for achieving enhanced receptor selectivity through multi-valent binding effects.

Herein we describe the synthesis and characterization of a model system which utilizes rhenium as the core metal and 3-isonitrilecarborane as the boron containing ligand. This particular system was selected because isonitrile complexes of ^{99m}Tc are widely used in clinical nuclear medicine and therefore have some of the intrinsic properties (stability, ease of synthesis in water, etc.) that are needed to construct metal-based BNCT agents. The goal of this work was to study the coordination chemistry of the carborane–isonitrile ligand in comparison to aliphatic isonitriles, as a means of evaluating the suitability of this ligand system for the synthesis of Re/^{99m}Tc-derived BNCT and BNCS agents.

2. Results and discussion

Zakharkin et al. reported the synthesis of a series of metal complexes using 3-isonitrilecarborane (L) **1** including [$Re(CO)_3L_2Br$], which was prepared from $Re(CO)_5Br$ [13]. Unfortunately, the extent of characterization of the reported compounds was typically limited to elemental analysis and IR. Moreover, $Re(CO)_5Br$ is an unsuitable starting material with respect to our long term goals because the corresponding ^{99m}Tc analogue is not currently accessible. We therefore sought to thoroughly investigate the reaction of 3-isonitrilecarborane with $[Re(CO)_3X_3]^n$ (X = Br, $n = -2$; X = THF, $n = +1$) [14], for which the analogous ^{99m}Tc complexes are readily available and frequently used for labelling biomolecules [15].

2.1. Reaction of compound **1** with $[Re(CO)_3Br_3]^{2-}$

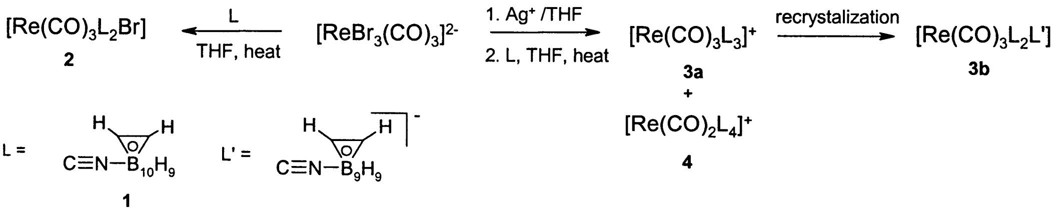
The isonitrile **1**, which was prepared following a literature method [16], was heated with the $[NEt_4]_2[Re(CO)_3Br_3]$ in THF overnight (Scheme 1) and the product, $Re(CO)_3L_2Br$, isolated by either preparative TLC or radial chromatography (20%). IR of **2** shows a series of CO stretches at 2042, 2004 and 1956 cm^{-1}, which are consistent with the expected symmetry of the product. These values are in reasonable agreement with the stretches reported for *fac*-$Re(CO)_3(CNMe)_2Br$ [17]. The BH stretch is observed at 2602 cm^{-1}, while the CN stretches are within expected values appearing at 2183 and 2132 cm^{-1}. The negative ion ESMS of the product contains the molecular ion at an *m/z* value of 687.5 and simulation of the spectrum is consistent with the isotopic distribution pattern expected for **2**.

At 96 MHz, the ^1H decoupled ^{11}B-NMR spectrum of **2** exhibited resonances at −1.76, −8.53, −12.22, and −13.29 ppm, which is consistent with two *closo*-carborane cages. The ^{13}C-NMR shows two peaks shifted downfield at 183.94 and 181.54 ppm corresponding to the CO and CN groups, respectively. The ^{13}C-NMR also indicates the presence of the carborane CH groups at 57.47 and 57.23 ppm. The ^1H-NMR exhibited a broad peak associated with the BH groups and one other resonance corresponding to the carborane CH.

2.2. Crystal structure of **2**

Single crystals of compound **2** were isolated and the structure is shown in Fig. 2. The compound contains two isonitriles and one bromide ligand and three CO ligands having the expected facial geometry. The compound crystallized with disordered THF in lattice. The average Re–(CO) distance (Table 1) is 1.976(6) Å ranging from 1.958(5) to 1.985(6) Å, the shortest being the ligand trans to the bromine. The C–O bond distances are 1.088(5), 1.134(5) and 1.132(6) Å, while the bromine–metal distance, 2.635(6) Å, clearly demonstrates the strong trans influence of the opposing CO ligand.

The Re–CNR bond distances are similar (2.075(5) and 2.063(5) Å) and only slightly shorter than the corresponding distances in $Tc(CO)_3(CN^tBu)_2Cl$ [14].



Scheme 1.

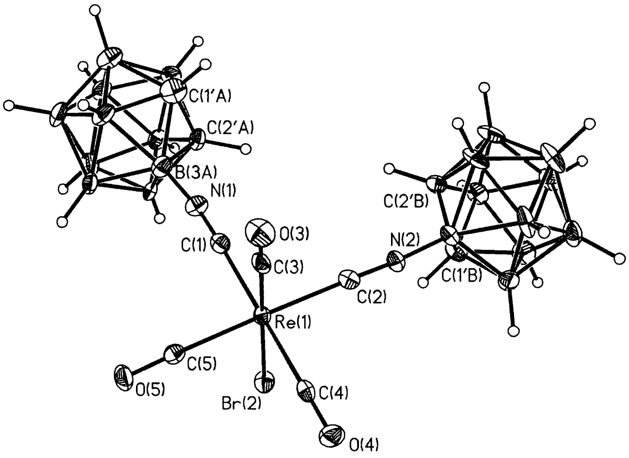


Fig. 2. ORTEP representation of compound **2** with thermal ellipsoids are shown at the 30% probability level. The disordered solvent of crystallization (THF) has been omitted for clarity.

The CN bond distances are 1.164(6) and 1.161(6) Å, which are very similar to that of the free ligand (1.157(4) Å) indicating little π-back donation from the metal to the isonitrile ligands. The N(1)–C(1)–Re(1) and N(2)–C(2)–Re(1) bond angles are nearly linear (178.1(5) and 177.0(4)°, respectively). Like that of the CN bond, the distances between the nitrogen atoms of the isonitriles and the boron atoms of the carboranes are on average very similar to the same distance for the free ligand. The structures of the carboranes themselves are unexceptional.

2.3. Reaction of compound *1* with $[Re(CO)_3(solv.)_3]^+$

Alberto et al. have demonstrated that it is possible to bind three isonitriles ligands to the $[Re(CO)_3]^+$ core by replacing the halide ligands with solvent (solv.) molecules prior to treatment with the desired ligand [18]. Following a similar procedure (Scheme 1), compound **1** was reacted with $[Re(CO)_3Br_3]^{2-}$, which had been previously treated with Ag^+ in THF to replace the bromide ligands with THF molecules. After heating to reflux overnight, TLC analysis of the reaction mixture showed a mixture of products, which were isolated chromatographically.

Table 1
Selected bond distances (Å) and angles (°) for compound **2**

Bond distances			
Re(1)–C(3)	1.958(5)	Re(1)–C(4)	1.984(5)
Re(1)–C(5)	1.985(6)	Re(1)–C(2)	2.063(5)
Re(1)–C(1)	2.075(5)	Re(1)–Br(2)	2.6351(6)
N(1)–C(1)	1.164(6)	N(1)–B(3A)	1.462(7)
C(2)–N(2)	1.161(6)	C(3)–O(3)	1.088(5)
C(4)–O(4)	1.134(5)	C(5)–O(5)	1.132(6)
Bond angles			
C(5)–Re(1)–C(1)	90.42(19)	C(2)–Re(1)–C(1)	87.63(19)
C(3)–Re(1)–Br(2)	178.48(13)	C(4)–Re(1)–Br(2)	88.18(13)
C(5)–Re(1)–Br(2)	87.60(13)	C(2)–Re(1)–Br(2)	87.31(12)
C(1)–Re(1)–Br(2)	89.20(12)	C(1)–N(1)–B(3A)	172.6(5)
N(1)–C(1)–Re(1)	178.1(5)	C(2)–N(2)–B(3B)	175.4(5)
N(2)–C(2)–Re(1)	177.0(4)	O(5)–C(5)–Re(1)	177.5(4)
O(4)–C(4)–Re(1)	179.4(4)	C(5)–Re(1)–C(2)	174.57(17)

The main reaction product was the tri-substituted metal complex **3a**, which is in agreement with the observations reported by Alberto and coworkers who used ^{t}BuNC as a ligand. The ESMS of **3a** is consistent with the calculated mass of the proposed target having an isotopic distribution characteristic of a ReB_{30} species. The IR showed $\nu_{(CN)}$ and $\nu_{(CO)}$ stretches at 2178, 2122, 2098 cm^{-1} and 2038, 2007, 1948 cm^{-1}, respectively, which are consistent with the peaks observed for $[Re(CO)_3(CNtol)_3][PF_6]$ [17]. The ^{11}B-NMR of **3a**, having peaks at −2.45, −3.69, −7.37, −9.76, and −13.56 ppm, indicates that the cages are all *closo* in nature.

2.4. Crystal structure of *3b*

Single crystals of **3b** were isolated after a slow evaporation of the reaction solvent in air and used to acquire the X-ray structure shown in Fig. 3. Upon refinement it was noted that the thermal occupancy for atom B(6) appeared to deviate from the accepted value for boron. This suggested that one of the three carborane cages underwent degradation to the corresponding nido cluster. The occupancy of the B(6) atomic position, when given a free variable, converged to 66% upon least-squares refinement. Similar treatment of other non-restrained atoms B(7), B(8) and B(12), confirmed complete (100%) occupancy at these sites. The remainder of the structure was determined from the corresponding symmetry elements inherent to the rhom-

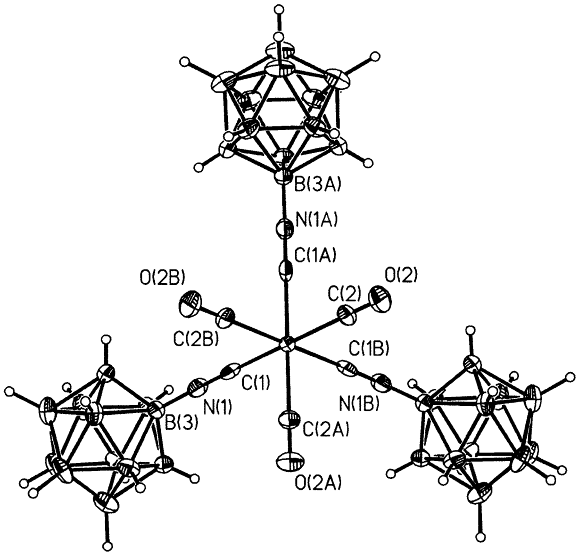


Fig. 3. ORTEP representation of compound **3b**. Thermal ellipsoids are shown at the 30% probability level.

bohedral $R3m$ space group. The final solution shown in Fig. 3 has the missing boron vertex ‘spread’ over the three carborane clusters which gives the false impression that all cages are *closo*.

The ^{11}B-NMR of **3a**, immediately after isolation (vide supra) clearly indicates that all three carborane cages are in fact *closo*. A $^{11}B\{^1H\}$ spectrum of the recrystallized material however, shows a substantially more complicated pattern clearly indicating that at least one of the clusters was converted to the nido-carborane during the prolonged crystallization process. The conversion of dicarba-*closo*-dodecaboranes to the corresponding nido-carboranes is typically brought about through the use of strong bases such as alkoxides [19], secondary amines [20,21] or fluoride ion [22]. There have been reports of the degradation of *closo*-carboranes under very mild conditions [23], however, the same reaction for carboranes substituted at the 3-position has not, to the best of our knowledge, been previously described. It is clear that coordination to the metal influences the compound to convert to the nido-cluster under milder conditions that of the free ligand which we have found to be stable in solution for prolonged periods of time. The formation of the nido-carborane in **3b** is further supported by the absence of any counter ion in the solid state structure which is consistent with the overall neutral charge of the deboranated complex.

Compound **3b** has a facial arrangement of CO ligands and three 3-isonitrilecarborane substituents. The Re–(CO) distance in **3b** is 2.01(2) Å which is slightly longer than the corresponding distance in $[Tc(CO)_3(CN^tBu)_3][NO_3]$ [18]. The Re–CNR distance is 2.08(2) Å while the CN distance is 1.19(2) Å, which is a little longer than that for compound **1**. The distance between the nitrogen atom and the carborane cage is 1.451(19) Å and the C(2)–Re(1)–C(1) and C(1)–N(1)–B(3) angles are nearly linear at 178.6(11) and 173.4(18)°, respectively.

2.5. Higher coordination numbers

During the reaction of **1** with $[Re(CO)_3(solv.)_3]^+$ a second product was isolated from the reaction mixture. Positive ion ESMS indicates that the product’s formula is $[Re(CO)_2(CNR)_4]^+$ and the observed isotopic distribution pattern is in fact consistent with a ReB_{40} distribution. The carboranes in **4** according to ESMS and NMR experiments do not degrade, unlike what was observed for compound **3a**, to form the corresponding nido-carboranes. The IR of **4** shows $\nu_{(BH)}$ at 2604 cm^{-1}, $\nu_{(CN)}$ at 2210, 2140 and 2095 cm^{-1} and $\nu_{(CO)}$ at 2025 and 2002 cm^{-1}. The patterns observed for the CN and CO stretches are consistent with the formation of a *cis* isomer [17].

The substitution of a CO ligand directly from the $[Re(CO)_3]^+$ core is not typically observed especially using simple isonitriles ligands and relatively mild reaction conditions. It has been reported however, that $[Re(CO)_2(CNtol)_4][PF_6]$ can be prepared from $Re(CO)_3(CNtol)_2Br$ under similarly benign reaction conditions [17]. Unfortunately, despite repeated attempts, an X-ray structure of **4** could not be obtained to unambiguously establish its structure. The isolation of **4** motivated us to look at the ESMS of the crude reaction mixture which contained compounds **3a** and **4** to see if there were any other derivatives of the type $[M(CO)_n(L)_{6-n}]$ ($n = 0$ or 1). Perhaps most interestingly, the positive ion ESMS showed a peak at 1202 having a ReB_{60} distribution which is consistent for formation of the hexakis derivative $[Re(L)_6]^+$. Unfortunately, the hexakis(isonitrile)Re(I) complex could not be isolated in appreciable quantities, however, the fact that we observed the product in ESMS suggest that it is possible to prepare a compound having six 3-isonitrile-carborane ligands around the metal center. This compound, which is the Re-carborane analogue of the hexakis(isocyanide) technetium complexes, prepared nearly 20 years ago [24], has 60 boron atoms and would therefore, as mentioned in Section 1, would be another attractive platform from which to construct metal-based BNCT and BNCS agents.

3. Conclusion

3-Isonitrilecarborane reacts with the $[Re(CO)_3]^+$ core in a manner similar to that of aliphatic isonitriles resulting in compounds of the general formulae $Re(CO)_3L_2Br$, $[Re(CO)_3L_3]^+$ and $[Re(CO)_3L_2L']$. Two of these compounds were characterized crystallographically. In addition, we observed that compound **1** has the apparently unique ability to displace CO ligands from $[Re(CO)_3(solv.)_3]^+$, which led to the formation of $[Re(CO)_2L_4]^+$. We are currently investigating the analogous chemistry with ^{99}Tc and ^{99m}Tc.

4. Experimental

4.1. Materials and procedures

All commercial reagents were used as supplied. THF and Et_2O were distilled under nitrogen from sodium and benzophenone. *ortho*-Carborane was purchased from Katchem Ltd. (Czech. Rep.) Analytical TLC was performed on silica gel 60-F_{254} Merck). Boron compounds were visualized with 0.1% $PdCl_2$ in HCl (3.0 M), which upon heating gave dark brown spots.

NMR spectroscopy experiments were performed on Bruker AV200, AV300 and DRX500 spectrometers. Tetramethylsilane and BF_3–Et_2O were used as internal standards for ^{1}H and ^{11}B spectra, respectively. For

NMR assignments, b refers to broad signals, s refers to singlets and m refers to multiplets. Electrospray mass spectrometry experiments were performed on a Micromass Quattro Ultima instrument. Samples were dissolved in 50:50 $CH_3CN–H_2O$. IR spectra were run on a Bio-Rad FTS-40 FTIR spectrometer.

Single-crystal X-ray diffraction data was collected with a Bruker SMART-1K CCD detector on a P4/RA diffractometer equipped with an Oxford Cryostream cooling system. The diffraction experiments were carried out with graphite-monochromated Mo–K_α X-radiation ($\lambda = 0.71753$ Å). Single crystals were mounted on the tips of glass fibers. Accurate cell parameters were determined at 173 K from a refinement of the setting angles (χ, ϕ, and 2θ) obtained from a chosen number of centered reflections in reciprocal space using the SMART [25] software. The SAINT program [26] was used to integrate the raw frame data and the structures were solved by direct methods and refined by full-matrix least-squares on F^2 for structure solution using the SHELXTL PLUS package [27]. Corrections were made to the integrated diffraction spots by applying Lp corrections. The SADABS program [28] was used for the application of a decay correction, and an empirical absorption correction based on redundant reflections Table 2.

Compound **2** crystallized in the monoclinic $P2_1/n$ space group ($Z = 4$) and crystallographic data are given in Table 3. A significant amount of electron density observed in the difference map was modeled as disordered solvent and assigned as oxygen, which is representative of the recrystallization solvent THF. All solvent atoms were assigned variable partial occupancy with isotropic thermal parameters. Hydrogen atoms were added as fixed contributors at calculated positions with isotropic thermal parameters, based on the atom to which they were bound. Compound **3b** crystallized in the highly symmetrical rhombohedral $R3m$ space group ($Z = 3$). Crystallographic data are given in Table 3.

Table 2
Selected bond distances (Å) and angles (°) for compound **3b**

Bond distances			
Re(1)–C(2)	2.01(2)	Re(1)–C(1)	2.08(2)
C(1)–N(1)	1.19(2)	N(1)–B(3)	1.451(19)
O(2)–C(2)	1.11(2)	B(3)–B(8)	1.744(9)
B(3)–B(9)	1.759(12)	B(6)–B(7)	1.751(13)
B(6)–B(11)	1.812(16)	B(7)–B(12)	1.794(14)
B(7)–B(11)	1.795(12)	B(7)–B(8)	1.801(12)
B(8)–B(9)	1.758(10)	B(8)–B(12)	1.770(15)
B(9)–B(12)	1.778(12)	B(11)–B(12)	1.774(13)
Bond angles			
C(2)–Re(1)–C(1)	178.6(11)	N(1)–C(1)–Re(1)	176.2(18)
C(1)–N(1)–B(3)	173.4(18)	O(2)–C(2)–Re(1)	177.2(18)

Table 3
Crystallographic data for compounds **2** and **3b**

Compound	**2**	**3b**
Empirical formula	$C_9H_{22}B_{20}BrN_2O_{8.15}Re$	$C_{12}H_{33}B_{29.03}N_3O_3Re$
Formula weight	771.00	767.46
Temperature (K)	173(2)	173(2) K
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Rhombohedral
Space group	$P2(1)/n$	$R3m$
a (Å)	15.353(2)	21.710(9)
b (Å)	10.5819(15)	21.710(9)
c (Å)	18.485(3)	6.410(4)
α (°)	90	90
β (°)	94.771(2)	90
γ (°)	90	120
V (Å^3)	2992.7(8)	2616(2)
Z	4	3
D_{calc} (Mg m^{-3})	1.711	1.461
Absorption coefficient (mm^{-1})	5.434	3.510
F(000)	1461	1111
Crystal size (mm)	0.26 × 0.03 × 0.03	0.14 × 0.04 × 0.03
θ Range for data collection (°)	1.66–27.53	1.88–27.49
Index ranges	$-19 \le h \le 19$, $-13 \le k \le 13$, $-23 \le l \le 23$	$-27 \le h \le 28$, $-27 \le k \le 27$, $-8 \le l \le 8$
Reflections collected	26 964	7733
Independent reflections	6873	1153
R_{int}	0.0661	0.0678
Final R indices [$I > 2s(I)$]	$R_1 = 0.0374$, $wR_2 = 0.0607$	$R_1 = 0.0345$, $wR_2 = 0.0648$
R indices (all data)	$R_1 = 0.0737$, $wR_2 = 0.0681$	$R_1 = 0.0354$, $wR_2 = 0.0651$
Goodness-of-fit on F^2	0.997	1.123
Largest difference peak and hole (e Å^{-3})	0.666 and −0.678	2.162 and −0.499

4.2. Synthesis of $Re(CO)_3(L_2)Br$ (2)

$[NEt_4]_2[Re(CO)_3Br_3]$ (65.5 mg, 85 µmol) and **1** (44.6 mg, 264 µmol) were dissolved in anhydrous THF (2.5 ml) and the resulting yellow heterogeneous reaction mixture brought to reflux overnight (18 h). The solvent was subsequently removed by rotary evaporation leaving a yellow solid, which was purified by either radial chromatography (40% ethyl ether in petroleum ether) or preparative TLC (30:20 DCM–C_5H_{12}) giving the desired product as a white crystalline solid. Yield: 20%. ESMS (negative ion): $m/z = 687.5$ $[Re(CO)_3(L_2)Br]$. ^{1}H-NMR ($CDCl_3$, 500 MHz): 4.03 (s, CH), 2.68–1.24 (BH). ^{13}C-NMR ($CDCl_3$, 125 MHz): 183.94, 181.54, 57.47, 57.23. ^{11}B-NMR (CD_2Cl_2, 160 MHz): −1.76, −8.53, −12.22, −13.29. IR (KBr, cm^{-1}): 2602, 2183, 2132, 2042, 2004, 1956.

4.3. The reaction of 1 with $[Re(CO)_3(solv.)_3]^+$

$Ag(PF_6)$ (114 mg, 0.45 mmol) was added to $[NEt_4]_2[Re(CO)_3Br_3]$ (116 mg, 0.15 mmol) in dry THF (3 ml) under Ar. After 20 min the reaction was filtered under Ar, the residue washed with 1 ml of dry THF, and the solution evaporated to dryness. Compound **1** (0.153 g, 0.904 mmol) was added as a solid followed by dry THF (1 ml). After heating to reflux overnight, the solvent was evaporated and the resulting solid dissolved in ether and two main products isolated by radial chromatography (100% petroleum ether to 100% ether in 5% intervals). Compound **3a**. Yield: 0.025 g. ESMS (positive ion): $m/z = 792.3$ $[Re(CO)_3(L_3)Na]$, 778.2 $[Re(CO)_3(L_3)]$. ^{1}H-NMR (CD_2Cl_2, 200 MHz): 4.48 (br s, CH), 4.18 (br s, CH), 4.18 (br s, CH), 3.47–1.13 (br, BH). ^{13}C-NMR (CD_2Cl_2, 50 MHz): 184.49, 58.78, 57.85, 57.68. ^{11}B-NMR ($CDCl_3$, 96 MHz): −2.45, −3.69, −7.37, −9.76, −13.56. IR (KBr, cm^{-1}): 2610, 2178, 2122, 2098, 2039, 2007, 1948.

Compound **4**. Yield: 0.051 g. ESMS (positive ion): $m/z = 919.7$ $[Re(CO)_2(L_4)]$. ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.49 (br s, CH), 2.96–0.84 (br, BH). ^{11}B-NMR ($CDCl_3$, 96 MHz): −2.12, −8.88, −13.27. IR (CH_2Cl_2, cm^{-1}): 2604, 2210, 2140, 2095, 2025, 2002.

5. Supplementary material

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 190572 and 190573, for complexes **2** and **3b**, respectively. Copies of this data may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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