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Derivatization chemistry of the double-decker dicobalt sandwich ion targeted to design biologically active substances*

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Abstract: A synthesis of the first double-decker sandwich ion [(1',2'-$C_2B_9H_{11}$)-3,3'-Co-(1,2-$C_2B_8H_{10}$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)]$^{2-}$ (**DD**$^{2-}$) derivatives is described, having been developed in connection with our search for biologically active substances. A series of B-substituted hydroxyl derivatives was prepared by direct hydroxylation of the ion using aqueous sulfuric acid. Two isomers of monohydroxy derivatives were isolated. The main product was substituted at the central "canastide" ion fragment, whereas the substitution site for the minor isomer corresponded to a B(8) atom of one of the terminal 11-vertex dicarbollide parts. Similarly, the disubstitution occurred slightly more preferentially on the "canastide" fragment providing the main isomeric derivative with a symmetric structure. The cesium salt of this ion was characterized by X-ray diffraction. Two other isomeric species have one substituent sitting on the "canastide" ion and the second present on the dicarbollide ligand in *apart* or *syn*-geometric arrangement. A new zwitterion anion [(1',2'-$C_2B_9H_{11}$)-3',3-Co-(8-$(CH_2)_4$O-1,2-$C_2B_8H_9$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)-]$^{1-}$ was prepared by the reaction of the parent ion with tetrahydrofuran (THF), activated by $BF_3{\cdot}OEt_2$. This new compound serves as a versatile building block for constructing organic derivatives, as exemplified by the ring cleavage by various amines or phenolate ions and the synthesis of a basic series of compounds of general formulation [(1',2'-$C_2B_9H_{11}$)-3',3-Co-(8-X-$(CH_2)_4$O-1,2-$C_2B_8H_9$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)]$^{n-}$ where the organic end-groups X adjacent to the "canastide" moiety via a B-oxatetramethylene spacer corresponds to $C_4H_9NH_2$, NC_5H_5, $N(C_2H_5)_3$, $(C_6H_5)_3P$ (n = 1), or (4-*t-Bu*-C_6H_4-1-O)$^-$ and (2-CH_3O-C_6H_4O)$^-$ (n = 2). We show that dicluster compounds with two identical **DD**$^{2-}$ anion units or asymmetric molecules containing two different clusters, the cobalt bis(dicarbollide) and the **DD**$^{2-}$ anion, are accessible using this building block. All compounds were characterized by high-resolution NMR (^{1}H, ^{13}C, and ^{11}B) and mass spectrometry. Some of the compounds were tested by in vitro assay for their ability to inhibit the HIV-protease (HIV-PR) enzyme. The majority of the tested species proved substantially high activity toward the HIV-PR, exhibiting on the other hand a noncompetitive mechanism of the inhibition.

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INTRODUCTION

Over the last decade, carboranes and metallacarboranes have started to receive considerably growing attention as potentially interesting hydrophobic pharmacophores [1–6].

During the past several years, we have focused our studies of metallacarborane scaffolds on inorganic, nonpeptidomimetic inhibitors of HIV-protease (HIV-PR) enzyme. This enzyme plays a key role in the HIV virus life cycle, cleaving *Gag* and *Gag-Pol* polypeptide precursors into structural viral proteins and functional enzymes, and thus is responsible for virus maturation. The symmetric structure of this aspartic PR is composed from two subunits, each consisting of 99 amino acids that are stabilized by a hydrogen-bond network of β-sheet formed by intertwining C- and N-termini (residues 1–4 and 96–99) of both subunits. Other functionally important parts of the enzyme involve two flexible β-hairpins, called flaps, closing over the active site upon the substrate or inhibitor binding. This enzyme attracted extraordinarily high attention as the primary target for a rational drug design for the treatment of HIV/AIDS and nine clinically currently approved organic inhibitors, a majority of which mimic the natural peptide substrate of the enzyme are available on the market [7–9].

As has been shown recently, boron cluster compounds, and, in particular, metal bis(dicarbollides), can serve as efficient inhibitors of HIV-PR enzyme and its drug-resistant isoforms [10–13]. Even the sodium salt of parent cobalt bis(dicarbollide) ion $[(1,2\text{-}C_2B_9H_{11})_2\text{-}3,3'\text{-}Co]^-$(**CD**$^-$) acts as a moderately active inhibitor. However, compounds substituted with larger hydrophobic fragments (aromatics or boron clusters) proved to be more than one order of magnitude higher in efficacy during in vitro assays. The highest activity was observed for anionic-zwitterionic species that are based on a symmetric linkage of two cluster anions to a central alkylammonium function via two flexible diethyleneglycol units. As follows from recent structural studies of the enzyme-inhibitor complexes [10,12,13], a larger part of these compounds exhibit a competitive mechanism. The compounds show novel binding mode: both terminal clusters accommodate into the flap proximate region located above the active center, blocking effectively the flaps closure that usually occurs upon binding of the substrate. Preliminary tests have shown that sodium salt of unsubstituted parent dicobalt double-decker sandwich anion $[(1',2'\text{-}C_2B_9H_{11})\text{-}3',3\text{-}Co\text{-}(1,2\text{-}C_2B_8H_{10})\text{-}6,3''\text{-}Co\text{-}(1'',2''\text{-}C_2B_9H_{11})\text{-}]^{2-}$ (**DD**$^{2-}$) is comparable in activity to the best inhibitors from the cobalt bis(dicarbollide) series. Therefore, this observation prompted us to focus on possible chemical modifications of this interesting large cluster ion.

The double-decker sandwich **DD**$^{2-}$ has been known for more than four decades, and its first report by M. F. Hawthorne [14,15], then accompanied closely the synthesis of the cobalt bis(dicarbollide)(1-) anion (**CD**$^-$) [16]. The chemistry of the smaller **CD**$^-$ ion [1,17], which is characterized by its unique stability, continues to receive considerable interest. This is due mainly to recently revealed synthetic options for easy introduction of this metallacarborane framework as a building block into larger functional molecules and materials [18–20]. The area of emerging applications includes efficient extraction agents for lanthanides and actinides [21–29]; additives and doping agents for conducting polymers [20,30–33]; potential use in biomedicine as HIV-PR inhibitors; boron labeling of DNA fragments for boron neutron capture therapy (BNCT), UV, IR, and electrochemical, UV, and IR markers [34–39]; boron-rich materials and dendrimers [40–44], etc. Also, aspects of the chemistry of polydecker sandwich complexes derived from small $\{C_2B_4H_6\}$, $\{C_2B_3H_5\}$, and $\{C_3B_2H_5\}$ carborane units as ligands in ferra and cobalta complexes are quite elaborated [1,45]. However, the chemistry of **DD**$^{2-}$ anion as a larger cluster counterpart has remained abandoned.

To design HIV-PR inhibitors and some other applications described above, it would seem advantageous to prepare available building blocks comprising a bulkier, chemically stable cluster moiety that can provide a larger hydrophobic cluster surface area, increased noncovalent interactions and sterical requirements. The **DD**$^{2-}$ seems to be an ideal candidate that might offer such properties. As shown in Fig. 1, the **DD**$^{2-}$ ion is composed from two terminal 11-vertex dicarbollide ligands and one central

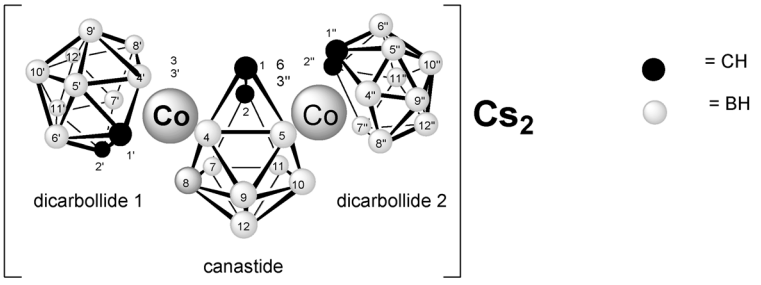


Fig. 1 Schematic drawing of the structure of cesium salt of the $\mathbf{DD}^{2-}$ ion showing the cage numbering. The skeletal hydrogen atoms are omitted for clarity.

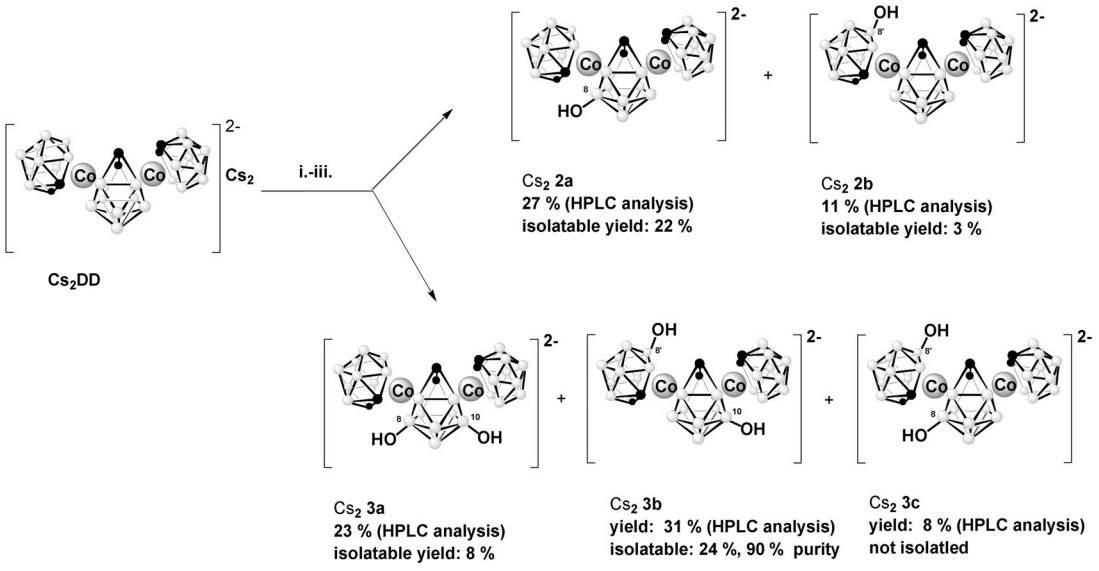
10-vertex dicarbaborane unit for which a trivial name, "canastide" ion (from the Spanish word, "canasta," meaning "basket"), was suggested by Hawthorne [14]. For purposes of this study, we number the $\mathbf{DD}^{2-}$ ion from the center and then to left and right side as depicted in Fig. 1, therefore, the 10-vertex "canastide" ion brings unmarked vertexes.

The substitution chemistry of $\mathbf{DD}^{2-}$ anion, based on large carborane units, has remained completely unexplored. Only structural studies of the unsubstituted parent ion and the recently reported larger polydecker complexes [46,47] were reported, along with studies of the solution of $\mathbf{DD}^{2-}$ aggregation behavior [48] and attempts to use this ion for extraction of radioactive cesium into the organic phase [49]. To our knowledge, no report describing at least basic reaction pathways on the cage of $\mathbf{DD}^{2-}$ and their stereochemistry exists in the literature. We report here the synthetic procedures providing a basic series of derivatives of the $\mathbf{DD}^{2-}$ ion. The selection of substituents addresses possible construction of larger functional molecules that contain organic fragments adjacent to boron atoms of the cluster, or may lead to larger ionic scaffolds containing two or more clusters in their structures.

The first series of such ionic species that we report here is based on hydroxylation of the cage of $\mathbf{DD}^{2-}$ ion and isolation of the respective isomeric hydroxy derivatives. Another building block reported here is based on the introduction of the cleavable ring substituent consisting of the tetrahydrofurane (THF) ring bound on boron atom of the "canastide" subcluster of $\mathbf{DD}^{2-}$. This paper outlines the scope of the bridge cleavage reactions of [(1',2'-$C_2B_9H_{11}$)-3',3-Co-(8-$(CH_2)_4O$-1,2-$C_2B_8H_9$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)]$^{1-}$ ($\mathbf{4}^-$), which proceeded smoothly with a large variety of nucleophiles producing a conveniently covalent bonding of the cage to various organic end-groups. The implications of use of these building blocks for the design of double cage inhibitors of the wild-type HIV-PR enzyme are also outlined, and results from in vitro tests of several substitution derivatives are presented and discussed.

RESULTS AND DISCUSSION

We found that as does the cobalt bis(dicarbollide) [50], the $\mathbf{DD}^{2-}$ ion similarly undergoes electrophile-induced nucleophilic substitution (EINS)-type hydroxylation reactions with aqueous sulfuric acid at higher temperatures (see Scheme 1). However, the composition of the products and the stereochemistry of the species are more complex than for the single cobalt $\mathbf{CD}^-$ sandwich complex. As has been verified by product isolation and periodic high-performance liquid chromatography (HPLC) monitoring, a slightly more abundant product that forms in the reaction mixture upon heating with sulfuric acid is a hydroxy derivative [(1',2'-$C_2B_9H_{11}$)-3',3-Co-(8-HO-1,2-$C_2B_8H_9$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)]$^{2-}$ ($\mathbf{2a}^{2-}$) substituted at the boron atom B(8) of the central 10-vertex "canastide" fragment. Only this electron-rich boron atom sitting opposite to both skeletal carbon atoms is affected by substitution in the "canastide" subcluster. Simultaneously, the reaction proceeds to a lower extent on one of the two dicarbollide ligands in position B(8',8"), resulting in the isomeric hydroxylated ion [(8'-HO-1',2'-$C_2B_9H_{10}$)-3',3-Co-



Scheme 1 Synthesis of hydroxy derivatives of the $\mathbf{DD}^{2-}$ ion. Experimental conditions: i. H_2SO_4 48 %, 100 °C, 7 h; ii. H_2O, extraction into Et_2O, precipitation by CsCl; iii. LPC CH_2Cl_2: *i*-PrOH, 9: 1 to 75: 25, crystallization from hot aqueous EtOH.

(1,2-$C_2B_8H_{10}$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)]$^{2-}$ ($\mathbf{2b}^{2-}$). The latter substitution pattern clearly resembles that observed at the 11-vertex ligands present in the cobalt bis(dicarbollide) ion. Both pure isomers could be separated successively in pure form by chromatography and crystallization. The formula drawn for isomer $\mathbf{2b}^{2-}$ in Scheme 1 is based on results of crystallographic studies of Cs_2**2b**, from which the site of the substitution could be reliably determined. However, due to disorders present in the structure, this could not be completely refined and data are not presented here.

Also, the dihydroxy derivatives form in the reaction mixture as can be expected, and became the main products upon prolonged heating. Two distinct fractions could be separated by chromatography. The fraction that is more retained on a silica gel column contains the symmetric isomer [(1',2'-$C_2B_9H_{11}$)-3',3-Co-(8,10-$(HO)_2$-1,2-$C_2B_8H_8$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)]$^{2-}$ ($\mathbf{3a}^{2-}$) that comprises two hydroxyl functions attached at both reactive sites of the "canastide" fragment. The structure of this isomer was unambiguously determined by X-ray crystallography. Nevertheless, the main, faster-moving fraction consisted of a mixture of two isomers, which could not be fully separated. Only fractions enriched by the main species [(8'-HO-1',2'-$C_2B_9H_{10}$)-3',3-Co-(10-HO-1,2-$C_2B_8H_9$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)]$^{2-}$ ($\mathbf{3b}^{2-}$) could be obtained with ca. 92 % isomeric purity. The presence of both isomeric species is easily distinguished by analytical HPLC or from ^{11}B, ^{1}H, and ^{13}C NMR spectra. Unfortunately, these species also co-crystallized together, which caused disorder of hydroxyl groups into two positions in the crystal, and thus for this reason the X-ray structure could not be fully refined. However, even here it was possible to reliably identify the sites of the substitution from the crystallographic data. Similar to the symmetric isomer, these two species have one of the hydroxyl groups occupying the B(8) atom at the "canastide" fragment, but the second substituent is bound to one from the two sites available at the dicarbollide ligands. From the availability of the two stereochemically different reaction sites at the dicarbollide ligands arise two possible orientations of the substitutes at the cage. The first isomer $\mathbf{3b}^{2-}$ has the hydroxyl groups most probably located *apart* and across the "canastide" subcluster; the second possible orientation of the groups corresponds to the substitution of the neighboring pentagon planes around the same cobalt atom. The arrangement of the substituent in this isomer

is depicted as *syn*-orientation in [(8'-HO-1',2'-$C_2B_9H_{10}$)-3',3-Co-(8-HO-1,2-$C_2B_8H_9$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)]$^{2-}$ (**3c**$^{2-}$) (See Scheme 1).

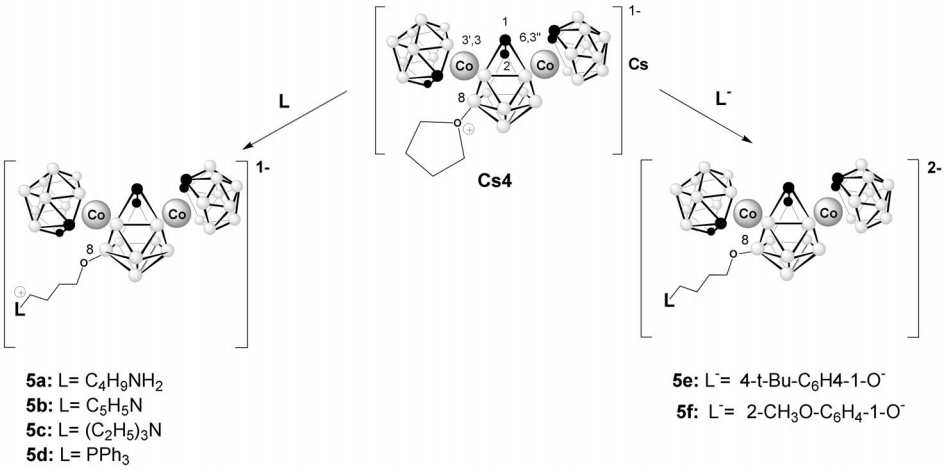
From initial reports by Jaromir Plešek et al. in 1983 [51] and 1991 [52], the cleavage of reactive rings attached to boron cluster anions became a widely employed tool for binding organic functional groups to the boron atoms of various cage structures. With exception of more recent results [1], the comprehensive review article that appeared in 2008 covered the scope of this approach with broad consequences in many different areas of synthetic and material chemistry [18].

Considering the described synthetic procedure leading to compounds with cleavable cyclic ether substituents, some general conclusions can be drawn with respect to the different reactivity of monovalent and divalent anions toward cyclic ethers, used most frequently to introduce the cleavable ring. Applying the usual activators ($BF_3{\cdot}OEt_2$ or $(MeO)_2SO_2$), compounds substituted by five-membered rings like THF are accessible in a preparative scale from divalent anions, whereas only the compounds substituted by six atom rings (dioxane, tetrahydropyrane) are isolatable in good yields from reactions of monovalent ions. As also verified here for the divalent **DD**$^{2-}$ anion, easier and higher yield synthesis and isolation were possible only for a compound containing the five-membered THF moiety. Attempts at substitution with a dioxane function led mainly to disubstitutions that were followed by stereochemical complications and also by the presence of appreciable quantities of side products arising from a partial ring opening. The assumed B(8) substituted compound could nevertheless be isolated, but only in a small yield (9 %) that was useless for assumed preparative purposes (details are not shown here).

On the other hand, only one single derivative and one pure isomer [(1',2'-$C_2B_9H_{11}$)-3',3-Co-(8-$(CH_2)_4$O-1,2-$C_2B_8H_9$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)]$^{1-}$ (**4**$^{-}$) forms by reaction with THF activated with the use of $BF_3{\cdot}OEt_2$ (see Scheme 2). This monovalent species could be isolated in a reasonable yield (up to 45 %) and good purity in the form of respective cesium salt. Compared to the well-known dioxane derivative of the **CD**$^{-}$ ion, the stability of the new compound is somewhat limited, but when carefully dried and maintained under argon in a refrigerator at a low temperature (–35 °C or below), the cesium salt Cs**4** can be stored for at least two weeks without significant decomposition. On the other hand, it seems advisable to prepare this derivative freshly only in quantities that can be directly spent in subsequent ring-opening reaction steps. With respect to the stereochemistry, according to NMR evidence and in comparison with **2a**$^{2-}$, the substitutent is located at the "canastide" subcluster in the skeletal position B(8), as expected sitting on the pentagonal plane ligating the cobalt atom in the position opposite to the two carbon atoms.

Scheme 2 Synthetic procedure leading to Cs**4**.

A convenient feature of the THF substituent is the oxonium character of the oxygen atom that enables ring-opening reactions (see Scheme 3). Derivative **4**$^{-}$ can be thus used to easily incorporate the very stable **DD**$^{2-}$ anion into various organic molecules, thereby resembling most of the previously reported boron cluster species with cleavable ether rings. An oxatetramethylene spacer forms on the ring cleavage by a nucleophilic particle that interconnects the terminal organic moiety to the cage. In



Scheme 3 The ring cleavage reactions of Cs**4** using different types of nucleophilic reagents.

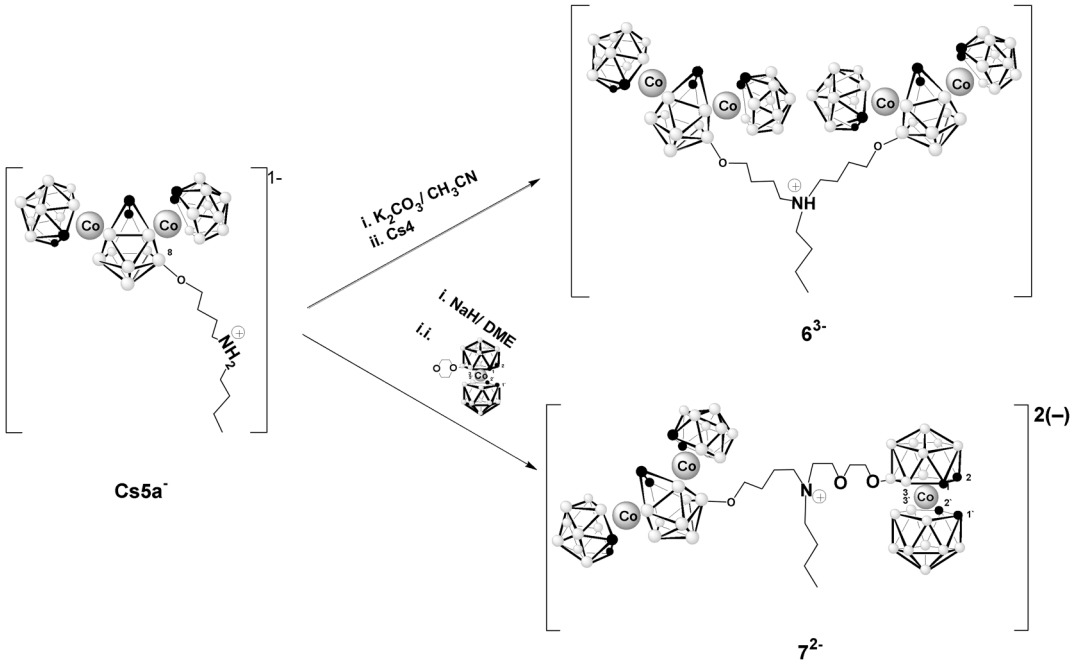
general, ring-cleavage reactions of $\mathbf{4}^-$ with uncharged N- or P-nucleophiles result after acidification (even on the silica gel column) in the formation of monovalent anions with positively charged terminal moiety (see Scheme 3). Thus, the room-temperature reactions of compound Cs**4** with amines or phosphines in THF solutions gave rise to the corresponding ammonium or phosphonium derivatives (see Scheme 3). For example, we report here five compounds with butylammonium ($\mathbf{5a}^-$), pyridinium ($\mathbf{5b}^-$), trimethylammonium ($\mathbf{5c}^-$), and triphenyl phosphonium ($\mathbf{5d}^-$) end-groups obtained in high yields of 88, 89, 84, and 68 %, respectively, when isolated in the form of respective tetramethylammonium or cesium salts.

We found that the reactions with phenolate anions as the nucleophiles proceed also with no difficulty providing the respective dianions with the oxygen are attached to the terminal moiety. Thus, we present here as examples synthesis and isolation of anions with 2-CH_3O-C_6H_4-1-O- and 4-*t*-Bu-C_6H_4-1-O- moieties (see Scheme 3) ($\mathbf{5e,f}^{2-}$), which were obtained in yields of 92 and 94 %.

The compound Cs**5a** with the terminal *n*-butylammonium group was selected for further attachment of the second cluster moiety by a double ring opening (see Scheme 4). These compounds were synthesized as structural analogues of previously reported efficient inhibitors of the HIV-PR enzyme (of the lead structure GB-48). Thus, the reaction with Cs**4** provided, after isolating the symmetric derivative $\mathbf{6}^{3-}$ containing two $\mathbf{DD}^{2-}$ clusters that were accommodated in one single trivalent ion (see Scheme 4). The reaction with dioxane of cobalt bis(dicarbollide) gave divalent ion $\mathbf{7}^{2-}$ with two different cluster moieties attached to the butylammonium residue and sitting at both sides of this ionic scaffold.

STRUCTURAL AND NMR CONSIDERATIONS

We present here NMR, MS, HPLC, and other data necessary for a complete characterization and purity assay of all derivatives. The purity of all species was determined by HPLC methods being better than 98 % [37]. The crystallographically determined molecular structures of derivatives Cs_2**3a** are presented in Fig. 2 along with selected interatomic distances and angles. The structure confirms the presence of the expected substituent covalently bound at the side sites of the central "canastide" ion on a pentagonal plane adjacent to a cobalt atom and at the boron atom position that is the most distant from cage carbon atoms. Bond distances and angles of all compounds correspond closely to that observed for the parent anion.



Scheme 4 Synthesis of the dicluster species.

Spectroscopic data are also consistent with the crystallographically determined structure. Despite the high number of 26 boron atoms present in the **DD**$^{2-}$ ion, the most important signals in the ^{11}B NMR spectra of the substitution derivatives can, surprisingly, be easily assigned. This is enabled by the presence of two distinguishable superimposed parts, one corresponding to the dicarbollide ligands and the other to the "canastide" subcluster. The whole "canastide" part is shifted more downfield in the spectrum, whereas the atoms B(5,11) and B(6) of the dicarbollide ligand are located in the highest field positions. Best separated in the spectrum of parent anion are the downfield positions of electron-rich B(8,10) "canastide" and B(8',8") dicarbollide atoms that are further affected by substitutions. Indeed, the substitution of the boron atoms by oxygen caused a significant downfield shift with a mean value around 14–21 ppm regardless of the substituted boron site. Thus, the resonance for B(8) atom of the "canastide" ion, originally present at ca. 14.5 ppm, moves to ca. 35 ppm upon substitution. In agreement, the B(8') NMR signal in the **CD**$^{-}$ part moves ca. 19 ppm downfield, to the value around 23 ppm that is very similar to that observed for the {B(8)-O-R} substituted derivatives of the cobalt bis(dicarbollide) anion. The difference of around 12 ppm observed between these two boron signals clearly indicates if the substitution occurred on "canastide" or dicarbollide subcluster. The spectrum of the species **2a**$^{2-}$, **4**$^{-}$, **5a–f**, and **6**$^{3-}$ bearing one substituent at B(8) atom of the canastide subcluster consists of 11 signals of intensities 1:1:2:2:2:1:1:4:6:4:2. The signals in the region from –6 to –8 ppm corresponding to boron atoms B(4,7,9,12) from all three cages remain overlapped by coincidence. Also, the signals corresponding to B(5',5",11',11") and B(6',6") of two dicarbollide ligands are usually unresolved. On the other hand, the resonances corresponding to (B8',8") and B(8,10) are separated each into two distinguishable signals of intensity 1 upon substitution. The spectrum of **2b**$^{2-}$ has more narrow spectral span and exhibits spectral pattern of intensities 1:2:1:4:1:9:2:2:2:1:1. In this case, the two resonances in highest field corresponding to B(5',5",11',11") and B(6',6") are split into two doublets due to substitution at one of the two dicarbollide ligands. The spectrum of **3a**$^{2-}$ has a symmetric pattern with relative intensities 2:2:4:2:2:6:2:4:2, the singlet of B(8,10)-OH atoms being shifted slightly less than with **2a**$^{2-}$,

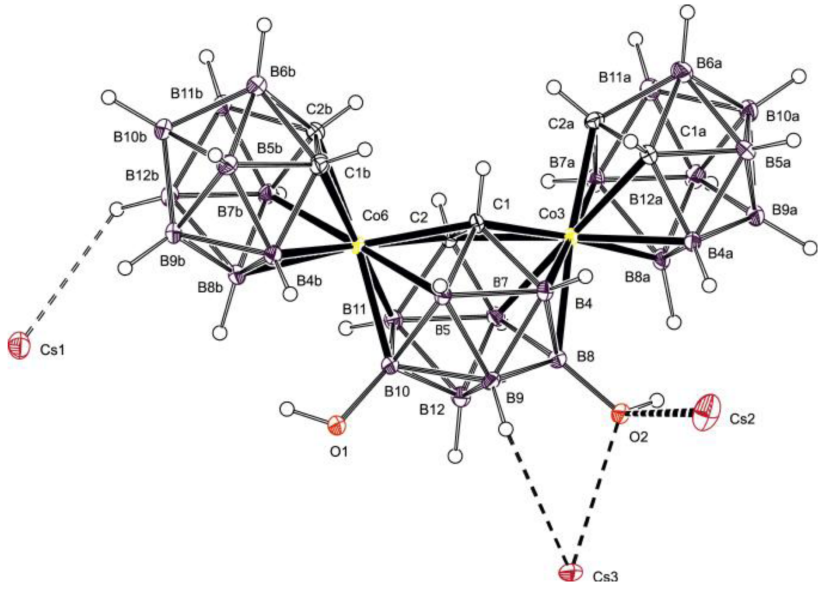


Fig. 2 Molecular structure of Cs_2**3a** salt (ORTEP view, 30 % probability level). Selected interatomic distances [Å] and angles [º]: O2-B8 1.425 (6), O1-B10 1.434 (6), O1-Cs2 2.993 (4), O1-Cs3 3.003 (3), Co3-B8 2.109 (5), Co3-B8A 2.106 (5), Co3-C1 2.069 (4), Co6-B10 2.105 (5), Co6-C1B 2.059 (5), Co6-C1 2.062 (4), C1A-C2A 1.618 (7), C1B-C2B 1.629 (7), B4-B8 1.827 (8), B8-B9 1.800 (7), O1-B10-Co6 122.3 (3), O1-B10-B11 126.9 (4), B8-O2-Cs2 105.1 (3), B8-O2-Cs3 110.6 (3), C2-Co3-C1A 132.6 (2), C1-Co3-B8 84.85 (19).

by about 14 ppm. The spectra of **3b**$^{2-}$ and **3c**$^{2-}$ both exhibit two singlets of intensity 1 located at 35.3 and 23.6 ppm, or 32.5 and 18.9 ppm, respectively.

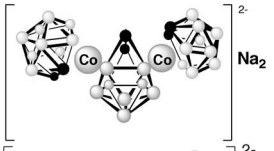
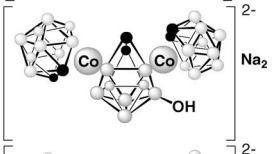
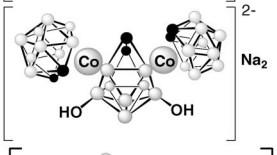
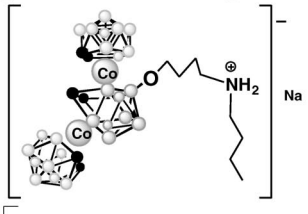
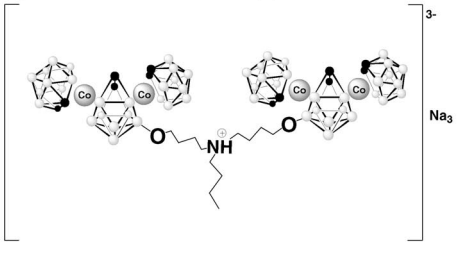
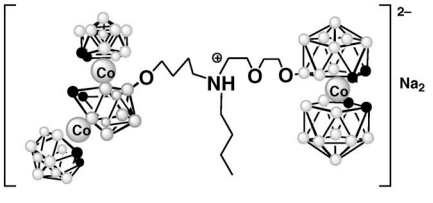
The ^{1}H and ^{13}C NMR spectra of all isolated salts of the respective ions are in complete agreement with the expected structures and product composition. The ratios of the cage CH signals vs. the respective signals of the CH_2 groups of the chain and end-groups in compounds from series **5a–d**$^{-}$, **5e,f**$^{2-}$, **6**$^{3-}$, and **7**$^{2-}$ are also in accord with the presence of the expected organic residues.

Almost all compounds exhibit the respective molecular *m*/*e* base peaks $[M]^{-}$, $[M]^{2-}$, or $[M]^{3-}$ for the respective ionic species in their ESI^{-} mass spectra. The only exception is for the reactive **4**$^{-}$ where only the peak corresponding to products from ring-opening reactions with solvent could be observed. For each particular boron cluster compound, the experimental and calculated isotopic patterns were in agreement with those calculated (using Mass Spectrometric's software, the EXcalibur).

INHIBITION ASSAYS

The parent compound and derivatives Na_2**2a**, Na_2**3a**, Na**5a**, Na_3**6**, and Na_2**7** were tested in the form of the respective sodium salts for their ability to inhibit cleavage of the peptide substrate KARVNle*NphEANle-NH_2 by the recombinant HIV-PR. The peptide substrate is modified in the vicinity of the scissile peptide bond so as to follow its hydrolysis spectrophotometrically as previously described [53]. Inhibitory concentrations needed to decrease the HIV-PR activity to one-half of its maximal value (IC_{50} values) were determined from the plot of the initial velocity of the enzymatic reaction vs. the inhibitor concentration. (The corresponding IC_{50} values are summarized in Table 1.)

Table 1

No.	Chemical formula	IC_{50}	Mechanism of inhibition
Na_2DD		100 nM	noncompetitive
Na_2**2a**		8.7 μM	
Na_2**3a**		1.8 μM	
Na5a		290 nM	uncompetitive
Na_3**6**		28 nM	low concentrations - noncompetitive high concentrations - mixed
Na_2**7**		95 nM	mixed

Interestingly, by inspecting the data in Table 1, a high decrease in the enzyme activity can be seen for the unsubstituted parent **DD**$^{2-}$ anion. The inhibition activity, in fact, is approximately 10 times higher than that observed for the **CD**$^{-}$ ion. The substitution by hydroxy groups, on the other hand, led in general to an appreciable decrease of the inhibitor's efficiency. Such an effect has been already observed for the hydroxy derivatives of the smaller **CD**$^{-}$ ion. The single cluster derivative **5a**$^{-}$ containing the terminal butylammonium group attached via flexible oxatetramethyl linker shows also a threefold decrease. On the other hand, both of the double cluster compounds Na_3**6** and Na_2**7** exhibit increased inhibition potency with IC_{50} values in the sub-micromolar range. Only a slight improvement in the IC_{50} value was observed for Na_2**7** incorporating two different clusters in the structure of **7**$^{2-}$. However, the binding to the enzyme was improved by a factor of four by designing a symmetric compound containing two larger **DD**$^{2-}$ clusters in **6**$^{3-}$.

Another question was whether a boron cluster of $\mathbf{DD}^{2-}$ anion might serve as convenient hydrophobic building blocks that can bring desired important hydrophobic interaction within the hydrophobic domain of PR close to the binding site. To answer that question, the mechanisms of inhibition were determined from the Lineweaver–Burk plots. Sodium salt of parent $\mathbf{DD}^{2-}$ ion exhibits a noncompetitive binding mode, and that follows from the double reciprocal Lineweaver–Burk plot of initial velocities of chromogenic peptide substrate cleavage against substrate concentration in three different concentrations of parent compound $\mathbf{DD}^{2-}$. A similar analysis of the other tested compounds provided equivalent results or revealed a mixed (competitive/noncompetitive) mechanism or even the quite unusual uncompetitive mode in the case of **5a** (data are shown in Table 1). This kinetic analysis suggests that tested $\mathbf{DD}^{2-}$ ions do not compete with the peptide substrate and, therefore, most probably are specifically bound outside the active cleft of the enzyme. Due to different mechanisms of inhibition, the inhibition constants (K_i values) could not be reliably determined. At this point, it seems difficult to discuss here the structure–activity relationships for noncompetitive or mixed inhibitors until structural information on the mode of binding for these compounds becomes available. The binding site might involve a functionally important part of the enzyme such as the dimerization domain or the flap region. A noncompetitive mode might also be theoretically caused by the formation of inhibitor aggregates binding outside the active site to other functionally important regions of the enzyme. Indeed, the aggregation of sodium salt of parent ion $Na_2\mathbf{DD}$ in aqueous solutions has already been described. On the other hand, we observe a consistent, specific dose-dependent enzyme inhibition pattern that seems not compatible with the model for nonspecifically occluding inhibitor molecules (aggregates) in the enzyme. More structural work is needed before we can conclusively address the mechanism of action of these compounds.

CONCLUSIONS

In this paper, we present the first attempts at the substitution chemistry of the $\mathbf{DD}^{2-}$ anion and their implications for design of HIV-PR inhibitors as the basis of larger and divalent ions. As has been outlined, the $\mathbf{DD}^{2-}$ ion easily undergoes hydroxylation reactions producing a series of mono- and disubstituted hydroxyl derivatives. The stereochemistry of these reactions and of the resulting products was experimentally determined. These compounds can serve further for convenient derivatization, however, even more versatile in this respect seems to be compound $\mathbf{4}^-$ substituted by a cleavable five-atom ring containing the oxygen atom. As proven by examples of reactions with a basic set of nucleophiles, this building block enables the easy covalent bonding of $\mathbf{DD}^{2-}$ cluster anion with amines, phosphines, and phenolate ions. As anticipated, the synthesis of this pilot series of compounds indicates further emerging possibilities to introduce the $\mathbf{DD}^{2-}$ fragment into various larger organic platforms, such as crown ethers, calixarenes, dendrimers, porphyrines, nucleosides, nucleotides, and many other functional molecules closely related to examples described with use of dioxane derivative of $\mathbf{CD}^-$ ion [18]. Thus, these compounds became easily accessible. The potential for construction of large molecular scaffolds is demonstrated by the synthesis of dicluster species containing two identical or different metallacarborane cages in the structure. The larger part of tested compounds inclusive of the parent ion are efficient, sub-micromolar inhibitors of the wild type of HIV-PR, the lowest IC_{50} value 28 nM being observed for dicluster molecule composed of two symmetrically bound $\mathbf{DD}^{2-}$ cages. The mechanism of inhibition corresponds to a noncompetitive or mixed mode. This suggests specific binding of inhibitors outside the active site, or it might also be explained by the activity of inhibitor aggregates that bind outside of the enzyme cavity.

EXPERIMENTAL

The cesium salt of double-decker dicobalta sandwich ion (**1**, Cs_2**DD**) was purchased from Katchem Ltd., Czech Republic. Solvents, i.e., THF, ethylene glycol dimethyl ether (DME), and toluene were dried with sodium diphenyl ketyl and distilled prior to use. Other chemicals and solvents were purchased from Aldrich, Lachema a.s., and Penta Ltd., Czech Republic, respectively, and used without purification. Analytical thin layer chromatography (TLC) was carried out on TLC plates Silufol® (silica gel layer on aluminum foil with starch as the binder) from Lachema, or RP-8-F_{254} S, Merck (0.25 mm layer of octyl silica on glass formers 20 × 5 cm) in the reverse phase mode. Unless otherwise specified, column chromatography was performed on a high-purity silica gel (Merck Grade, Type 7754, 70–230 mesh, 60 Å).

All reactions were performed using standard vacuum or inert-atmosphere techniques as described by Shriver [54], although some operations, such as flash chromatography and crystallization, were carried out in the air.

Melting points were determined in sealed capillaries on the BŰCHI Melting Point B-545 apparatus and are not corrected. Nevertheless, the identity of all the reported compounds has been unambiguously proven by a combination of the ^{11}B, ^{13}C, ^{1}H NMR spectral data (complete assignment of the resonances), with mass spectrometry (two decimal digits resolution), m.p., TLC, elemental analysis and other methods. The purity of the isomeric hydroxy derivative was assessed by an analytical HPLC with diode array detector (DAD), except for **3b**$^{2-}$ (and **3c**) being better than 98 %.

Instrumental techniques

^{1}H, ^{13}C, and ^{11}B NMR spectra were measured on a Varian Mercury 400^{Plus} Instrument. The spectra of all compounds were measured immediately after dissolution. ^{11}B NMR (120 MHz) chemical shifts are given in ppm to high-frequency (low field) to $F_3B{\cdot}OEt_2$ as the external reference. Residual solvent ^{1}H resonances were used as internal secondary standards. Coupling constants $^{1}J(^{11}B–^{1}H)$ are taken from resolution-enhanced ^{11}B spectra with a digital resolution of 2 Hz. The NMR data are presented in the text as follows: ^{11}B NMR: ^{11}B chemical shifts $\delta(^{11}B)$ (ppm), multiplicity, coupling $J(^{11}B–^{1}H)$ constants are given in Hz. Signal assignments are based on [^{11}B-^{11}B] correlation spectroscopy (COSY) NMR spectroscopy. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz): chemical shifts $\delta(^{1}H)$ are given in ppm relative to Me_4Si (0 ppm) as the external standard, coupling constants $J(H,H)$ in Hz.

Mass spectrometry measurements were performed on a Thermo-Finnigan LCQ-Fleet Ion Trap instrument using electrospray ionization (ESI) with detection of negative ions. Samples dissolved in acetonitrile (concentrations approximately 100 ng·ml^{-1}) were introduced to the ion source by infusion of 5 µl/min^{-1}, source voltage –5.48 kV, tube lens voltage –114.7 V, capillary voltage –49.0 V, drying temperature was 160 °C, drying gas flow 6 l min^{-1}, and auxiliary gas pressure 6 bar. In most cases, the negative ions corresponding to the molecular ion were observed with 100 % abundance for the highest peak in the isotopic distribution plot. Molecular ions $[M]^-$ were detected for all univalent or $[M]^{2-}$ and $[M]^{3-}$ for polyvalent anions as the base peaks in the spectra. Full agreement of the experimental and calculated isotopic distribution pattern was observed for all isolated compounds. The isotopic distribution in the boron plot of all peaks is in perfect agreement with the calculated spectral pattern. The data are presented for the most abundant mass in the boron distribution plot (100 %) and for the peak corresponding to the *m/e* value.

Analytical HPLC was performed on Merck-Hitachi HPLC system LaChrom 7000 series equipped with a DAD 7450 detector and an Intelligent Injector L7250. *Chromatographic conditions used for hydroxyl derivatives*: The chromatographic IP-RP procedure based on the methods previously reported [55] for the separation of hydrophobic borate anions was applied by using a buffer containing 4.5 mmol/l hexylamine acetate in 53 % aqueous CH_3CN, pH 6.5. Column: RP Separon™ SGX C8, 7 µm (silica with chemically bonded octyl groups), Tessek Prague, Czech Republic. Capacity factors

$k' = (t_R - t_0)/t_0$ (where t_R is retention time, t_0 is the void retention time of a nonretained peak) are given for individual compounds; $k' = 4.16$ was observed for the parent unsubstitute $\mathbf{DD}^{2-}$ ion which was 4.16 under the same chromatographic conditions. The purity assay was based on the peaks area on the chromatograms of the individual compounds.

X-ray structure determinations: Crystal data for Cs_2**3a**: $Cs_2{\cdot}C_6H_{32}B_{26}Co_2O_2$ M = 801.06, monoclinic, *C*2/*c* (No 15), a = 33.4520 (5) Å, b = 7.09890 (10)Å, c = 24.0007 (3)Å, β = 104.7199 (9)º, V = 5512.44 (13)Å^3, Z = 8, D_x = 1.930 Mg m^{-3}. A red crystal of dimensions 0.25 × 0.2 × 0.15 mm was mounted on glass capillary with epoxy glue and measured at Nonius Kappa-CCD diffractometer by monochromatized MoKα radiation (λ = 0.71073 Å) at 150(2) K. The data were corrected for absorption using numerical correction (μ = 3.82 mm^{-1}, T_{min} = 0.361, T_{max} = 0.552); a total of 35 170 measured reflections (θ_{max} = 27.5º), from which 6302 were unique (R_{int} = 0.042), 5380 observed according to the $I > 2\sigma(I)$ criterion. The structure was solved by direct methods (SIR92) and refined by full-matrix least squares based on F^2 (SHELXL97) [56]. The hydrogen atoms were fixed into idealized positions (riding model) and assigned temperature factors $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom). The refinement converged (Δ/σ_{max} = 0.001) to R = 0.047 for observed reflections and wR = 0.123, GOF = 1.03 for 350 parameters and all 6302 reflections. The final difference map displayed peaks ($\Delta\rho_{max}$ = 3.52), ($\Delta\rho_{min}$ –4.82 e.Å^{-3}). The highest positive as well as lowest negative maxima occur in the vicinity of Cs2 and Cs3 atoms. One Cs is placed in special position on a twofold axis and therefore has an occupancy factor equal to 0.5. The other two Cs atoms are in positions with site symmetry 1, however, to comply with the overall composition of title compound, one of these must have an occupational factor also equal to 0.5. The interactions of Cs atoms with carborane cages and –OH moieties form a complicated polymeric structure.

Synthetic procedures

General method to hydroxy derivative 2a,b^{2-} and 3a–c^{2-}: Only reaction conditions and results from one experiment out of two others (differing in shorter and longer reaction times) are described below, under which the $\mathbf{DD}^{2-}$ disappeared completely from the reaction mixture and the product composition and yields fit to all the isolatable species depicted in Scheme 1. The cesium salt Cs_2DD (1.0 g) was poured into 48 % aqueous sulfuric acid (40 ml) and the resulting slurry was vigorously stirred and heated to 100 °C and stirring was continued for 7 h. After cooling down, water (100 ml) was added and the products were extracted into ether (3 × 30 ml). Water (20 ml) was added to the combined ether extracts, and ether was evaporated under reduced pressure. An aqueous solution of CsCl was added to the resulting dark red aqueous solution, the precipitate was filtered, redissolved in hot aqueous ethanol (30 %), and the solution was left to crystallize for 2 days. The crystals were collected. Mono- and disubstituted derivatives and the respective isomers were separated using LPC on Merck Lobar® LiChroprep® Si60(40–63 µm) column, Size C, using CH_2Cl_2–CH_3CN 3:7 solvent mixture for elution, flow rate 15 ml/min, and visual and UV detection at 270 nm. The first collected fraction contained the monosubstituted species **2a,b**, the second well-separated band the dihydroxy derivatives **3b**$^{2-}$ and **3c**$^{2-}$, and last fraction pure symmetric dihydroxy derivative **3a**$^{2-}$. The second separated fraction was evaporated and once more separated by chromatography and under the same conditions recovered the species Cs_2**3a** and Cs_2**3b**. The first chromatographic fracture was evaporated, dissolved in CH_2Cl_2-i-PrOH (9:1), injected atop a silica gel column (25 × 1.8 cm I.D.) and, eluted with the same solvent mixture as mobile phase, eluting essentially pure Cs_2**2a** and Cs_2**2b**. The reaction mixture and the collected chromatographic fractions were monitored by the HPLC method described above. All isolated products were crystallized from hot water, producing dark violet crystals in the case of Cs_2**2a** and Cs_2**2b** and Cs_2**3a** submitted for crystallographic studies. The isolatable yields and data for charaterization are given below.

$Cs_2[(1',2'\text{-}C_2B_9H_{11})Co(8\text{-}HO\text{-}C_2B_8H_9)Co(1'',2''\text{-}C_2B_9H_{11})]$ ($Cs_2$2a)

Yield: 225 mg, 22 %, m.p. > 360 °C (dec.); HPLC k' 2.23; ^{1}H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 4.24 (2H, s, carborane C*H*), 3.81 (1H, s, O*H*), 3.50 (2H, s, carborane C*H*), 3.21 (2H, s, carborane C*H*); δ_{B-H} resonances in ^{1}H{^{11}B} NMR found in the range 3.40–1.29 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 35.50 (1B, s, B8), 14.48 (1B, d, *J* = 137 Hz, B10), 4.61 (2B, d, *J* = 137 Hz, B8',8''), –0.34, –1.67 (4B, 2d, *J* = 157 and 158 Hz, B4,7,5,11), –3.45, –4.81 (2B, 2d, *J* = 153 and 155 Hz, B10',10''), –7.0, –9.71 (4 + 6B, 2d, overlap, B(4',4'',7',7'',9, 9',9'',12,12',12''), –19.32 (4B, d, *J* = 149 Hz, B5',5'',11',11''), –23.74 (2B, d, overlap, *J* ≈ 150 Hz, B6',6''). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 53.8 (2C, carborane *C*H), 49.2 (2C, carborane *C*H), 48.0 (2C, carborane *C*H). *m/z* (ESI$^-$): 261.67 (10 %), 259.67 (100 %) $[M]^{2-}$; Calcd. 261.68 and 259.69. Anal.: found C, 8.9; H, 4.0. Calcd. for $B_{26}C_6H_{32}OCo_2Cs_2$: C, 9.18; H, 4.11.

$Cs_2[(8'\text{-}HO\text{-}1',2'\text{-}C_2B_9H_{10})\text{-}3',3\text{-}Co(1,2\text{-}C_2B_8H_{10})\text{-}6,3''\text{-}Co(1'',2''\text{-}C_2B_9H_{11})]$ ($Cs_2$2b)

Yield: 30 mg, 3 %, m.p. > 360 °C; HPLC k' 1.96; ^{1}H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 4.33 (2H, s, carborane C*H*), 3.81 (1H, br, O*H*), 3.45 (2H, s, carborane C*H*), 3.20 (2H, s, carborane C*H*), δ_{B-H} resonances in ^{1}H{^{11}B} NMR found in the range 3.15–1.11 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 23.51 (1B, s, B8'), 21.99, 21.59 (2B, 2d, overlap, B8,10), 4.49 (1B, d, *J* = 143 Hz, B8''), –0.05 (4B, d, *J* = 152 Hz, B4,7,5,11), –3.43, –6.28 (2B, 2d, *J* = 137 Hz, B10',10''), –7.71, –9.85 (8 and 2B, 2d, overlap, B4',4'',7',7'',9,9',9'',12,12',12''), –19.39, –21.03 (4B, 2d, *J* = 196 and 180 Hz, B5',5'',11',11''), –24.19 (1B, d, *J* = 168 Hz, B6''), –31.59 (1B, d, *J* = 171 Hz, B6'). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 53.8 (2C, carborane *C*H), 49.2 (2C, carborane *C*H), 48.0 (2C, carborane *C*H). *m/z* (ESI$^-$): 261.67 (10 %), 259.67 (100 %) $[M]^{2-}$, Calcd. 261.68 and 259.69. Anal.: found C, 8.9; H, 4.0. Calcd. for $B_{26}C_6H_{32}OCo_2Cs_2$: C, 9.18; H, 4.11.

$Cs_2[(1',2'\text{-}C_2B_9H_{11})\text{-}3',3\text{-}Co(8,10\text{-}(HO)_2\text{-}1,2\text{-}C_2B_8H_8)\text{-}6,3'''\text{-}Co(1'',2''\text{-}C_2B_9H_{11})]$ ($Cs_2$3a)

Yield: 85 mg, 8 %, m.p. > 360 °C; HPLC k' 1.59; ^{1}H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 3.89 (2H, s, O*H*), 3.56 (4H, s, carborane C*H*), 3.34 (2H, s, carborane C*H*); δ_{B-H} resonances in ^{1}H{^{11}B} NMR found in the range 3.20–1.42 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 28.78 (2B, s, B8,10), 4.59 (2B, d, *J* = 137 Hz, B8',8''), –2.23 (4B, d, *J* = 137 Hz, B4,7,5,11), –4.16 (2B, d, *J* = 150 Hz, B10',10''), –6.53, –7.85 –8.99 (2 + 6 + 2B, 3d, B4',4'',7',7'',9,9',9'',12,12',12''), –18.98 (4B, d, *J* = 147 Hz, B5',5'',11',11''), –22.99 (2B, d, B6',6''). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 53.8 (2C, carborane *C*H), 49.2 (2C, carborane *C*H), 48.0 (2C, carborane *C*H). *m/z* (ESI$^-$): 269.67 (10 %), 267.75 (100 %) $[M]^{2-}$. Calcd. 269.68 and 267.68. Anal.: found C, 8.8; H, 3.9. Calcd. for $B_{26}C_6H_{32}O_2Co_2Cs_2$: C, 9.00; H, 4.03.

$Cs_2[(1',2'\text{-}C_2B_9H_{11})\text{-}3,3'\text{-}Co(8\text{-}(HO)\text{-}1,2\text{-}C_2B_8H_9)\text{-}6,3''\text{-}Co(8''\text{-}HO\text{-}1'',2''\text{-}C_2B_9H_{11})]$ ($Cs_2$3b *apart*-isomer)

Yield: 250 mg, 24 %, isomeric purity 92 % (HPLC), m.p. > 360 °C; HPLC k' 1.28; ^{1}H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 4.00 (2H, s, carborane C*H*), 3.89 (2H, s, O*H*), 3.31 (2H, s, carborane C*H*), 3.22 (2H, s, carborane C*H*). δ_{B-H} resonances in ^{1}H{^{11}B} NMR found in the range 3.10–1.20 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 35.45 (1B, s, B8), 23.70 (1B, s, B8''), 14.74 (1B, d, *J* = 143 Hz, B10), 4.59 (2B, d, *J* = 137 Hz, B8'), –0.36, –2.10 (4B, 2d, *J* = 156 and 157 Hz, B4,7,5,11), –4.16 (2B, d, *J* = 141 Hz, B10',10''), –8.19 (10B, 3d, overlap, B4',4'',7',7'',9,9',9'',12, 12',12''), –19.25 –21.03 (4B, 2d, *J* = 165 and 166 Hz, B5',11', 5'',11''), –23.48 (1B, d, *J* = 158 Hz, B6'), –31.40 (1B, d, *J* = 161 Hz, B6''). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 52.7 (2C, carborane *C*H), 48.3 (2C, carborane *C*H), 44.4 (2C, carborane *C*H). *m/z* (ESI$^-$): 269.67,

(10 %), 267.75, (100 %) $[M]^{2-}$. Calcd. 269.68 and 267.68. Anal.: found C, 8.6; H, 3.8. Calcd. for $B_{26}C_6H_{32}O_2Co_2Cs_2$: C, 9.00; H, 4.03.

Cs_2[(1',2'-$C_2B_9H_{11}$)-3,3'-Co(8-(HO)-1,2-$C_2B_8H_9$)-6,3"-Co-(8"-HO-1",2"-$C_2B_9H_{11}$)] ($Cs_2$3c *syn*-isomer)

HPLC k' 1.41; NMR signals could be only subtracted from an enriched isomeric mixture containing ca. 40 % of this isomer. ^{1}H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 4.36 (2H, s, carborane C*H*), 3.84 (2H, s, O*H*), 3.43 (2H, s, carborane C*H*), 3.10 (2H, s, carborane C*H*). ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 32.64 (1B, s, B8), 23.70 (1B, s, B8'), 17.23 (1B, d, J = 143 Hz, B10), 4.59 (2B, d, J = 137 Hz, B8"), –0.36, –2.10 (4B, 2d, J = 156 and 157 Hz, B4,7,5,11), –4.59 (2B, d, J = 141 Hz, B10',10"), –8.19 (10B, 3d, overlap, B4',4",7',7",9,9',9",12,12',12"), –19.25 –21.03 (4B, 2d, J = 165 and 166 Hz, B5',11', 5",11"), –23.48 (1B, d, J = 158 Hz, B6'), –31.40 (1B, d, J = 161 Hz, B6"). *m/z* (ESI$^-$): 269.67, (10 %), 267.75, (100 %) $[M]^{2-}$. Calcd. 269.68 and 267.68.

Cs[(1',2'-$C_2B_9H_{11}$)-3,3'-Co(8-$(CH_2)_4O$)-1,2-$C_2B_8H_9$)-6,3"-Co(1",2"-$C_2B_9H_{11}$)] (Cs4)

Freshly distilled $F_3B{\cdot}OEt_2$ (450 µl, 3.65 mmol) was added in one portion to a suspension of dry Cs_2**1** (2.56 g, 3.33 mmol) in dry THF (120 ml). After stirring for 8 h at an ambient temperature, a second portion of $F_3B{\cdot}OEt_2$ (300 µl, 2.43 mmol) was added. A resulting wine red reaction mixture was stirred overnight. Afterward, the volatiles were removed in vacuo. The residue was mixed with high-purity silica gel (ca. 6 g) and dried in vacuo for an additional 30 min. The desired tetrahydrofuranate derivative (cesium salt, Cs**2**) was isolated by flash column chromatography using CH_2Cl_2–CH_3CN (4:1, v/v) solvents mixture as the mobile phase. The first minor rapidly moving red–orange band was not collected. The next wine red band contained the desired product. The elution of this fraction continued until two distinct red spots of the product on TLC (R_F = 0.25; CH_2Cl_2–CH_3CN 3:1, v/v) eluted. Cs**4** was isolated as a wine red crystalline solid after removing the volatiles in vacuo. The yield was 1.08 g (46 %). The title compound can be stored for several weeks under an argon atmosphere in a freezing box (ca. –35 °C). The melting point was not measured. ^{1}H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 4.75 (4H, t, OCH_2), 4.20 (2H, s, carborane C*H*), 3.58 (4H, s, carborane C*H*), 2.25 (4H, m, OCH_2CH_2); $\delta_{B–H}$ resonances in ^{1}H{^{11}B} NMR found in the range 3.50–1.30 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 31.20 (1B, s, B8), 17.72 (1B, d, J = 147 Hz, B10), 5.57 and 4.73 (2B, 2d, overlap, J = 131 and 134 Hz, B8',8"), –1.47, –3.26 (4B, d, $J \approx$ 152 Hz, B4,7,5,11), –4.97 (2B, d, B10',10"), –6.56 (8B, d, overlap, B4',4",7',7",9',9",12',12"), –10.29 (2B, d, J = 134 Hz, B9,12), –18.17 (4B, d, J = 128 Hz, B5',5",11',11"), –23.21 (2B, d, J = 119 Hz, B6',6"). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 81.7 (2C, OCH_2), 53.5 (2C, carborane *C*H), 50.6 (4C, carborane *C*H), 25.2 (2C, OCH_2CH_2). *m/z* (ESI$^-$, MeOH): 591.4 (100 %), 596.4 (5 %) $[M + OH]^-$, 574.4 (92 %), 579.40 (4 %) $[M^-]$. Calcd. 574.36 and 579.41. Anal.: found C, 16.6; H, 5.4. Calcd. for $B_{26}C_{10}H_{39}OCo_2Cs$: C, 16.98; H, 5.56.

Me_4N[(1',2'-$C_2B_9H_{11}$)Co(8-($BuH_2N(CH_2)_4O$)-$C_2B_8H_9$)Co(1",2"-$C_2B_9H_{11}$)] (Me_4N5a)

Cs**4** (800 mg, 1.13 mmol) was dissolved in dry THF (30 ml) and and *n*-butylamine (335 µL, 3.39 mmol) was added. The reaction mixture was stirred for 2 days at an ambient temperature. The reaction mixture was then filtered, and the wine red filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (25 ml). Resulting wine red solution of the crude product was washed with aqueous HCl (3 × 10 ml) and then with water (2 × 10 ml). The wine red organic layer was separated and mixed with water (10 ml). The ethyl acetate was then carefully removed in vacuo. Ethanol (ca. 10 ml) was added to the residue, thereby giving a clear solution. The product was precipitated by an excess of aqueous Me_4NCl, the solid was filtered and dried under reduced pressure. Me_4N**5a**, yield

723 (88 %). m.p. 157–159 °C. TLC (CH_2Cl_2–CH_3CN 3:1 by volume): R_F = 0.28. ^1H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 8.62 (2H, br, BuH_2N), 4.44 (2H, s, carborane C*H*), 3.83 (2H, br t, OCH_2), 3.58 (2H, t, $J_{H–H}$ = 6 Hz, NCH_2), 3.50 (2H, s, carborane C*H*), 3.44 (12H, s, Me_4N), 3.32 (2H, s, carborane C*H*), 3.18 (2H, br m, NCH_2), 1.92 (4H, br m, CH_2CH_2), 1.77 (2H, m, CH_2), 1.43 (2H, m, CH_2), 1.11 (3H, t, $J_{H–H}$ = 7 Hz, CH_3); $\delta_{B–H}$ resonances in $^1H\{^{11}B\}$ NMR found in the range 3.20–1.20 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 34.95 (1B, s, B8), 17.70 (1B, d, *J* = 146 Hz, B10), 4.99 (2B, d, *J* = 150 Hz, B8',8"), –3.25, –4.025 (6B, 2d, B4,7,5,11,10',10"), –6.83, –8.02, (10B, 2d, overlap, B4',4",7',7",9,9',9",12,12',12"), –19.19 (4B, d, *J* = 158 Hz, B5',5",11',11"), –23.87 (2B, d, *J* = 141 Hz, B6',6"). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 69.2 (1C, OCH_2), 56.0 (4C, m, Me_4N), 54.0 (2C, carborane *C*H), 49.5 (2C, carborane *C*H), 49.3 (1C, NCH_2), 48.8 (2C, carborane *C*H), 48.4 (1C, NCH_2), 30.9 (1C, CH_2), 28.9 (1C, CH_2), 26.1 (1C, CH_2), 20.6 (1C, CH_2), 13.9 (1C, CH_3). *m/z* (ESI$^-$): 651.50 (10 %), 647.50 (100 %) $[M]^-$, Calcd. 651.50 and 647.52. Anal.: found C, 29.5; H, 8.5. Calcd. for $B_{26}C_{18}H_{62}ON_2Co_2$: C, 29.96; H, 8.66.

$Me_4N[(1',2'\text{-}C_2B_9H_{11})Co(8\text{-}(C_5H_5N(CH_2)_4O)\text{-}C_2B_8H_9)Co(1'',2''\text{-}C_2B_9H_{11})]$ (Me_4N**5b**)

The compound was prepared reacting Cs**4** (707 mg, 1.00 mmol) in dry THF (30 ml) with pyridine (120 µl, 1.50 mmol). Pure crystalline dark red Me_4N**5b** isolated similarly as Me_4N**5b** and dried for ca. 8 h at 50 °C in vacuo. Yield 700 mg (89 %), m.p. 236 °C (dec.). TLC (CH_2Cl_2–CH_3CN 3:1 by volume): R_F = 0.10. ^1H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 9.22 (2H, d, $J_{H–H}$ = 6 Hz, H_{ortho}-Py), 8.72 (1H, t, $J_{H–H}$ = 8 Hz, H_{para}-Py), 8.25 (2H, t, $J_{H–H}$ = 7 Hz, H_{meta}-Py), 4.97 (2H, t, $J_{H–H}$ = 7 Hz, NCH_2), 4.73 (2H, s, carborane C*H*), 3.77 (2H, t, $J_{H–H}$ = 5 Hz, OCH_2), 3.56 (4H, s, carborane C*H*), 3.43 (12H, s, Me_4N), 2.20 (2H, m, CH_2), 1.55 (2H, m, CH_2). $\delta_{B–H}$ resonances in $^1H\{^{11}B\}$ NMR found in the range 3.30–1.10 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 35.57 (1B, s, B8), 16.30 (1B, d, *J* = 141 Hz, B10), 4.49, 3.92 (2B, 2d, *J* ≈ 140 Hz, B8',8"), –2.10, –4.77 (6B, 2d, B4,7,5,11 and B10',10"), –7.00, –8.79, –9.45 (10B, 3d, B4',4",7',7",9,9',9",12,12',12"), –19.36 (4B, d, *J* = 152 Hz, B5',5",11',11"), –23.88 (2B, d, *J* = 151 Hz, B6',6"). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 146.4 (1C, C_{para}-Py), 146.0 (2C, C_{ortho}-Py), 129.2 (2C, C_{meta}-Py), 68.5 (1C, OCH_2), 68.5 (1C, NCH_2), 56.1 (4C, m, Me_4N), 53.9 (2C, carborane *C*H), 49.8 (2C, carborane *C*H), 49.2 (2C, carborane *C*H), 30.6 (1C, OCH$_2$$CH_2$), 28.4 (1C, NCH$_2$$CH_2$). *m/z* (ESI$^-$): 657.33 (10 %), 653.33 (100 %) $[M]^-$; Calcd. 657.47 and 653.47. Anal.: found C, 29.8; H, 7.6. Calcd. for $B_{26}C_{19}H_{56}ON_2Co_2$: C, 31.36; H, 7.76.

$Me_4N[(1',2'\text{-}C_2B_9H_{11})Co(8\text{-}(Et_3N(CH_2)_4O)\text{-}C_2B_8H_9)Co(1'',2''\text{-}C_2B_9H_{11})]$ (Me_4N**5c**)

The procedure for synthesis and isolation was similar to that used for Me_4N**5a** reacting Cs**4** (707 mg, 1.00 mmol) and triethylamine (420 µl, 3.00 mmol). The product was isolated as a wine red powder. Me_4N**5c**, yield 630 (84 %), m.p. 177–180 °C. TLC (CH_2Cl_2–CH_3CN 3:1 by volume): R_F = 0.09. ^1H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 4.85 (2H, s, carborane C*H*), 3.67 (2H, t, $J_{H–H}$ = 5 Hz, OCH_2), 3.50–3.40 (22H, m, Me_4N, carborane C*H*, NCH_2 and N(C$H_2$$CH_3$)$_3$), 1.88 (2H, m, C$H_2$), 1.58 (2H, m, C$H_2$), 1.41 (9H, t, $J_{H–H}$ = 5 Hz, N(CH$_2$CH_3)$_3$). $\delta_{B–H}$ resonances in $^1H\{^{11}B\}$ NMR found in the range 3.30–1.10 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 35.11 (1B, s, B8), 16.11 (1B, d, *J* = 134 Hz, B10), 4.70, 3.28 (2B, 2d, *J* = 162 and 153 Hz, B8',8"), –1.67, –3.5, –4.81 (6B, 3d, B4,7,5,11,10',10"), –7.31, –8.28, –9.23, –9.87 (10B, 4d, B4',4",7',7",9,9',9",12,12',12"), –19.46 (4B, d, *J* = 156 Hz, B5',5",11',11"), –22.90, –24.60 (2B, 2d, *J* = 81 and 85 Hz, B6',6"). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 67.7 (1C, OCH_2), 58.1 (1C, NCH_2), 56.1 (4C, m, Me_4N), 53.9 (2C, carborane *C*H), 53.5 (3C, N($CH_2$$CH_3$)$_3$), 50.6 (2C, carborane *C*H), 49.1 (2C, carborane *C*H), 19.9 (1C, NCH$_2$$CH_2$), 7.9 (3C, N(CH$_2$$CH_3$)$_3$), the missing resonance of the OCH$_2$$CH_2$ carbon is overlapped by the signal of acetone-d_6. *m/z* (ESI$^-$): 679.20 (10 %), 675.33 (100 %) $[M]^-$; Calcd. 679.54 and 675.55. Anal.: found C, 31.8; H, 8.7. Calcd. for $B_{26}C_{20}H_{66}ON_2Co_2$: C, 32.04; H, 8.87.

Cs[(1',2'-$C_2B_9H_{11}$)-3,3'-Co-(8-($Ph_3P(CH_2)_4O$)-1,2-$C_2B_8H_9$)-6,3"-Co-(1",2"-$C_2B_9H_{11}$)] (Cs5d)

Cs_2**4** (270 mg, 0.38 mmol) was dissolved in dry THF (25 ml) and Ph_3P (108 mg, 0.41 mmol) was added. The reaction mixture was stirred for 2 days at an ambient temperature. The solids were then filtered off, washed with THF (2 × 10 ml) and the wine red filtrate was evaporated to dryness under reduced pressure. The crude reaction mixture was separated by column chromatography. The first minor rapidly moving red band of unidentified byproduct was eluted by dichloromethane. The wine red product was then eluted by CH_2Cl_2–CH_3CN solvents mixture (4:1, v/v) as a second band leaving an unidentified dark red band atop the column. Removal of all volatiles under reduced pressure gave a Cs**5d**, yield of 250 mg (68 %), m.p. 225–228 °C. TLC (CH_2Cl_2–CH_3CN 3:1 by volume): R_F = 0.20. ^1H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 8.05–7.66 (15H, m, Ph moieties), 4.77 (2H, s, carborane C*H*), 3.77 (4H, m, carborane C*H* and OCH_2), 3.52 (4H, m, carborane C*H* and PCH_2), 1.68 (4H, br m, CH_2CH_2). $\delta_{B–H}$ resonances in $^1H\{^{11}B\}$ NMR found in the range 3.20–1.10 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 35.64 (1B, s, B8), 16.40 (1B, br d, J = 141 Hz, B10), 4.82, 4,06 (2B, 2d, overlap, B8',8"), –1.74, –3,48, –4.59 (6B, 3d, overlap, B4,7,5,11,10',10"), –7.83, –8.75, –9.61 (10B, 3d, overlap, B4',4",7',7",9,9',9",12,12',12"), –19.32 (4B, d, J = 140 Hz, B5',5",11',11"), –23.00 and –24.00 (2B, d, overlap, J ≈ 115 and 118 Hz, B6',6"). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 135.7 (3C, d, $J_{C–P}$ = 2 Hz, C_{para}-Ph), 134.6 (6C, d, $J_{C–P}$ = 10 Hz, C_{ortho}-Ph), 134.6 (6C, d, $J_{C–P}$ = 12 Hz, C_{meta}-Ph), 119.9 (3C, d, $J_{C–P}$ = 86 Hz, C_{ipso}-Ph), 69.4 (1C, OCH_2), 53.9 (2C, carborane *C*H), 50.3 (2C, carborane *C*H), 49.2 (2C, carborane *C*H), 32.1 (1C, d, $J_{C–P}$ = 16 Hz, OCH$_2$*C*H$_2$), 21.9 (1C, d, $J_{C–P}$ = 50 Hz, P*C*H$_2$CH$_2$), 21.8 (1C, d, $J_{C–P}$ = 3 Hz, PCH$_2$*C*H$_2$). ^{31}P NMR δ_P(161.9 MHz; acetone-d_6; H_3PO_4, 295 K, ppm) 25.1. *m/z* (ESI$^-$): 840.42 (10 %), 836.50 (100 %) $[M]^-$; Calcd. 836.52 and 840.50. Anal.: found C, 34.3; H, 5.4. Calcd. for $B_{26}C_{28}H_{54}OPCo_2Cs$: C, 34.59; H, 5.61.

$(Me_4N)_2$[(1',2'-$C_2B_9H_{11}$)-3,3'-Co(8-(4-*t*-BuPhO(CH_2)$_4$O)-$C_2B_8H_9$)-6,3"-Co(1",2"-$C_2B_9H_{11}$)]

[(Me_4N)$_2$**5e**] 4-*t*-butylphenol (165 mg, 1.10 mmol) and potassium carbonate (690 mg, 5.00 mmol) were reacted in dry acetonitrile (25 ml) for 2 h at an ambient temperature, then Cs**4** (707 mg, 1.00 mmol) was added and the resulting wine red suspension was stirred for 2 days at room temperature. The reaction mixture was filtered and the wine red filtrate was evaporated to dryness in vacuo. The crude product was then dissolved in ethyl acetate and washed with aqueous HCl and water. The wine red (Me_4N)$_2$**5e** was precipitated in the form of its bis(tetramethylammonium) salt, recrystallized from hot aqueous ethanol, the solid was filtered and dried for 4 h in vacuo. Yield 820 mg (94 %), m.p. 142–145 °C. TLC (reverse phase, CH_3OH–H_2O 3:1 by volume): R_F = 0.60. ^1H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 7.29 (2H, d, $J_{H–H}$ = 9 Hz, H_{meta}-Ph), 6.85 (2H, d, $J_{H–H}$ = 8 Hz, H_{ortho}-Ph), 5.11 (2H, s, carborane C*H*), 3.97 (2H, t, $J_{H–H}$ = 7 Hz, OCH_2), 3.86 (2H, s, carborane C*H*), 3.66 (2H, t, $J_{H–H}$ = 6 Hz, OCH_2), 3.49 (2H, s, carborane C*H*), 3.44 (24H, s, Me_4N), 1.80 (2H, m, CH_2), 1.63 (2H, m, CH_2), 1.27 (9H, s, C(CH_3)$_3$); $\delta_{B–H}$ resonances in $^1H\{^{11}B\}$ NMR found in the range 3.25–1.30 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 34.50 (1B, s, canastide-B8), 16.14 (1B, d, J = 143 Hz, canastide-B10), 4.60, 1.41 (2B, 2d, J = 140 and 137 Hz, B8',8"), –1.86, –3.88, –4.73 (6B, 3d, overlap, B4,7,5,11, B10',10"), –6.86, –7.94, –9.50, –10.25 (10B, 4d, B4',4",7',7",9,9',9",12,12',12"), –19.44 (4B, d, J = 153 Hz, B5',5",11',11"), –23.52, –24.10 (2B, 2d, B6',6"). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 157.9 (1C, C_{ipso}-Ph), 143.4 (1C, C_{para}-Ph), 126.9 (2C, C_{meta}-Ph), 114.8 (2C, C_{ortho}-Ph), 68.6 (1C, O*C*H$_2$), 68.3 (1C, O*C*H$_2$), 56.1 (8C, m, Me_4N), 53.9 (2C, carborane *C*H), 51.6 (2C, carborane *C*H), 49.1 (2C, carborane *C*H), 34.5 (1C, *C*(CH$_3$)$_3$), 31.9 (3C, C(*C*H$_3$)$_3$), 27.2 (2C, br, *C*H$_2$*C*H$_2$). *m/z* (ESI$^-$): 363.83 (10 %), 361.92 (100 %) ($[M]^{2-}$; Calcd. 363.76 and 361.76. Anal.: found C, 38.3; H, 8.5. Calcd. for $B_{26}C_{28}H_{76}O_2N_2Co_2$: C, 38.57; H, 8.79.

$(Me_4N)_2[(C_2B_9H_{11})Co(8\text{-}(2\text{-}CH_3OPhO(CH_2)_4O)\text{-}C_2B_8H_9)Co(C_2B_9H_{11})]$ [$(Me_4N)_2$**5f**)]

The procedure was similar with the preparation and isolation of $(Me_4N)_2$**5e** reacting Cs**4** (707 mg, 1.00 mmol) with 2-methoxy-1-phenol (136 mg, 1.10 mmol) deprotonated with potassium carbonate (690 mg, 5.00 mmol). The product was isolated as a wine red powder similar to the compound $(Me_4N)_2$**5e**. Yield 778 mg (92 %), m.p. 122–125 °C. TLC (reverse phase, $CH_3OH–H_2O$ 3:1 by volume): R_F = 0.70. ^{1}H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 6.98 (1H, m, *H6*-Ph), 6.92 (1H, m, *H5*-Ph), 6.86 (2H, m, *H3,4*-Ph), 5.10 (2H, s, carborane C*H*), 4.00 (2H, t, $J_{H–H}$ = 6 Hz, OCH_2), 3.84 (2H, s, carborane C*H*), 3.79 (3H, OCH_3), 3.67 (2H, t, $J_{H–H}$ = 6 Hz, OCH_2), 3.48 (2H, s, carborane C*H*), 3.43 (24H, s, Me_4N), 1.83 (2H, m, CH_2), 1.64 (2H, m, CH_2); $\delta_{B–H}$ resonances in ^{1}H{^{11}B} NMR found in the range 3.25–1.20 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O·BF_3$, 295 K, ppm): 34.54 (1B, s, B8), 16.11 (1B, d, *J* = 146 Hz, B10), 4.56 and 1.49 (2B, d, *J* = 137 and 137 Hz, B8',8"), –1.85, –3.81, –4.78 (6B, 3d, overlap, B4,7,5,11, B10',10"), –6.92, –7.74, –9.49 to –10.23 (10B, 3d, overlap, B4',4",7',7",9,9',9",12,12',12"), –19.41 (4B, d, *J* = 153 Hz, B5',5",11',11"), –23.55 and –24.18 (2B, d, B6',6"). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 150.6 (1C, *C2*-Ph), 149.9 (1C, *C1*-Ph), 121.8 (1C, *C5*-Ph), 121.6 (1C, *C4*-Ph), 114.4 (1C, *C6*-Ph), 113.3 (1C, *C3*-Ph), 69.6 (1C, O*C*H_2), 68.4 (1C, O*C*H_2), 56.3 (1C, O*C*H_3), 56.1 (8C, m, Me_4N), 53.9 (2C, carborane *C*H), 51.5 (2C, carborane *C*H), 49.1 (2C, carborane *C*H), 29.6 (1C, *C*H_2), 27.3 (1C, *C*H_2). *m/z* (ESI$^-$): 348.83 (10 %), 350.83 (100 %) $[M]^{2-}$; Calcd. 348.74 and 350.73. Anal.: found C, 35.4; H, 8.2. Calcd. for $B_{26}C_{25}H_{70}O_3N_2Co_2$: C, 35.50; H, 8.34.

$(Me_4N)_3\{(N,N\text{-}C_4H_9NH)[(1',2'\text{-}C_2B_9H_{11})\text{-}3',3\text{-}Co(8\text{-}(CH_2)_4O\text{-}C_2B_8H_9)\text{-}6,3''Co(1'',2''\text{-}C_2B_9H_{11})]_2\}$ [$(Me_4N)_3$**6**)]

Cs**5a** (391 mg, 0.50 mmol) was deprotonated with potassium carbonate (690 mg, 5.0 mmol) in dry acetonitrile and solution of Cs**4** (354 mg, 0.50 mmol) in acetonitrile (20 ml) was added and the reaction slurry was stirred overnight. The reaction mixture was filtered and the wine red filtrate was evaporated to dryness in vacuo. The crude product was then dissolved in ethyl acetate and washed with aqueous HCl and water. The wine red product $(Me_4N)_3$**6** was precipitated in the form of its bis(tetramethylammonium) salt, recrystallized from hot aqueous ethanol, the deposited solid was filtered and dried for 4 h in vacuo. Yield 635 mg (88 %), m.p. 200–202 °C. TLC (reverse phase, $CH_3OH–H_2O$ 3:1 by volume, R_F = 0.63). ^{1}H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 9.65 (1H, br, Bu*H*N), 4.75 (4H, s, carborane C*H*), 3.85 (4H, br, OCH_2), 3.68 (4H, br, NCH_2), 3.56 (4H, s, carborane C*H*), 3.44 (36H, s, Me_4N), 3.40 (4H, s, carborane C*H*), 3.20 (4H, br, NCH_2), 1.92 (4H, br, OCH_2CH_2), 1.62 (4H, m, OCH_2 CH_2CH_2 and $CH_2CH_2CH_3$), 1.45 (2H, m, CH_2CH_3), 1.02 (3H, t, $J_{H–H}$ = 7 Hz, CH_3); $\delta_{B–H}$ resonances in ^{1}H{^{11}B} NMR found in the range 3.30–1.10 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O·BF_3$, 295 K, ppm): 35.00 (2B, s, B8), 16.49 (2B, d, B10), 4.48 (4B, d, *J* ≈ 131 Hz, B8',8"), –1.93, –3.5, –4.55 (12B, 3d, overlap, B4,7,5,11,10',10"), –7.05, –8.22, –11.30 (20B, 3d, overlap, B5,11 and B4',4",7',7",9,9',9",12,12',12"), –19.33 (8B, d, *J* = 150 Hz, B5',5",11',11"), –23.38 (4B, br. d, B6',6"). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 68.4 (2C, O*C*H_2), 56.1 (12C, m, Me_4N), 53.9 (4C, carborane *C*H), 53.4 (2C, N*C*H_2), 50.1 (4C, carborane *C*H), 49.3 (4C, carborane *C*H), 49.1 (1C, N*C*H_2), 26.5 (1C, NCH_2CH_2), 22.4 (2C, NCH_2CH_2), 20.9 (1C, *C*H_2), 14.1 (1C, *C*H_3), the missing resonance of the two OCH_2CH_2 carbons is overlapped by the signal of acetone-d_6. *m/z* (ESI$^-$): 409.00 (10 %), 407.00 (100 %) $[M]^{3-}$; Calcd. 409.50 and 407.52. Anal.: found C, 29.5; H, 8.8. Calcd. for $B_{52}C_{25}H_{124}O_2N_4Co_4$: C, 29.96; H, 8.66.

Cs_2{(*N,N*-C_4H_9NH)-[(1',2'-$C_2B_9H_{11}$)-3',3-Co(8-$(CH_2)_4O$-$C_2B_8H_9$)-6,3''Co(1'',2''-$C_2B_9H_{11}$)][(8-$(CH_2CH_2O)_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-Co]} (Cs_2**7**)

Cs**5a** (391 mg, 0.15 mmol) was deprotonated with solid NaH (10 mg, 95 %, 0.4 mmol) in dry DME (10 ml) over 2 h and solution of **CD**-dioxane [(8-O$(CH_2CH_2)_2$O-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-Co] zwitterion (15 mg, 0.15 mmol) in DME (5 ml) was syringed and the reaction slurry was stirred for 48 h. The reaction was quenched by the careful addition of EtOH (2 ml) followed by a few drops of 3 M acetic acid. The solution was evaporated to dryness under reduced pressure, dissolved in CH_3CN–CH_2Cl_2 (1:2) solvent mixture and introduced atop a silica gel column (20 × 1.5 cm I.D.) and eluted using the same solvent composition as the mobile phase. The second dark band contained the crude product and was purified by repeated chromatography using identical conditions. The main band was then collected, solvents were evaporated under reduced pressure, and the residue was dissolved in 40 % aqueous ethanol. The dark red product was precipitated by addition of aqueous solution of CsCl in excess, filtered, washed with water (2 × 3 ml) and dried in vacuo. Yield 140 mg (62 %), m.p. 182–186 °C. TLC (reverse phase, CH_3OH–H_2O 3:1 by volume, $R_F = 0.46$). ^{1}H NMR δ_H(400 MHz, acetone-d_6, 295 K, ppm): 9.40 (1H, br s, Bu*H*N), 4.21 (2H, s, carborane C*H*), 4.18 (2H, s, carborane C*H*), 3.98 (2H, br m, OCH_2), 3.83 (2H, br t, OCH_2), 3.80 (2H, s, carborane C*H*), 3.64 (2H, s, carborane C*H*), 3.64 (2H, s, carborane C*H*), 3.50 (4H, br t, OCH_2), 3.37 (4H, m, NCH_2), 2.95 (2H, m, NCH_2), 1.98 (2H, br t, OCH_2CH_2 and $CH_2CH_2CH_3$), 1.70 (2H, m, $OCH_2CH_2CH_2$), 1.45 (2H, m, CH_2CH_3), 1.01 (3H, t, $J_{H–H}$ = 7 Hz, CH_3); $\delta_{B–H}$ found at 3.36–0.88 ppm. ^{11}B NMR δ_B(128 MHz, acetone-d_6, $Et_2O{\cdot}BF_3$, 295 K, ppm): 34.71 (1B, s, B8), 23.46 (1B, s, B8-**CD**$^-$), 15.50 (1B, br d, B10), 4.86 (3B, d, B8',8'',B8'-**CD**$^-$), 0.37, –2.62 (4B, 2d overlap, B10',10'', B10,10'-**CD**$^-$), –4.38 (6B4,7, 4',4'',7',7'',B4,7-**CD**$^-$, –7.90 (10B, 5d, overlap B5,11,9',9'',12',12'',B9,9',12,12'-**CD**$^-$), –17.39, –19.33 (8B, 4d, J = 150 Hz, B5',5'',11',11'', B5,5',11,11'-**CD**$^-$), –22.50 (2B, br m, overlap, B6',6''), –28.61 (1B, br d, overlap, B6-**CD**$^-$). ^{13}C NMR δ_C(100 MHz, acetone-d_6, 295 K, ppm): 62.9 (2C, OCH_2), 69.1 (2C, OCH_2), 65.46 (2C, OCH_2), 54.5 (4C, carborane *C*H), 53.4 (2C, NCH_2), 52.1 (2C, carborane *C*H), 49.3 (1C, NCH_2), 47.3 (4C, carborane *C*H), 29.3 (1C, OCH_2CH_2) 26.7 (1C, NCH_2CH_2), 20.9 (2C, NCH_2CH_2), 20.1 (1C, CH_2), 14.0 (1C, CH_3). *m/z* (ESI$^-$): 531.0 (5 %), 528.10 (100 %) $[M]^{2-}$; Calcd. 531.40 and 528.16; 1080.6 (12 %), 1088.6 (2 %) $[M + Na]^+$; Calcd. 1080.31 and 1088.79; Anal. Cs_2**7**: found C, 19.4; H, 5.7. Calcd. for $B_{44}C_{22}H_{78}O_3NCo_3$: C, 19.97; H, 5.94.

HIV-1-PR INHIBITION ASSAYS

HIV-1 protease (HIV-1 PR) enzyme: Protease expression, refolding, and purification were performed as described before [53]. The HIV-1 PR coding region from pNL4-3 isolate was amplified by PCR and cloned into the pET24a expression vector. HIV-1 PR encoded in the expression plasmid was expressed as inclusion bodies in *Escherichia coli* BL21 (DE3). Inclusion bodies were then washed and solubilized in 67 % (v/v) aqueous acetic acid. Protease was refolded by diluting in an excess of water and dialysis as described and purified to homogeneity by cation exchange FPLC using a MonoS column (Pharmacia Amersham, Uppsala, Sweden).

Inhibition of HIV PRs: The IC_{50} values were determined by spectrophotometric assay with the chromogenic substrate KARVNleNphEANle-NH_2 as described previously [12]. The mechanisms of inhibition were analyzed by plotting initial reaction rates vs. concentrations of substrate in the presence of various concentrations of inhibitor according to Lineweaver–Burk.

SUPPORTING INFORMATION AVAILABLE

Crystallographic data (CIF) for Cs_2**3a**. This material is available free of charge from the Crystallographic Data Centre under the deposition number CCDC874111.

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