Supporting Information

Design of HIV protease inhibitors based on inorganic polyhedral metallacarboranes.

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Supporting Information contents:

Table S1.

List of mutations and enzyme characteristics [K_m, k_{cat} and catalytic efficiencies (k_{cat}/K_m)] of PR variants analyzed in this study.

HIV-1 protease	Mutations	K_m [µM]	k_{cat} [s^{-1}]	k_{cat} / K_m [$mM^{-1}. s^{-1}$]
PR	---	15	30	1990
PR 1	D30N, N88D	18	24	1320
PR 2	M46I, A71V, V82T, I84V	48	14	300
PR 3	A71V, V82T, I84V	36	11	300
PR 4	V32I, I47A	35	7.5	220
PR 5	L10I, I15V, E35D, N37S, R41K, I62V, L63P, A71V, G73S, L90M	8.3	12	1450
PR 6	L10I, L24I, L33F, M46L, I54V, L63P, A71V, V82A, I84V	14	6.4	460
PR 7	L10F, L19I, K20R, L33F, E35D, M36I, R41K, F53L, I54V, L63P, H69K, A71V, T74P, I84V, L89M, L90M, I93L	13	10	800

Table S2.

Ki values [nM] for the inhibition of PR mutants by 7 clinically used inhibitors and by selected metallacarborane inhibitors. The inhibition constants were determined using spectrophotometric assay at the pH optimum of the protease (pH 4.7).

	Ki [nM]											
HIV-1 PR	SQV[a]	IDV[a]	NFV[a]	LPV[a]	APV[a]	AZV[a]	DRV [a]	1 [a]	2[a]	4	5	13
PR	0.04 ± 0.01	0.12 ± 0.02	0.07 ± 0.01	0.018 ± 0.009	0.18 ± 0.02	0.024 ± 0.005	0.0053 ± 0.0036	4.9 ± 2.1	2.2 ± 1.2	4.7 ± 1.2	2.7 ± 1.1	0.27 ± 0.33
PR 1	0.51 ± 0.07	0.88 ± 0.07	18 ± 1	0.026 ± 0.006	0.13 ± 0.04	0.055 ± 0.006	0.011 ± 0.001	8.1 ± 1.5	3.7 ± 2.2	4.0 ± 1.2	4.2 ± 0.5	1.4 ± 0.6
PR 2	13 ± 2	21 ± 4	3.8 ± 1.1	0.029 ± 0.007	0.90 ± 0.10	0.76 ± 0.04	0.032 ± 0.011	22 ± 5	9.0 ± 3.4	4.3 ± 1.5	12 ± 4	30 ± 11
PR 3	12 ± 1	13 ± 1	3.2 ± 0.2	0.060 ± 0.004	0.82 ± 0.13	0.23 ± 0.01	0.0043 ± 0.0007	21 ± 8	11 ± 4	4.5 ± 0.5	6.1 ± 1.3	6.7 ± 2.1
PR 4	0.22 ± 0.01	56 ± 6	10 ± 1	2.4 ± 0.5	15 ± 3	0.17 ± 0.02	0.31 ± 0.04	5.0 ± 1.1	2.7 ± 1.3	5.1 ± 1.5	1.6 ± 0.1	1.9 ± 1.9
PR 5	2.9 ± 0.3	5.5 ± 0.3	2.1 ± 0.3	0.029 ± 0.006	0.15 ± 0.05	0.076 ± 0.004	0.015 ± 0.004	40 ± 17	4.6 ± 2.7	2.5 ± 1.5	2.7 ± 0.7	16 ± 1
PR 6	180 ± 20	47 ± 3	130 ± 9	0.44 ± 0.09	4.1 ± 0.3	1.2 ± 0.4	0.02 ± 0.06	13 ± 3	24 ± 5	14 ± 4	18 ± 4	n.d.
PR 7	71 ± 6	33 ± 1	32 ± 2	0.50 ± 0.03	0.13 ± 0.05	0.054 ± 0.003	< 0.001	14 ± 1	39 ± 6	31 ± 7	25 ± 3	n.d.

Abbreviations: SQV, saquinavir; IDV, indinavir; NFV, nelfinavir; LPV, lopinavir; APV, amprenavir; AZV, atazanavir; DRV, darunavir.

[a] data published in our previous work[1]

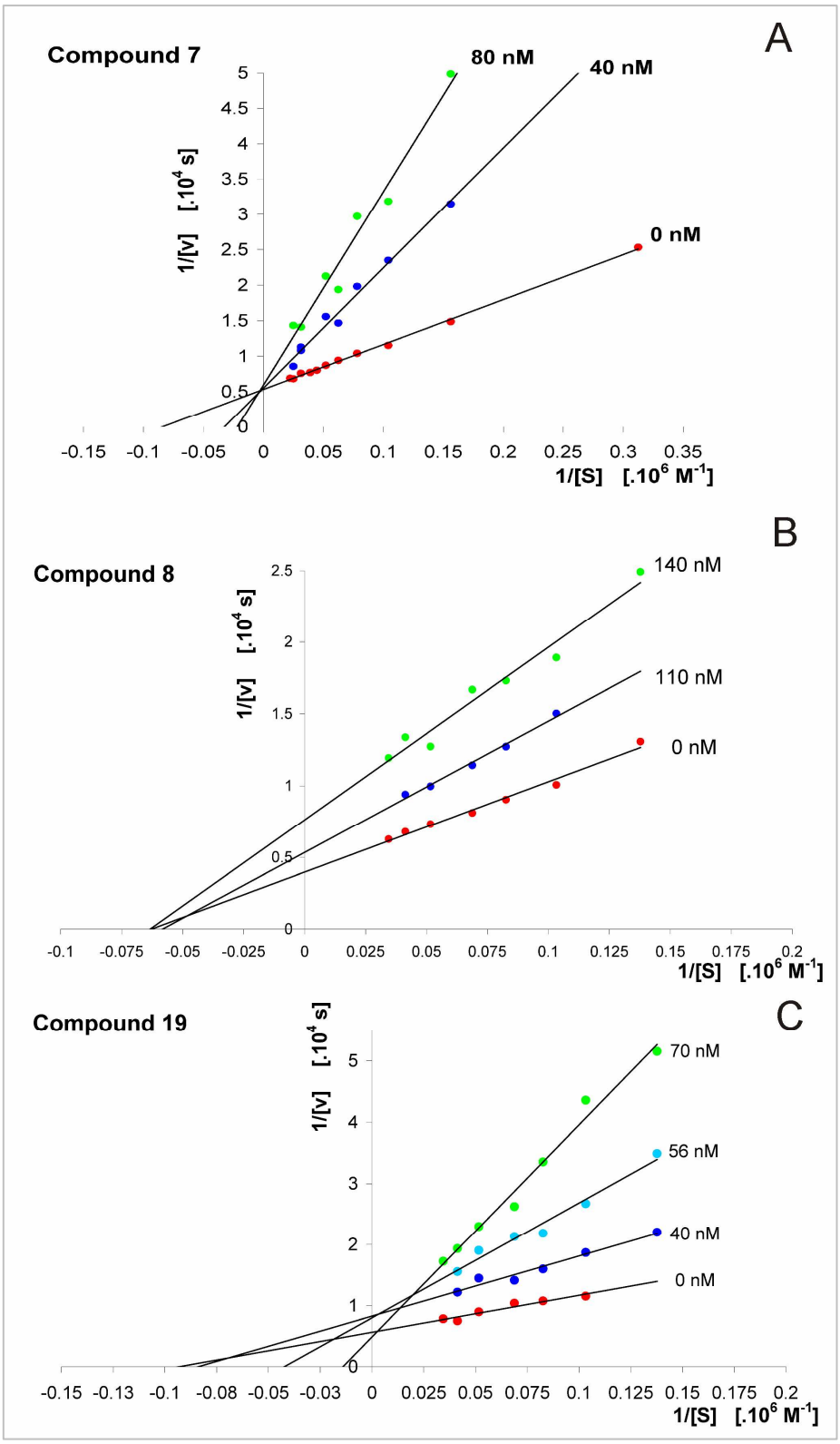


Figure S1. The examples of plots used for determination of inhibition mechanisms using double reciprocal Lineweaver-Burk plot[2]. **A.** competitive inhibition by compound **7**, **B.** noncompetitive inhibition by **8**, **C.** inhibitor concentration dependent inhibition by **12**.

Experimental Methods of Chemical Syntheses

Genaral Method of Chemical Syntheses. Cesium cobalt bis(dicarbollide), o-carborane, *nido*-[7-NH_3-7-$CB_{10}H_{12}$] and *closo*-[1-NH_3-1-$CB_{11}H_{11}$] derivatives[3, 4], were purchased from Katchem, Ltd., Prague, Czech Rep. [8-O(CH_2CH_2)$_2$O-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-Co]^0 (**8-dioxane-1**)[5]**,** [8,8'-μ-H_2N<(1,2-$C_2B_9H_{10}$)-3,3'-Co]^0 zwitterion[6], Et_3NH[7,8-$C_2B_9H_{12}$] [7], [(8-H_3N-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-Co] [8], [(8-*n*-$C_4H_9NH_2$-(CH_2CH_2O)$_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-Co]^0 derivative[9] were prepared according published procedures. All boron chemicals were carefully dried (12h at 60 ^oC on vacuum line) prior the use. Dry, high surface sodium hydride (Institute of Inorg. Chemistry, Rez near Prague) with a surface area of about 2 m^2g^{-1} was used. Organic amines were purchased from Aldrich. Liquid amines were dried over 4Å molecular sieves (Sigma-Aldrich), other amines in vacuum (12h). Other chemicals were reagent or analytical grade (Lachema or Penta, Czech Rep.) and were used as purchased. Toluene was freshly distilled from sodium, diethyleneglycol dimethyl ether was distilled from sodium phenyl ketyl. Column chromatography was carried out on high purity silica gel (Merck Grade, Type 7754, 70-230 mesh, 60 Å), and analytical TLC on Silufol™ sheets (Kavalier, Czech. Rep. (starch as the binder), yellow – orange spots, eventually detected by diiodine vapors followed by 2% aqueous $AgNO_3$ spray).

All reactions were performed with the use of standard vacuum or inert-atmosphere (nitrogen, purity 99.999, Messer, Czech Rep.) techniques as described by Shriver [10], although some operations, such as column chromatography and crystallizations were carried out in air. Melting points were determined in sealed capillaries on BŰCHI Melting Point B-545 apparatus and are uncorrected.

Instrumental Techniques. ^1H and ^{11}B NMR and ^{13}C NMR spectroscopy were performed on Varian Mercury 400 Plus Instrument at 400, 128 and 100 MHz, respectively. NMR chemical shifts are given in ppm to high-frequency (low field) to $F_3B{\cdot}OEt_2$ as the external reference. Residual solvent ^1H resonances were used as internal secondary standards. Coupling constants $^1J(^{11}B–^1H)$ are taken from resolution-enhanced ^{11}B spectra with a digital resolution of 2 Hz and are given in Hz. The NMR data are presented

in the text below in the following format: ^{11}B NMR: ^{11}B chemical shifts $\delta(^{11}B)$ (ppm), multiplicity, coupling $J(^{11}B–^{1}H)$ constants are given in Hz. Peak assignment is based on previously published data for substituted cage with simpler substitutions[8, 11]. ^{1}H NMR: chemical shifts $\delta(^{1}H)$ are given in ppm, coupling constants J(*H,H*) in Hz, $\delta(^{11}B\{^{11}B\})$ data are presented in square brackets, assignment is based on selectively decoupled $\delta(^{1}H)$-{^{11}B selective}NMR experiments and analogies with similar published compounds.

Mass spectrometry measurements were performed on a Thermo-Finnigan LCQ-Fleet Ion Trap instrument using Electrospray Ionization (ESI). Negative ions were detected. Samples dissolved in acetonitrile (concentrations approx. 100 ng.ml^{-1}) were introduced to the ion source by infusion of 0.25 mL.h^{-1}, source voltage 5.57 kV, tube lens voltage 49.8 V, capillary voltage 10.0 V, drying temperature was 188°C, drying gas flow 8 L min^{-1}, auxiliary gas pressure 6 Bar.- The data are presented for the most abundant mass in the boron distribution plot (100%) and for the peak corresponding to the *m/z* value.

Analytical HPLC: . A Merck-Hitachi HPLC system LaChrom 7000 series equipped with DAD 7450 detector and an intelligent injector was used. Chromatographic procedure was basen on published methods[12]: Column: RP Separon™ SGX C8, 7μm (silica with chemically bonded octyl groups) Tessek Prague, Czech Rep. Chromatographic conditions: Solvent 3 mmol/ L hexylamine acetate in 65% aqueous acetonitrile, detection DAD, fixed wavelengths 254, 290 and 312 nm; sensitivity range 0.2 A.U.F.S; samples of concentration approx. 0.5 mg·mL^{-1} in the mobile phase or CH_3CN were injected (1-5 μL); the method allowed the resolution of most of the compounds from the real reaction mixtures and for the purity assay and control. Capacity factors $k' = (t_R-t_0)/t_0$ (where t_R is retention time, t_0 is the void retention time of an non retained peak) are given for individual compounds. The purity of all compounds, as determined by HPLC, was better than 98%.

Sodium hydrogen *t*-butylimino bis-8,8-[5-(3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide)]di-ate (1-), [*t*-C_4H_9NH-(8-$(C_2H_4O)_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-$Co)_2$]Na, (**5**). *t*-Butyl amine was used as the respective reagent. Yield 285 mg (77 %); M. P. 279^oC (decomp.); TLC (acetonitrile/chloroform 1:2 v/v) R_F = 0.27; HPLC k'= 5.39; M.S. 894.72 (100%) (calcd. 899.72), *m/z* = 899.66 (1%) $[M]^-$ (calcd. 899.72); ^1H {^{11}B} NMR (400 MHz, Acetone-d_6), [$^1H\{^{11}B_{selective}\}$ in square brackets]: δ 7.08 s (1H, NH), 4.186 s (4H, CH_{carb}), 4.133 s (4H, CH_{carb}), 3.971 (t, 4H, *J* = 7.9, O-CH_2-CH_2O), 3.646 (m, 8H, OCH_2-CH_2O), 3.053 m (m, *J* = 6.0, 4H, O-CH_2-*CH_2*-N), 1.613 (s, 9H, *t*-BuN), [2.92] (H10'), [2.73] (H8') [2.71] (H4',7'), [2.68] (H10), [2.85 s, 2.02 s, 1.81 s] (H 4, 7, 9, 12, 9',12'), [1.67] (H6'), [1.62] (H5', 11'), [1.53] (H5, 11), [1.43] (H6); $^{13}C\{^1H\}$ NMR, (100 MHz, Acetone-d_6): δ 73.19 (CH_2-O), 69.48 (CH_2-O), 67.41 (CH_2-O) 66.22 (CH_2-N), 54.16 (CH_{carb}), 47.36 (CH_{carb}), 25.39 (*t*-BuN); ^{11}B NMR (128MHz, Acetone-d_6): δ 23.75 (s, 2B, B8), 5.17 (d, *J* = 143, 2B, B8'), 0.39 (d, *J* = 140, 2B, B10'), -2.53 (d, *J* = 150, 2B, B10), -4.6 (d, *J* = 142, B4',7'), -7.08 d, -7.81 d (3d, overlap,12B, B4, 7, 9, 12, 9',12'), -17.3 (d, *J* = 156, 4B, B5', 11'), -20.13 (d, *J* = 152, 4B, B5, 11), -22.17 (d, *J* = 164, 2B, B6'), -28.69 (d, *J* = Hz, 2B, B6).

Sodium hydrogen 1,1-(dihydroxymethyl)-2-n-ethanolimino bis-8,8-[5-(3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide)]di-ate (1-), [$(HOCH_2)_3$C-NH-(8-$(C_2H_4O)_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-$Co)_2$]Na (**6**). 1,1-(dihydroxymethyl)-2-hydroxyethylamine was used as the respective reagent. Yield mg 344 mg (89%); M. p. 278 ^oC; TLC (acetonitrile/chloroform 1:2 v/v), R_F = 0.23; HPLC k'= 0.7; MS-ESI (*m/z*): 942.58 (100%) 947.58 (2%) $[M]^-$ calcd. 947.70; ^1H {^{11}B} NMR (400MHz, Acetone-d_6), [$^1H\{^{11}B_{selective}\}$ in square brackets]: δ 4.20 (s, 4H, CH_{carb}), 4.174 (s, 4H, CH_{carb}), 3.673 (m, *J* = 5.2, 8H, O-CH_2-CH_2-N), 3.558 (t, *J* = 4.6, 8H, O-CH_2-CH_2-O), 2.992 (s, 6H, O-CH_2C);

[2.86] (H10'), [2.72] (H4',7'), [2.68] (H10), [2.67] (H8'), [2.89 s, 2.02 s, 1.81 s] (H 4, 7, 9, 12, 9',12'), [1.68] (H6'), [1.63] (H5', 11'), [1.54] (H5, 11), [1.45] (H6); $^{13}C\{^1H\}$ NMR (100MHz, Acetone-d_6): δ 72.91 (CH_2-O), 72.87 (CH_2-O), 69.66 (CH_2-O), 65.49 (CH_2-O), 59.21 (CH_2-N), 56.12 (C-CH_2-O),

53.91 (CH_{carb}), 47.35 (CH_{carb}), 31.5 ($NCCH_2$); ^{11}B NMR (128 MHz, Acetone-d_6): δ 23.53 (s, 2B, B8), 4.84 (d, *J* = 150, 2B, B8'), 0.44 (d, *J* = 140, 2B, B10'), -2.44 (d, *J* = 143, 2B, B10), -4.58 (d, *J* = 149, B4',7'), -7.25 d, -7.60, -8.45 (3d, overlap, 12B, B4, 7, 9, 12, 9',12'), -17.30 (d, *J* = 153, 4B, B5', 11'), -20.39 (d, *J* = 161, 4B, B5, 11), -22.13 (d, *J* = 158, 2B, B6'), -28.52 (d, *J*(B,H) = 170, 2B, B6).

Sodium hydrogen (1-carboxy)-propyl-3-imino bis-8,8-[5-(3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide)]di-ate (1-), $[OOCC_3H_6NH\text{-}(8\text{-}(C_2H_4O)_2\text{-}1,2\text{-}C_2B_9H_{10})(1',2'\text{-}C_2B_9H_{11})\text{-}3,3'\text{-}Co)_2]Na_2$ (**7,**). γ-aminobutanoic acid was used for the ring cleavage. Yield 140 mg (37%); M. p. 147 °C; TLC (acetonitrile/ chloroform 1:2 v/v) R_F = 0.35; HPLC k'= 0.72; MS-ESI (*m/z*): 461.58 (15%), 464.894 (0.5%) $[M]^{2-}$ calcd. 464.84; 924.76 (100%), 929.66 (2%) $[M+H]^-$ calcd. 929.69; ^{1}H {^{11}B} NMR (400MHz, CD_3CN), [^{1}H{$^{11}B_{selective}$} in square brackets]: δ 4.105 (s, 4H, CH_{carb}), 4.026 (s, 4H, CH_{carb}), 3.660 (t, *J* = 4.4, 4H, O-CH_2-CH_2O), 3.576 (m, *J* = 4.0, 4H, O-CH_2-*CH_2*N), 3.496 (t, *J* = 5.2, 4H, O-CH_2-CH_2O), 3.467 (t, *J* = 4.8, 4H, O-CH_2-CH_2O), 3.066 (t, *J* = 7.6, 2H, *CH_2*-N), 2.174 (br. t, 2H, OOC-*CH_2*-CH_2), 1.901 (p, *J* = 3.2, 2H, O-CH_2-*CH_2*-CH_2N); [2.81] (H10'), [2.74] (H8'), [2.59] (H4',7'), [2.58] (H10), [1.96, 1.70] (H 9, 12, 9', 12'), 2.79 [4, 7], [1.64] (H6'), [1.54] (H5', 11'), [1.46] (H5, 11), [1.39] (H6); ^{13}C{^{1}H} NMR (100MHz, CD_3CN): δ 207.66 (COO), 72.21 (4C, CH_2-O), 69.29 (2C, CH_2-O), 61.19 (2C, CH_2-O), 54. 4 (1C, CH_2-N), 53.91 (4C, CH_{carb}), 47.35 (4C, CH_{carb}), 32.13 (1C, $OOCCH_2$), 23.4 (1C, -CH_2-); ^{11}B NMR (128 MHz, CD_3CN): δ 23.91 (s, 2B, B8), 5.15 (d, *J* = 137, 2B, B8'), 0.01 (d, *J* = 140, 2B, B10'), -2.79 (d, *J* = 143, 2B, B10), -5.12 (d, *J* = 149, B4', 7'), -7.33 (2d, *J* = 140, 8B, B 9, 12, 9',12'), -9.14 (d, *J* = 140, B4, 7, 4B,), -17.44 (d, *J* = 156, 4B, B5', 11'), -20.46 (d, *J* = 159, 4B, B5, 11), -22.34 (d, *J* = 158, 2B, B6'), -28.59 (d, *J*(B,H) = 170, 2B, B6).

Sodium hydrogen (1-sulfoxy)-ethyl-2-imino bis-8,8-[5-(3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide)]di-ate (2-), $[O_3SC_2H_4NH\text{-}(8\text{-}(C_2H_4O)_2\text{-}1,2\text{-}C_2B_9H_{10})(1',2'\text{-}C_2B_9H_{11})\text{-}3,3'\text{-}Co)_2]Na_2$ (**8**). 1-sulfoxy-ethyl-2- amine was used for the ring cleavage. Yield 99 mg (25%); M. p. 198 °C; TLC (acetonitrile/ chloroform 1:2 v/v) R_F = 0.49; HPLC k'= 1.12; MS-ESI (*m/z*): 473.42 (100%), 475.88

(1%) $[M]^{2-}$ calcd. 475.81; 968.76 (15%), 974.68 (1%) $[M+Na]^-$ calcd. 974.62; ^1H {^{11}B} NMR (400MHz, CD_3CN), [^1H{$^{11}B_{selective}$} in square brackets]: δ 4.176 (s, 4H, CH_{carb}), 4.155 (s, 4H, CH_{carb}), 3.676 (br. t, *J* = 4.4, 4H, O-CH_2-CH_2O), 3.619 (t, *J* = 4.8, 4H, O-CH_2-*CH_2*N), 3.566 (m, *J* = 4.4, 8H, O-CH_2-CH_2N), 3.328 (br. s., 4H, S-CH_2-CH_2-N), [2.92] (H10'), [2.71] (H4',7'), [2.69] (H8'), [2.68] (H10), [2.02, 1.82] (H 4, 7, 9, 9' 12,12'), 2.89 [4, 7], [1.68] (H6'), [1.62] (H5', 11'), [1.53] (H5, 11), [1.45] (H6); ^{13}C{^1H} NMR (100MHz, CD_3CN): δ 72.52 (CH_2-O), 69.528 (CH_2-O), 67.32 (CH_2-N), 53.97 (CH_2), 53.44 (CH_{carb}), 51.78 (CH_2), 47.65 (CH_{carb}); ^{11}B NMR (128 MHz, Acetone-d_6): δ 23.63 (s, 2B, B8), 5.01 (d, *J* = 140, 2B, B8'), 0.49 (d, *J* = 140, 2B, B10'), -2.41 (d, *J* = 143, 2B, B10), -4.61 (d, *J* = 149, B4',7'), -7.15 (2d, overlap, 8B, B4, 7, 9, 12), -8.52 (d, *J* = 150, 4B, B9',12'), -17.20 (d, *J* = 156, 4B, B5', 11'), -20.37 (d, *J* = 159, 4B, B5, 11), -22.06 (d, *J* = 159, 2B, B6'), -28.43 (d, *J*(B,H) = 168, 2B, B6).

Sodium hydrogen benzylimino bis-8,8-[5-(3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide)]di-ate (1-) [$C_6H_5CH_2NH$-(8-$(C_2H_4O)_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-Co)$_2$]Na (**9**). Benzylamine was used for the ring cleavage. Yield 339 mg (89%); M. p. 263 °C (decomp.); TLC (acetonitrile/chloroform 1:2 v/v) R_F = 0.33; HPLC k'= 6.84; M. S. (*m/z*): 928.76 (100%) (calcd. 928.73), 834.66 (1%) $[M]^-$ (calcd. 934.70).^1H {^{11}B} NMR (400MHz, Acetone-d_6), [^1H{$^{11}B_{selective}$} in square brackets]: δ 7.602 (m, 2H, Ar), 7.461 (m, 3H, Ar), 4.58 (br. s, 1H, NH), 4.156 (s, 4H, CH_{carb}), 4.094 (s, 4H, CH_{carb}), 3.933 (br. t, 4H, O-CH_2-CH_2O), 3.695 (t, *J* = 4.0, 4H, OCH_2-CH_2O), 3.627 (t, *J* = 4.9, 4H, OCH_2-CH_2O), 3.437 (m, 4H, O-CH_2-*CH_2*-N), 2.073 (m, 2H, *CH_2*N); [2.92] (H10'), [2.83] (H8'), [2.71] (H4',7'), [2.68] (H10), [2.85 s, 2.05 s, 1.84 s] (H 4, 7, 9, 12, 9',12'), [1.62] (H6'), [1.61] (H5', 11'), [1.54] (H5, 11), [1.45] (H6); ^{13}C{^1H} NMR (100MHz, Acetone-d_6): δ 132.07 (Ar), 130.85 (Ar), 129.82 (Ar), 72.92 (CH_2-O), 69.63 (CH_2-O), 65.97 (CH_2-O), 58.70 (CH_2-N), 53.82 (CH_{carb}), 53.30 (CH_2-N), 47.43 (CH_{carb});^{11}B NMR (128 MHz, Acetone-d_6): δ 23.98 (s, 2B, B8), 5.53 (d, *J* = 137, 2B, B8'), 0.44 (d, *J* = 142, 2B, B10'), -2.51 (d, *J* = 147, 2B, B10), -4.65 (d, *J* = 140, B4',7'), -7.05 d, -7.81 (2d, overlap B9, 12, 9',12'), -17.24 (d, *J* = 153, 4B, B5', 11'), -20.20 (d, *J* = 155, 4B, B5, 11), -21.85 (d, *J* = 158, 2B, B6'), -28.48 (d, *J*(B,H) = 137, 2B, B6).

Sodium hydrogen (4-methyl-phenyl-1-sulfonamido) bis-8,8-[5-(3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide)]di-ate (2-) [$(CH_3C_6H_4S(O)_2$-N-(8-$(C_2H_4O)_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-Co)$_2$]Na_2 (**10**). Yield 345 mg (83%); M. p. 263 ^oC; TLC (acetonitrile/ chloroform 1:2 v/v) R_F = 0.28; HPLC k'= 1.05; MS-ESI (*m/z*): 495.98 (100%), 498.88 (1%) $[M]^{2-}$ calcd. 498.83; 1014.74 (69%), 1019.62 (1%) $[M+Na]^-$ calcd. 1019.64; ^1H {^{11}B} NMR (400MHz, Acetone-d_6), [$^1H\{^{11}B_{selective}\}$ in square brackets]: δ 7.786 (d, *J* = 8.0, 2H, Ar), 7.418 (d, *J* = 7.9, 2H, Ar), 4.261 (s, 8H, CH_{carb}), 4.155 (s, 4H, CH_{carb}), 3.588 (2t, *J* = 6.1, 8H, O-CH_2-CH_2O), 3.475 (t, *J* = 5.1, 4H, O-CH_2-CH_2-N), 3.387 (m, 4H, O-CH_2-CH_2N), 2.440 (s, 3H, CH_3), [2.95] (H10'), [2.94] (H8'), [2.76] (H4',7'), [2.70] (H10), [2.43, 2.04, 1.79] (H 4, 7, 9, 12,9',12'), [1.66] (H5', 11'), [1.60] (H6'), [1.56] (H5, 11), [1.43] (H6); $^{13}C\{^1H\}$ NMR (100MHz, Acetone-d_6): δ 144.06 (Ar), 138.09 (Ar), 72.64 (CH_2-O), 70.27 (CH_2-O), 69.15 (CH_2-O), 55.17 (4C, CH_{carb}), 49.23 (CH_2-N), 47.30 (4C, CH_{carb}), 21.48 (CH_3); ^{11}B NMR (128 MHz, Acetone-d_6): δ 22.94 (s, 2B, B8), 3.96 (d, *J* = 137, 2B, B8'), 0.51 (d, *J* = 140, 2B, B10'), -2.37 (d, *J* = 146, 2B, B10), -4.22 (d, *J* = 146, B4',7'), -7.15, -8.07 (3d, overlap, 8B, B4, 7, 9, 12, 9',12'), -17.16 (d, *J* = 156, 4B, B5', 11'), -20.34 (d, *J* = 159, 4B, B5, 11), -22.16 (d, *J* = 159, 2B, B6'), -28.43 (d, *J*(B,H) = 168, 2B, B6).

Sodium hydrogen (7-carba undecabora)-yl-7-imino) bis-8,8-[5-(3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide)]di-ate (2-) tetrahydrate, [7''-$CB_{10}H_{12}$-7''-NH-**(8-$(C_2H_4O)_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-Co)$_2$]Na_2** (**11**). *Nido*-[7-NH_3-7-$CB_{10}H_{12}$]^0 (60 mg, 40 mmol) in toluene-DME (3: 1, 15 mL) was stirred with NaH (22 mg, 0.84 mmol) for 2H, and then **8-dioxane-1** (165 mg, 41 mmol) in the same solvent (15 mL) was injected. After stirring for 16h, additional portion of sodium hydride (11 mg, 0.42 mmol) was added followed by drop-wise addition of the second equivalent of **1** (165 mg, 0.41 mmol) in 15 mL of toluene-DME (3: 1). The general synthetic method described above was used for product isolation. Yield 280 mg (69%); M. p. >410 ^oC; TLC (acetonitrile/ chloroform 1:2 v/v) R_F = 0.16; HPLC k'= 1.17; MS-ESI (*m/z*): 485.48 (100%), 487.88 (1%) $[M]^{2-}$ calcd. 487.91; 991.83 (28%), 997.70 (1%) $[M+Na]^-$ calcd. 997.82; ^1H {^{11}B} NMR (400MHz, Acetone-d_6), [$^1H\{^{11}B_{selective}\}$ in square brackets]: δ 7.12 (br. s, 1H, NH), 4.216 (2s, 8H, CH_{carb}), 3.92 (t, *J* = 4.4, 4H, O-CH_2-CH_2O), 3.638 (m, 12H, O-CH_2-

CH_2O, O-CH_2-*CH_2*N), 2.91 (s, 8H, H_2O), [2.93] (H10'), [2.90] (H, CB_{10}) [2.74] (H4',7'), [2.68] (H10), [2.57] (H8'), [2.81, 2.01, 1.81] (H 4, 7, 9, 12,9',12'), [1.71] (H, CB_{10}) [1.66] (H5', 11'), [1.64] (H, CB_{10}) [1.60] (H6'), [1.56] (H5, 11), [1.46] (H6), [0.55] (H, CB_{10}), [1.37] (H, CB_{10}), [-3.36] (μ-H, CB_{10}) ; $^{13}C\{^1H\}$ NMR (100MHz, Acetone-d_6): δ 73.19 (CH_2-O), 69.56 (CH_2-O), 65.82 (CH_2-O), 58.96 (CH_2-N), 56.1 (CH_{carb}), 54.94 (CH_{carb}), 47.35 (C, CH_{carb}); ^{11}B NMR (128 MHz, Acetone-d_6): δ 23.27 (s, 2B, B8), 4.51 (d, *J* = 137, 2B, B8'), 0.39 (2d, *J* = 140, 3B, B10', B5''), -2.58 (d, *J* = 146, 2B, B10), -4.34 (d, *J* = 146, B4',7'), -7.29, -8.17 (3d, overlap, 8B, B4, 7, 9, 12, 9',12'), -9.87 (d, 2B, CB_{10}) -13.38 (d, *J* = 131, 2B, CB_{10}), -17.20 (d, *J* = 156, 4B, B5', 11'), -20.32 (d, *J* = 159, 4B, B5, 11), -22.08 (d, *J* = 159, 2B, B6', 2B CB_{10}), -25.34 (d, *J* =131, 1B, B1'') -28.55 (d, *J*(B,H) = 168, 2B, B6), -32.78 (d, *J* = 143, 2B, CB_{10}).

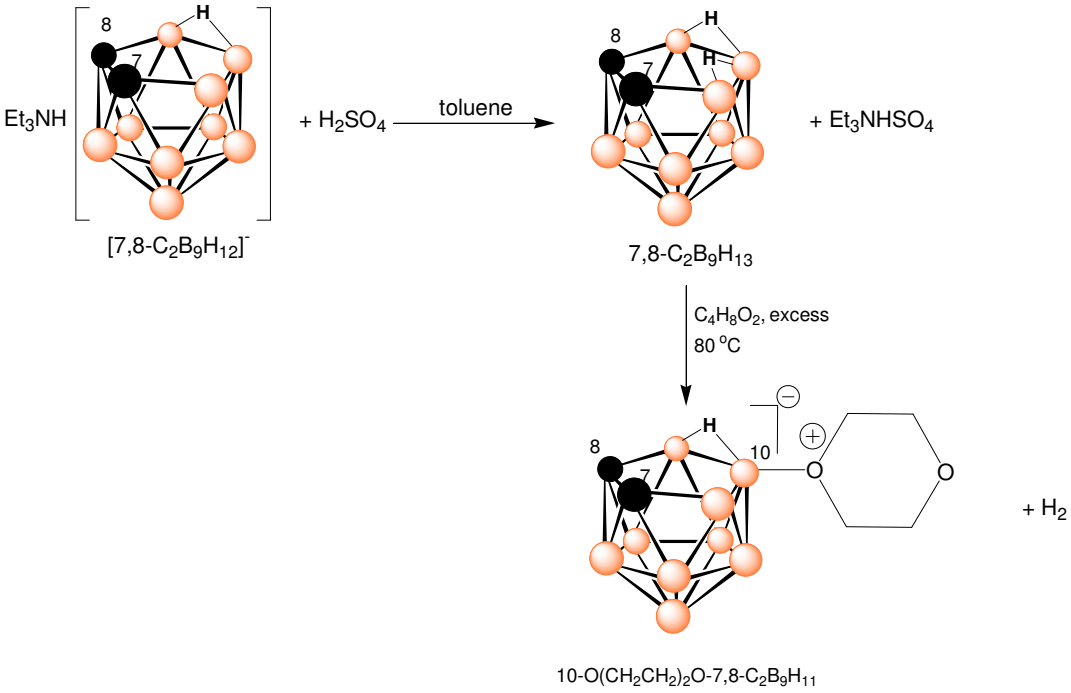
Sodium hydrogen *closo*-1-carba-dodecaboryl-1-imino bis-8,8-[5-(3-oxa-pentoxy)-3-cobalt bis(1,2-dicarbollide)]di-ate (2-), [1''-$CB_{11}H_{11}$-1''-NH-**(8-(C_2H_4O)$_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-Co)$_2$]Na_2 (**12**). The [1-NH_3-$CB_{11}H_{11}$][1] (64 mg, 0.40 mmol) derivative was dissolved in toluene- DME (3: 1, 15 ml) and deprotonated with sodium hydride (22 mg, 0.84 mmol). Then the **8-dioxane-1** (170 mg, 0.41 mmol) dissolved in toluene- DME (3: 1, 15 ml) was injected from a syringe. After stirring for 12h, additional portion of sodium hydride (11 mg, 0.42 mmol) was added followed by drop-wise addition of the second equivalent of **8-dioxane-1** (170 mg, 0.41 mmol in toluent-DME, 3: 1, 15 mL). The general synthetic method (see above) was used for isolation. Yield 84 mg (21 %); M. P. 156 ^oC; TLC (acetonitrile/chloroform 1:2 v/v) R_F = 0.11; HPLC k'= 0.11; M.S. 489.67 (35) (calcd. 489.58), *m*/*z* = 492.58 (2) calcd. 492.58 $[M]^{2-}$, 979.92 (100) calcd. 979.84, *m*/*z* = 987.67 (1%) $[M+H]^-$ calcd. 987.84; $^1H\{^{11}B\}$ NMR (400 MHz, Acetone-d_6), [$^1H\{^{11}B_{selective}\}$ in square brackets]: δ 4.24 (s, 8H, CH_{carb}), 4.18 (br. s, 1H, NH), 3.620 (br. t, *J* = 5.2, 4H, O-CH_2-CH_2-N), 3.501 (t *J* = 5.2, 4H, O-CH_2-CH_2O), 3.427 (t, *J* = 6.8, 4H, O-CH_2-CH_2O), 2.974 (m, *J* = 6.8, 4H, O-CH_2-CH_2O), [3.08] (H8'), [2.94] (H10'), [2.73] (H4',7'), [2.68] (H10), [2.90 s, 2.00 s, 1.78 s] (H 4, 7, 9, 12, 9',12'), 1.66 (H12'', $NHCB_{11}H_{11}$), [1.65] (H5', 11'), [1.60] (H6'), [1.53] (H5, 11), [3.11, 1.47] (H2''-10'', $NHCB_{11}H_{11}$), [1.41] (H6); $^{13}C\{^1H\}$

NMR, (100 MHz, Acetone-d_6): δ 72.53 (CH_2-N), 71.48 (CH_2-O), 69.29 (CH_2-O), 56.02 (CH_2-O), 55.12 (CH_{carb}), 54.37 (CH_{cB11}), 47.29 (CH_{carb}). ^{11}B NMR (128 MHz, Acetone-d_6): δ 23.10 s (2B, B8), 4.08 d (^1J(B,H) = 130 Hz, 2B, B8'), 0.49 d (^1J(B,H) = 142 Hz, 2B, B10'), -2.41 (d, ^1J(B,H) = 149 Hz, 2B, B10), -4.36 (^1J(B,H) = 147 Hz, 4B, B4' ,7'), -7.36 d, -7.91 d (overlap, 8B, B9, 12, 9',12'), -11.73 (d, overlap, 1B, $NHCB_{11}H_{11}$, B12"), -13.95, -14.76 2d (overlap, 10B, $NHCB_{11}H_{11}$, B2"-B11"), -17.18 (d, ^1J(B,H) = 153 Hz, 4B, B5', 11'), -20.37 (d, ^1J(B,H) = 159 Hz, 4B, B5, 11), -22.1 (d, ^1J(B,H) = 164, Hz, 2B, B6'), -28.48 d, (^1J(B,H) = 162 Hz, 2B, B6).

Double cluster compounds prepared by use of the eleven vertex 10-O(CH_2CH_2)O-7,8-$C_2B_9H_{12}$ building block

Synthesis of 10-dioxane-*nido*-7,8-dicarbaundecaborate zwitterion 15 The synthesis was carried out according to Scheme S1. The known neutral *nido* carborane[13] $C_2B_9H_{13}$ was generated by treatment of a slurry of $Et_3NH[C_2B_9H_{12}]$ salt (7.0g, 29.7 mmol) in toluene (50 ml) with concentrated sulfuric acid (12 ml) under vigorous stirring. After dissolution of the solid material (10 min.), the toluene layer was separated and filtered. To this solution stirred under nitrogen, dioxane (5 ml, 58.4 mmol) was injected and the reaction mixture was heated and stirred at 80 ^oC for 8h. After cooling down, the solvents were removed in vacuum and the resulting waxy solid was dissolved in $CHCl_3$ (10 ml), injected onto a top of silica gel column (150 x 30 mm) and the compound was eluted with chloroform. The combined fractions containing the products were evaporated in vacuum to dryness. Yield 4.98 g (75%), white crystalline solid. M.S., ^{1}H and ^{11}B NMR spectra were identical with the literature data reported for this compound[13].

Scheme S1: Simple synthetic route to the 10-dioxane-7,8-$C_2B_9H_{12}$ derivative *via* the neutral carborane 7,8-$C_2B_9H_{13}$



[*n*-C_4H_9NH-(10-$(C_2H_4O)_2$-7,8-$C_2B_9H_{11})_2$]Na, 14. Compound **15** (88 mg, 0.41 mmol) was reacted with *n*-butylamine (88 mg, 0.40 mmol) in toluene/DME (4:1, 25 mL) solution to which NaH (22 mg, 0.82 mmol) was added. After stirring for 4h at 60 °C, additional portions of NaH (11 mg, 0.41 mmol) and **15** (88 mg, 41 mmol in toluene/DME 4:1, 15 mL) were added and the reaction mixture was stirred for additional 6h at 60 °C. After cooling down, the product was isolated following the general method described above. Yield 110 mg (51 %); M. P. 69 °C; TLC (acetonitrile/ chloroform 1:2 v/v) R_F = 0.17; HPLC k'= 0.82; MS (m/z) 513.58 (100) (calc. 513.56), 516.44 (14) $[M]^-$ (calc. 516.53); ^1H {^{11}B} NMR (400 MHz,Acetone-d_6), [$^1H\{^{11}B_{selective}\}$ in square brackets]: δ 9.15 br. s (1H, NH), 3.943 (t, *J* = 5.1, 4H, O-CH_2-*CH_2*-O), 3.652-3.540 (m, 12H, O-CH_2-*CH_2*-O, O-*CH_2*-*CH_2*-N), 3.387-3.340 (m, 2H, *CH_2*-N), 1.546 s (4H, CH_{carb}), 1.87 m (2H, *CH_2*-CH_2N), 1.452 (q, 2H, *J* = 7.6 Hz, CH_2), 0.987 (t, 3H, ^1J = 7.7 Hz, CH_3), [2.16] (H 9,12), [1.43] (H3), [1.38] (H5,6) [1.18] (H2,4), [0.47] (H1) [-0.51] ([1.43] (μH10-9,11); $^{13}C\{^1H\}$ NMR, (100 MHz, Acetone-d_6): δ 73.67 (CH_2-O), 70.38 (CH_2-O), 64.58 (CH_2-O), 54.55

(CH_2-N, C_4H_9), 52.93 (CH_2-N), 39.96 (CH_{carb}), 26.42 (CH_2), 20.38 (CH_2), 13.75 (CH_3); ^{11}B NMR (128 MHz, Acetone-d_6): δ -9.74 (s, 2B, B10), -12.47 (d, *J* = 131, 4B, B 9,11), -17.30 (d, *J* = 131, 4B, B5,6), -23.72 (d, *J* = 150, 4B, B2,4), -24.89 (d, *J* = 155, 2B, B3), -40.39 (d, *J* = 137, 2B, B1).

Experimental Methods Molecular Modeling

Molecular dynamics/quenching (MD/Q) calculations AMBER8 package[14] was used to scan the conformational space available to the linker of **1** in complex with PR. Force-field parameters used for PR were from ff99 force field[15] while bond lengths of boron-containing bonds of **1** were calculated by use of quantum chemical (QM) calculations and force constants of these bonds were transferred from the all-atom Universal force field (UFF)[16]. Partial charges for atoms of **1**were obtained using restrained fit to the electrostatic potential (RESP) protocol at the B3LYP/cc-pVTZ level with a dielectric constant of ε = 4 applied[15]. Structures were collected every 100 ps and the total simulation time was 2 ns. We applied integration step of 0.5 fs and a generalized Born solvent model[17] at a temperature of 500 K. The obtained structures were optimized using molecular mechanics (MM) by the conjugate gradient method.

QM/MM calculations All the structures obtained by the MD/Q procedure described above were further optimized by use of QM/MM. These calculations were carried out using our own QM/MM code which acts as an interface between the Turbomole package[18] (QM calculations) and the AMBER8 package[14] (MM calculations) (described in detail in [19]). The QM region comprised the molecule of **1** and its sodium counterions in positions 121 and 121' (119 atoms altogether) and was treated with the density functional theory (DFT) approach, augmented by empirically parameterized dispersion corrections (DFT-D)[20]. We applied the resolution of the identity (RI) approximation[21] to the DFT method with the TPSS functional and SVP (3s2p1d/2s1p) basis set.

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