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Syntheses of C-substituted icosahedral dicarbaboranes bearing the 8-dioxane-cobalt bisdicarbollide moiety

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ABSTRACT

The treatment of 1,2-, 1,7- and 1,12-carbaborane lithiated isomers with $[3,3'\text{-Co-8-(CH}_2\text{CH}_2\text{O)}_2\text{-(1,2-C}_2\text{B}_9\text{H}_{10})\text{-(1',2'-C}_2\text{B}_9\text{H}_{11})]$ (**1**) at molar ratios 1:1 or 1:2 at room temperature in THF leads generally to the formation of a series of orange double-cluster mono and dianions. These were characterized by NMR and MS methods as $[1''\text{-X-1'',2''-closo-C}_2\text{B}_{10}\text{H}_{11}]^-$, **[2]**[−]; $[1''\text{-X-1'',7''-closo-C}_2\text{B}_{10}\text{H}_{11}]^-$, **[3]**[−] and $[1''\text{-X-1'',12''-closo-C}_2\text{B}_{10}\text{H}_{11}]^-$, **[4]**[−] for the monoanions, whereas $[1'',2''\text{-X}_2\text{-1'',2''-closo-C}_2\text{B}_{10}\text{H}_{10}]^{2-}$, **[2]**^{2−}; $[1'',7''\text{-X}_2\text{-1'',7''-closo-C}_2\text{B}_{10}\text{H}_{10}]^{2-}$, **[3]**^{2−}; and $[1'',12''\text{-X}_2\text{-1'',12''-closo-C}_2\text{B}_{10}\text{H}_{10}]^{2-}$, **[4]**^{2−} for the dianions (where X = 3,3'-Co-8-(CH₂CH₂O)₂-(1,2-C₂B₉H₁₀)-1',2'-(C₂B₉H₁₁)). Moreover, these borane-cage subunits can be easily modified via attaching variable substituents onto cage carbon and boron vertices, which makes these compounds structurally flexible potential candidates for BNCT of cancer and HIV-PR inhibition.

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1. Introduction

Since the discovery of nucleophilic oxonium ring-opening (ORO) reactions in the carborane and metallacarborane series by Plešek et al. [1–3], has elapsed more than 30 years. These reactions represent an important feature of substitution boron chemistry and many examples can be found in the literature of these last years [4–10]. Moreover, a recent exhaustive review by Semioshkin et al. [11] has been published on this field. Relevant for this communication is that five years ago Sivaev et al. [12] demonstrated that the THF ring of the $\text{B}_{12}\text{H}_{11} \cdot \text{THF}^-$ anion can be opened by all three isomers (1,2-, 1,7- and 1,12-) of $\text{LiC}_2\text{B}_{10}\text{H}_{11}$ to obtain dianions of general constitution $[\text{1-B}_{12}\text{H}_{11}\text{O}(\text{CH}_2)_4\text{-1,2-C}_2\text{B}_{10}\text{H}_{11}]^{2-}$, $[\text{1-B}_{12}\text{H}_{11}\text{O}(\text{CH}_2)_4\text{-1,7-C}_2\text{B}_{10}\text{H}_{11}]^{2-}$, and $[\text{1-B}_{12}\text{H}_{11}\text{O}(\text{CH}_2)_4\text{-1,12-C}_2\text{B}_{10}\text{H}_{11}]^{2-}$ containing two different boron clusters. In this paper, we would like to extend this viable structural feature by our results on the isolation of mono and dianions of structures combining both the $[3,3'\text{-Co(1,2-C}_2\text{B}_9\text{H}_{11})_2]^-$ and $\text{C}_2\text{B}_{10}\text{H}_{12}$ structural motifs.

2. Results and discussion

Scheme 1 shows that treatment of $\text{LiC}_2\text{B}_{10}\text{H}_{11}$ (1,2-, 1,7- and 1,12-isomers) with $[3,3'\text{-Co-8-(CH}_2\text{CH}_2\text{O)}_2\text{-(1,2-C}_2\text{B}_9\text{H}_{10})\text{-(1',2'-C}_2\text{B}_9\text{H}_{11})]$ (**1**) (molar ratio 1:1) at room temperature in THF leads

generally to the formation of a series of orange double-cluster monoanions, which were identified by NMR and MS methods as $[1''\text{-X-1'',2''-closo-C}_2\text{B}_{10}\text{H}_{11}]^-$, **[2]**[−]; $[1''\text{-X-1'',7''-closo-C}_2\text{B}_{10}\text{H}_{11}]^-$, **[3]**[−]; $[1''\text{-X-1'',12''-closo-C}_2\text{B}_{10}\text{H}_{11}]^-$, **[4]**[−] (where X = 3,3'-Co-8-(CH₂CH₂O)₂-(1,2-C₂B₉H₁₀)-1',2'-(C₂B₉H₁₁)). It should be noted that the reaction of 1-Li-1,12-C₂B₁₀H₁₁ is accompanied by the formation of a doubly substituted tricluster dianion $[1'',12''\text{-(8-CH}_2\text{CH}_2\text{OCH}_2\text{-CH}_2\text{O-1,2-C}_2\text{B}_9\text{H}_{10}\text{-3,3'-Co-1',2'-C}_2\text{B}_9\text{H}_{11})_2\text{-1'',12''-C}_2\text{B}_{10}\text{H}_{10}]^{2-}$, **[4]**^{2−}, arising from the ring-opening reaction involving the contaminant $[\text{1,12-C}_2\text{B}_{10}\text{H}_{10}]^{2-}$ anion with two molecules of compound **1**. The anions were isolated as either Cs⁺ or $[\text{N}(\text{CH}_3)_4]^+$ salts and can be converted into other salts via metathesis with suitable counter-cations. It is evident that the formation of these anions is a consequence of the attack of the nucleophilic $[\text{C}_2\text{B}_{10}\text{H}_{11}]^-$ or $[\text{R-C}_2\text{B}_{10}\text{H}_{10}]^-$ anions at one of the dioxane carbon atoms adjacent to the oxonium O atom in structure **1**, followed by the ring opening under the formation of carborane-substituted 1,4-dioxahexane chain.

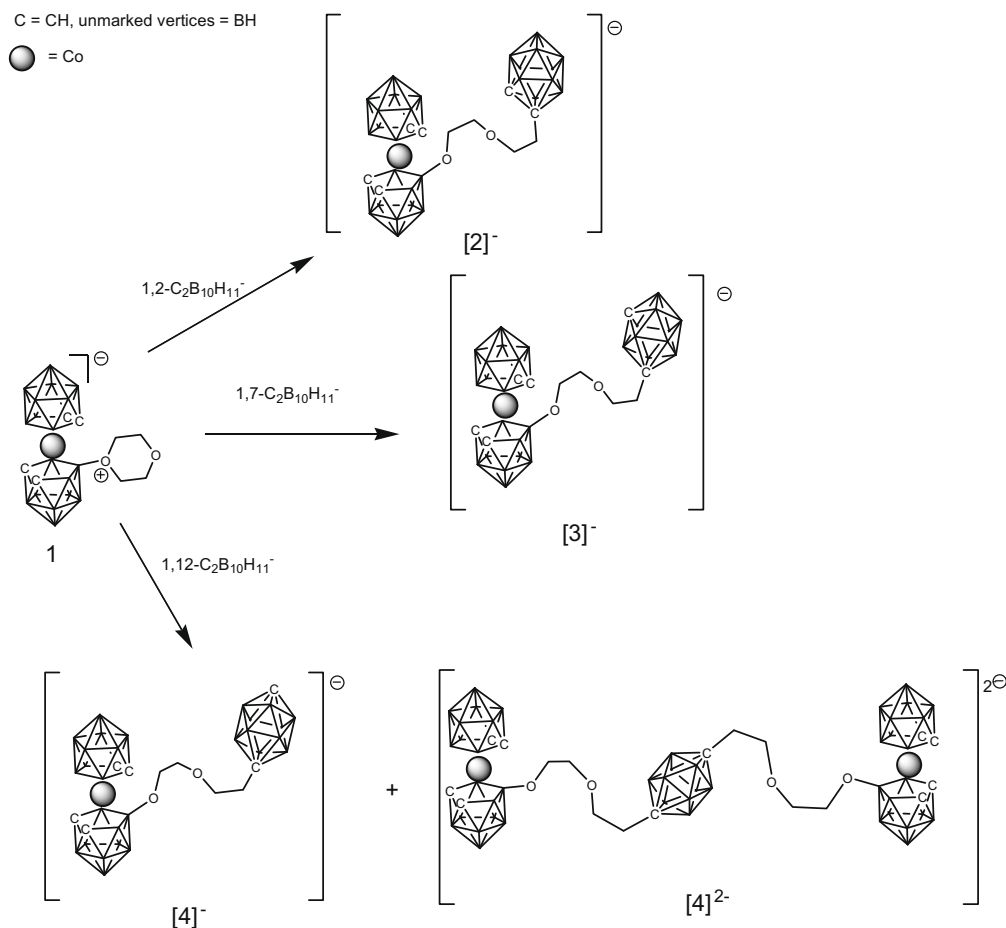
Application of the same synthetic procedure to the $\text{Li}[1\text{-R-1,2-C}_2\text{B}_{10}\text{H}_{10}]^-$ anions (where R = Me and Ph) led to a straightforward isolation of the methylated and phenylated analogues which analyze as $[1''\text{-X-2''-Me-1'',2''-closo-C}_2\text{B}_{10}\text{H}_{10}]^-$, **[Me-2]**[−] and $[1''\text{-X-2''-Ph-1'',2''-closo-C}_2\text{B}_{10}\text{H}_{10}]^-$, **[Ph-2]**[−].

As anticipated, an analogous treatment of the corresponding dilithia carboranes $\text{Li}_2\text{C}_2\text{B}_{10}\text{H}_{10}$ (1,2-, 1,7- and 1,12-isomers) with dioxanate **1** (molar ratio 1:2) at room temperature in THF leads generally to the formation of a series of orange triple-cluster dianions formulated as $[1'',2''\text{-X}_2\text{-1'',2''-closo-C}_2\text{B}_{10}\text{H}_{10}]^{2-}$, **[2]**^{2−}, $[1'',7''\text{-X}_2\text{-1'',7''-closo-C}_2\text{B}_{10}\text{H}_{10}]^{2-}$, **[3]**^{2−} and $[1'',12''\text{-X}_2\text{-1'',12''-}$

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Scheme 1. Treatment of $\text{LiC}_2\text{B}_{10}\text{H}_{11}$ (1,2-, 1,7- and 1,12-isomers) with $[3,3'\text{-Co-8-(CH}_2\text{CH}_2\text{O)}_2\text{-(1,2-C}_2\text{B}_9\text{H}_{10}\text{)-(1',2'-C}_2\text{B}_9\text{H}_{11}\text{)}]$ (**1**).

$\text{closo-C}_2\text{B}_{10}\text{H}_{10}]^{2-}$, $[4]^{2-}$. A full account on the Me and Ph derivatives and the dianionic compounds will be given in a full paper together with more detailed structural data.

The structure of all compounds isolated in this study has so far been suggested on the basis NMR and MS methods [13]. The ^{11}B NMR spectra of the cobaltabisdicarbollide part of all monoanionic and dianion compounds isolated bear distinct similarities to that of the dioxanate **1**, consisting of a downfield B8 singlet and eleven doublets of approximate areas 1:1:1:2:2:2:2:2:1:1, some of which being approximately overlapped. This section of the spectrum, however, coincides with that of the carboranyl $\text{C}_2\text{B}_{10}\text{H}_{11}$ substituent, the shape of which is dictated by the symmetry of the corresponding monosubstituted carborane cage, i.e. C_2 for anions $[2]^-$ and $[3]^-$ and C_{5v} for anion $[4]^-$. The most diagnostic feature of the ^1H NMR spectra of monoanions $[2]^-$, $[3]^-$ and $[4]^-$ is the presence of cage $\text{C}_{\text{cluster}}\text{-H}$ signals of integral intensity 4 along with one carborane $\text{C}_{\text{cluster}}\text{-H}$ resonance of relative area 1 in the case of unsubstituted carborane $[4]^-$ species. The $\text{C}_{\text{cluster}}\text{-H}$ signals of the BOCH_2 , CH_2OCH_2 and $\text{CH}_2\text{-carborane}$ units of the interconnecting 1,4-dioxahexane chain usually occur within the range of δ 3.7–1.9 ppm.

3. Conclusions

It should be concluded that reactions between lithiated 12-vertex carboranes and the dioxanate **1** lead generally to monoanionic and dianionic compounds that contain both metallabisdicarbaborane and carborane structural motifs in one molecule. Moreover, these borane-cage subunits can be easily modified *via* attaching

variable substituents onto cage carbon and boron vertices, which makes these compounds structurally flexible potential candidates for BNCT [14,15] of cancer and HIV-PR inhibition. One of the most important reasons for the growing interest in the use of metallacarboranes in biological systems is the suspected high lipophilicity of metallacarborane derivatives, which is a bottleneck for their application in human body. Consequently, these compounds were primarily designed to help to elucidate the effect of steric and hydrophobic interactions on the efficiency of the HIV-PR inhibition in the region of enzyme flaps and the effect of overall charge on the mechanism of the inhibition as well. Corresponding HIV-PR inhibition tests on compounds discussed in this study are being in high progress in our laboratories.

4. Experimental

For the purpose of this paper, the experimental procedure is demonstrated by the isolation of $[4]^-$ and $[4]^{2-}$, but is generally valid for the synthesis of all compounds mentioned above: In a typical experiment, a solution of 1,12- $\text{C}_2\text{B}_{10}\text{H}_{12}$ (200 mg, 1.39 mmol) in THF (5 ml) was treated with 2.5 M *n*-BuLi in THF (0.6 ml, 1.5 mmol) at ca. -33°C . The solution of 1-Li-1,12- $\text{C}_2\text{B}_{10}\text{H}_{11}$ thus obtained was stirred for 1 h at ambient temperature and then treated with a solution of **1** (600 mg, 1.46 mmol) in THF (20 ml). After stirring for additional 4 h, the mixture was then decomposed by adding EtOH (1 ml) and 3 M HCl (0.25 ml) and the organic volatiles were removed by vacuum evaporation. The viscous orange residue was digested with Et₂O (15 ml) and 3 M HCl (7 ml) under shaking. The Et₂O layer was separated, treated with water (2×10 ml) and

evaporated. After adding CH₃OH until dissolution of the solid residue and filtration, the filtrate was precipitated with an excess of aqueous CsCl. The orange Cs salts were isolated by filtration. Crystallizations from hot aqueous ethanol and additional crystallization of the solids from CH₂Cl₂–hexane gave the main bulk of Cs[4] (300 mg, 20.8%) The salts obtained by evaporation of the mother liquors from the first crystallization in ethanol were subjected to LC on silica gel, using CH₂Cl₂–CH₃CN (from 4:1 to 3:1) as the mobile phase to obtain additional Cs[4] (300 mg, total yield 20.8%, *R_f* 0.27) and the second orange fraction of *R_f* 0.13 contained [Cs]₂[4] (450 mg, 17.5 %).

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- [13] Selected structural data: Data for **2**⁺: Yield 76.8 %; *R_f* (CH₂Cl₂:CH₃CN 3:1) 0.27; HPLC *k'* 5.75; ¹B NMR (128.3 MHz, acetone-*d*₆, 293K): δ = 23.2 (s, 1B, B8), 4.5 (d, *J* = 141, 1B, B8'), 0.4 (d, *J* = 139, 1B, B10'), –2.7, –2.8 (d, 2B, B10, 9'), –4.5 (d, 2B, B4', 7'), –5.9 (d, 1B, B12'), –7.3, (d, 2B, B4, 7), –7.9 (d, 4B, B9, 9', 12, 12), –9.9 (d, 2B, B8', 10'), –10.7 (d, *J* = 152, 2B, B4', 5'), –11.9 (d, 2B, 3', 6'), –12.7 (d, 2B, 7', 11'), –17.3 (d, *J* = 155, 2B, B5', 11'), –20.4 (d, *J* = 159, 2B, B5, 11), –22.1 (d, *J* = 165, 2B, B6'), –28.4 (d, *J* = 165, 1B, B6); ¹H NMR (400 MHz, acetone-*d*₆, 293K): δ = 4.80 (s, 1H, H2''-carborane CH), 4.23, 4.20 (2s, H, H1, 2, 1', 2' cage CH), 3.60 (t, ³J(H,H) = 5.6 Hz, 4H, OCH₂), 3.46 (t, ³J(H,H) = 4.8 Hz, 2H, OCH₂), 2.61 (t, ³J(H,H) = 5.6 Hz, 2H, CH₂); MS (ESI⁺): *m/z* (%) 554.60 (100), 558.50 (5) [M]⁺ (calcd. 558.50). Anal. Calc. for C₁₀H₄₀B₂₈CoCs (686.94): C, 17.48; H, 5.86. Found: C, 17.62; H, 5.71%. Data for **3**⁺: Yield 568 mg, (23.7%), *R_f* (CH₂Cl₂:CH₃CN 3:1) 0.27; HPLC *k'* 5.83; ¹B NMR (128.3 MHz, acetone-*d*₆, 293 K): δ = 22.7 (s, 1B, B8), 3.7 (d, *J* = 134, 1B, B8'), 0.5 (d, *J* = 136, 1B, B10'), –2.4 (d, 1B, B10), –4.1 (2d, 3B, B4', 7', 5'), –7.4 (d, 2B, B4, 7), –8.2 (d, 2B, 9', 12'), –9.2 (d, 1B, B12'), –10.9 (d, 4B, 9, 12, 9', 10'), –13.5, –14.9 (d, 4B, B4', 6', 8', 11'), –16.6 (d, *J* = 180, 2B, B2', 3'), –17.3 (d, *J* = 159, 2B, B5', 11'), –20.4 (d, *J* = 159, 2B, B5, 11), –21.8 (d, *J* = 160, 1B, B6'), –28.3 (d, *J* = 164, 1B, B6); ¹H NMR (400 MHz, acetone-*d*₆, 293 K): δ = 4.26 (s, 4H, H1, 2, 1', 2' cage CH), 3.62 (s, 1H, H7''-carborane CH), 3.52 (t, ³J(H,H) = 5.8 Hz, 2H, BOCH₂), 3.41 (2t, ³J(H,H) = 6.8 Hz, 4H, OCH₂), 2.20 (t, ³J(H,H) = 6.8 Hz, 2H, CCH₂); MS (ESI⁺): *m/z* (%) 554.60 (100), 558.50 (5) [M]⁺ (calcd. 558.50). Anal. Calc. for C₁₀H₄₀B₂₈CoCs (686.94): C, 17.48; H, 5.86. Found: C, 17.78; H, 5.93%. Data for **4**⁺: Yield 300 mg, (20.8%), *R_f* (CH₂Cl₂:CH₃CN 3:1) 0.28; HPLC *k'* 6.18; ¹B NMR (128.3 MHz, acetone-*d*₆, 293 K): δ = 22.5 (s, 1B, B8), 3.5 (d, *J* = 130, 1B, B8'), 0.5 (d, *J* = 136, 1B, B10'), –2.4 (d, *J* = 140, 1B, B10), –4.1 (d, *J* = 156, 2B, B4', 7'), –7.5 (d, 2B, B4, 7), –8.3 (d, 4B, B9, 9', 12, 12'), –12.4 (d, *J* = 162, 5B, B2''–B6''), –15.1 (d, *J* = 165, 5B, B7''–11''), –17.3 (d, *J* = 156, 2B, B5', 11'), –20.5 (d, *J* = 155, 2B, B5, 11), –21.8 (d, *J* = 170, 1B, B6'), –28.4 (d, *J* = 171, 1B, B6). ¹H {¹B} NMR (400 MHz, acetone-*d*₆), ¹H NMR (400 MHz, acetone-*d*₆, 293K): δ = 4.29 (s, 4H, H1, 2, 1', 2' cage CH), 3.50 (s, 1H, H12'', carborane CH), 3.22 (br. t, 2H, OCH₂), 3.04 (br. t, 4H, OCH₂), 1.92 (br. t, 2H, CCH₂). MS (ESI⁺): *m/z* (%) 555.62 (100), 558.54 (5) [M]⁺ (calcd. 558.50). Anal. Calc. for C₁₀H₄₀B₂₈CoCs (686.94): C, 17.48; H, 5.86. Found: C, 17.81; H, 5.54%. Data for **4**²⁺: Yield 450 mg, (17.5%), *R_f* (CH₂Cl₂:CH₃CN 3:1) 0.13; HPLC *k'* 2.60; ¹B NMR (128.3 MHz, acetone-*d*₆, 293 K): δ = 23.5 (s, 1B, B8), 3.5 (d, *J* = 140, 1B, B8'), 0.4 (d, *J* = 144, 1B, B10'), –2.4 (d, *J* = 140, 1B, B10), –4.1 (d, *J* = 159, 2B, B4', 7'), –7.5 (d, 2B, B4, 7), –8.3 (d, 4B, B9, 9', 12, 12'), –12.7 (d, *J* = 162, 10B, B2'–B11''), –17.3 (d, *J* = 152, 2B, B5', 11'), –20.5 (d, *J* = 155, 2B, B5, 11), –22.0 (d, *J* = 170, 1B, B6'), –28.4 (d, *J* = 170, 1B, B6). ¹H NMR (400 MHz, acetone-*d*₆, 293 K): δ = 4.28 (s, 8H, H1, 2, 1', 2' cage CH), 3.50 (t, 4H, ³J(H,H) = 5.8 Hz, OCH₂), 3.21 (t, 8H, ³J(H,H) = 7, 8 Hz, OCH₂), 1.92 (t, ³J(H,H) = 7, 2 Hz, 4H, CCH₂); MS (ESI⁺): *m/z* (%) 482.33 (100), 486.58 (8) [M]²⁺ (calcd. 486.40); 962.75 (12), 969.75 (1) [M+H]⁺ (calcd. 969.81); 1096.75 (11), 1102.75 (1) [M+Cs]⁺ (calcd. 1102.71).
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