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Dedicated to the 90th Anniversary of Academician M.G. Voronkov

Halogenation of the 7,8-Dicarba-*nido*-undecaborate Anion Derivatives $[10\text{-RO-7,8-}C_2B_9H_{11}]^-$

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Abstract—Iodination and bromination of 10-alkoxyderivatives of 7,8-dicarba-nido-undecaborate anion $[10\text{-RO-7,8-}C_2B_9H_{11}]^-$ has been studied. The corresponding monoiodo, diiodo and dibromo derivatives were prepared.

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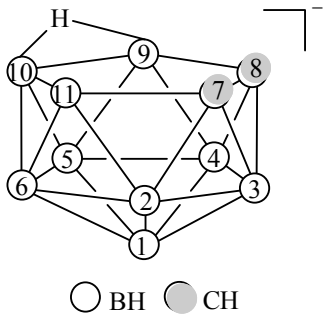
Carborane derivatives are promising compounds for use in various fields of medicine, in particular, in radionuclide imaging and boron neutron capture therapy of cancer [1, 2]. The last one is a binary method for cancer treatment where the reaction of two practically harmless components results in formation of highly toxic products destroying the cancer cell. This method is based on selective accumulation of non-radioactive ^{10}B isotope in cancer followed by their treatment with the thermal neutron flux. The irradiation results in the formation of high linear energy transfer products having short path lengths, comparable with the cell size, that allows selective destruction of tumors cells without damage to healthy tissues [3, 4]. The introduction of a radionuclide halogen label into the carborane cage facilitates considerably the control of distribution of the boron neutron therapy agents in human body and their accumulation in the tumor that allows to choose the optimal time and doses of irradiation, as well as to use them in radionuclide imaging [5, 6].

Earlier we reported the synthesis of carboxy derivatives of 7,8-dicarba-*nido*-undecaborate anion $[10\text{-HOOC-}z\text{-}C_6H_4O(CH_2CH_2O)\text{-7,8-}C_2B_9H_{11}]^-$ and $[10\text{-HOOC-}z\text{-}C_6H_4O(CH_2)_4O\text{-7,8-}C_2B_9H_{11}]^-$ (*z* = *ortho*, *meta*, *para*) [7], whose terminal functional group can be used for attachment of the carborane fragment to biomolecules specific to cancer cells.

The goal of this work was to study bromination and iodination of the 10-alkoxy derivatives of *nido*-carborane $[10\text{-RO-7,8-}C_2B_9H_{11}]^-$.

Earlier it was shown that the reactions of 7,8-dicarba-*nido*-undecaborate anion with halogens result in substitution of the hydrogen atoms at the boron atoms in positions 9 and 11 of the carborane cage with formation of mono- and dihalogen derivatives $[9(11)\text{-X-7,8-}C_2B_9H_{11}]^-$ and $[9,11\text{-}X_2\text{-}C_2B_9H_{10}]^-$ (X = Cl, Br, I) [8–11].

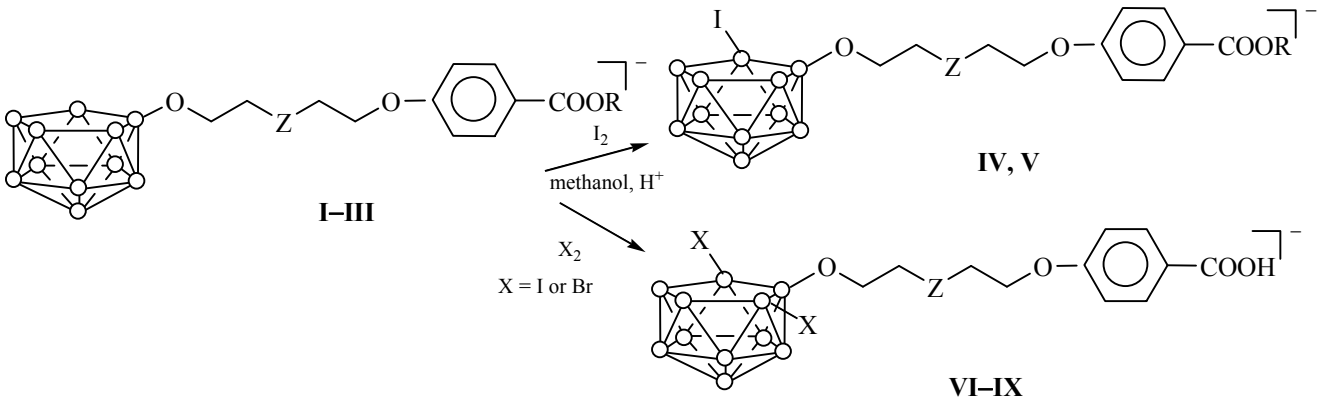


Halogenation of C- [12–15] and B-derivatives [16–19] of 7,8-dicarba-*nido*-undecaborate anion proceeds in a similar way. It should be noted that in the case of asymmetrically substituted derivatives of *nido*-carborane $[7(8)\text{-R-7,8-}C_2B_9H_{11}]^-$, the substitution of one hydrogen atom by halogen results in a mixture of diastereomers $[9(11)\text{-X-7(8)R-7,8-}C_2B_9H_{10}]^-$ and $[9(11)\text{-X-8(7)-R-7,8-}C_2B_9H_{10}]^-$ [15]. Obviously, the halogenation of derivatives with a substituent in the

position 10 of *nido*-carborane $[10\text{-RO-}7,8\text{-}C_2B_9H_{11}]^-$ cannot give a mixture of diastereomers and, therefore, is of special interest. The iodine (^{123}I, ^{124}I) and bromine (^{75}Br, ^{76}Br, ^{77}Br) isotopes are most often used as a radiohalogen isotopic label in nuclear medicine [20]. That was why our attention was directed to study of iodination and bromination of the 10-alkoxyderivatives $[10\text{-RO-}7,8\text{-}C_2B_9H_{11}]^-$ [R = HOOC-4-$C_6H_4O(CH_2)_4$ (**I**), HOOC-4-$C_6H_4(OCH_2CH_2)_2$ (**II**), MeOOC-4-$C_6H_4\cdot(OCH_2CH_2)_2$ (**III**)], prepared by the ring-opening reactions of the tetrahydrofuran and dioxane derivatives of *nido*-carborane [7].

Our attempt to carry out the iodination reaction under the conditions reported earlier for synthesis of the monoiodo derivatives of *nido*-carborane and its C-substituted derivatives (1 equiv. of iodine, reflux in methanol) led to complete oxidative destruction of the carborane cage with the formation of boric acid.

Carrying out the reaction at 0°C and in the presence of small amount of trifluoroacetic acid allowed to suppress the oxidative destruction and resulted in the corresponding monoiodo derivatives **IV** and **V**.



I, IV, Z = –, R = H; **II**, V, Z = O, R = Me; **III**, Z = O, R = Me; **VI**, Z = –, X = I; **VII**, Z = O, X = I; **VIII**, Z = –, X = Br; **IX**, Z = O, X = Br.

The diiodo and dibromo derivatives were obtained by the reaction with the excess of iodine or bromine, respectively, in the presence of trifluoroacetic acid at 0°C.

The structure of the synthesized compounds was established using ^1H and ^{11}B NMR spectroscopy. The ^{11}B NMR spectra of the starting compounds **I–III** contain one singlet of ^{10}B atom bound to the oxygen at δ_B –9 ppm, and a set of doublets with the ratio of integral intensities 1:2:2:2:1:1. The introduction of one halogen atom to position 9(12) decreases the symmetry of the molecule and removes the degeneracy of the signals. Therefore, two singlets at δ_B –9 and –19 ppm, corresponding to the boron atoms bound to the oxygen and iodine atoms respectively, and seven doublets corresponding to nonequivalent unsubstituted boron atoms are observed in the spectra of monoiodo derivatives **IV** and **V**. The introduction of the second halogen atom into the *nido*-carborane cage results in the formation of symmetric molecule and two singlets at δ_B –11 and –23 ppm, corresponding to the boron atoms bound to the oxygen and iodine atoms respectively, and three doublets from unsubstituted boron atoms at δ_B –15, –21 and –40 ppm with the ratio of integral intensities 1:3:2:2:1 are observed in the ^{11}B NMR spectra of diiodo derivatives **VI** and **VII**. Similarly, the ^{11}B NMR spectra of dibromo derivatives **VIII** and **IX** contain two singlets at δ_B –8 and –13 ppm, corresponding to the boron atoms bound to the bromine and oxygen atoms respectively, and four doublets from unsubstituted boron atoms at δ_B –16, –23, –25, and –41 ppm with the ratio of integral intensities 2:1:2:2:1:1.

The ^1H NMR spectra of the synthesized halogen derivatives contain a set of signals typical for the *para*-substituted aromatic ring. It proves that the reactions of halogenation proceed exclusively at the boron atoms of the carborane cage. It is noteworthy that the introduction of one halogen atom results in a splitting of the signal of the carborane CH protons in the ^1H NMR spectra of compounds **IV** and **V** into two broadened singlets, whereas the introduction of the second halogen atom gives rise to the appearance of the plane of symmetry of the molecule and to a single signal of

the carborane CH protons in the ^{1}H NMR spectra of compounds **VI–IX**.

All synthesized compounds were isolated as potassium salts, which are readily soluble in water, but, in contrast to the earlier described halogenated derivatives of 7,8-dicarba-*nido*-undecaborate anion, they are poorly stable at storage and are slowly oxidized in the air at room temperature.

Therefore, we have prepared and characterized the monoiodo, diiodo and dibromo derivatives K[10-(4-HOOCC$_6$H$_4$O)-C$_4$H$_8$O-7,8-C$_2$B$_9$H$_{11}$] and K[10-(4-ROOCC$_6$H$_4$O)-CH$_2$CH$_2$OCH$_2$CH$_2$O-7,8-C$_2$B$_9$H$_{11}$] (R = H or CH$_3$). The obtained results are of interest for the design of the drugs for the radionuclide imaging and boron neutron capture therapy of cancer.

EXPERIMENTAL

Salts K[10-(4-HOOCC$_6$H$_4$O)-C$_4$H$_8$O-7,8-C$_2$B$_9$H$_{11}$] (**I**) and K[10-(4-HOOCC$_6$H$_4$O)-CH$_2$CH$_2$OCH$_2$CH$_2$O-7,8-C$_2$B$_9$H$_{11}$] (**II**) were synthesized by the earlier described procedures [7]. ^{1}H and ^{11}B NMR spectra were registered on a Bruker Avance-400 spectrometer. The chemical shifts are given relative to Me$_4$Si and BF$_3$·Et$_2$O, respectively.

Potassium 10-{2-[2-(4-methylcarboxyphenoxy)ethoxy]ethoxy}undecahydro-7,8-dicarba-*nido*-undecaborate (III). A mixture of 0.80 g (3.6 mmol) of [10-O(CH$_2$CH$_2$)$_2$O-7,8-C$_2$B$_9$H$_{11}$], 0.55 g (3.6 mmol) of methyl *p*-hydroxybenzoate, and 5.01 g (22.7 mmol) of K$_2$CO$_3$ in 60 ml of acetonitrile was refluxed for 6 h. After cooling of the reaction mixture, the excess of K$_2$CO$_3$ was filtered off, the filtrate was evaporated in a vacuum. To the obtained residue 10 ml of ethanol and 2 ml of water was added. The solution was partially evaporated at a reduced pressure and cooled to 0°C. The formed precipitate was filtered off and dried over P$_2$O$_5$ to obtain 0.95 g (66%) of solid. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: –0.5–2.9 br.s (10H, BH), 1.50 s (2H, CH$_{carb}$), 3.62 m (4H, OCH$_2$), 3.83 s (3H, CH$_3$), 3.86 t (2H, OCH$_2$), 4.25 t (2H, OCH$_2$), 7.08 d (2H, Ar), 7.95 d (2H, Ar). ^{11}B NMR spectrum (acetone-d_6), δ$_B$, ppm (*J*, Hz): –9.5 s (1B), –12.5 d (2B, *J* 135), –17.3 d (2B, *J* 134), –23.8 d (2B, *J* 154), –25.2 d (1B, *J* 177), –40.5 d (1B, *J* 142).

Potassium 10-[4-(4-carboxyphenoxy)butoxy]-9(11)-iododecahydro-7,8-dicarba-*nido*-undecaborate (IV). To the solution of 0.2 g (0.48 mmol) of **I** in 10 ml of methanol several drops of trifluoroacetic acid were added and the solution was cooled to 0°C. To the obtained mixture 0.12 g (0.48 mmol) of I$_2$ in 10 ml of methanol was added dropwise in the course of 20 min. The solvent was removed under a reduced pressure. To the obtained residue 15 ml of water was added and the target product was extracted with 30 ml of CH$_2$Cl$_2$. The solvent was removed in a vacuum to obtain 0.17 g (69%) of oily product. ^{1}H NMR spectrum (CD$_3$OD), δ, ppm: 1.3–3.2 br.s (10H, BH), 1.62 s (1H, CH$_{carb}$), 1.74 m (4H, OCH$_2$C<u>H$_2$</u>C<u>H$_2$</u>CH$_2$O), 2.21 s (1H, CH$_{carb}$), 3.88 m (2H, OC<u>H$_2$</u>CH$_2$CH$_2$CH$_2$O), 4.29 m (2H, OCH$_2$CH$_2$·CH$_2$C<u>H$_2$</u>O), 6.83 d (2H, Ar), 7.91 d (2H, Ar). ^{11}B NMR spectrum (CD$_3$OD), δ$_B$, ppm (*J*, Hz): –5.5 d (1B, *J* 133), –10.5 s (1B), –12.7 d (1B, *J* 133), –16.9 d (1B, *J* 133), –19.4 d (1B, *J* 163), –19.9 s (1B), –22.9 d (1B, *J* 147), –25.8 d (1B, *J* 137), –40.4 d (1B, *J* 142).

Potassium 10-{2-[2-(4-methylcarboxyphenoxy)-ethoxy]ethoxy}-9(11)-iododecahydro-7,8-dicarba-*nido*-undecaborate (V). The synthesis was performed similar to **IV** using 0.06 g (0.15 mmol) of **III** and 0.04 g (0.15 mmol) of I$_2$. 0.05 g (63%) of an oily product was obtained. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 0.5–3.0 br.s (10H, BH), 1.53 s (1H, CH$_{carb}$), 2.19 s (1H, CH$_{carb}$), 3.62 m (4H, OCH$_2$), 3.83 s (3H, CH$_3$), 3.86 m (2H, OCH$_2$), 4.25 m (2H, OCH$_2$), 7.06 d (2H, Ar), 7.94 d (2H, Ar). ^{11}B NMR spectrum (acetone-d_6), δ$_B$, ppm (*J*, *Hz*): –5.1 d (1B, *J* 138), –8.8 s (1B), –17.3 d (1B, *J* 140), –19.1 d (1B, *J* 160), –19.6 s (1B), –24.0 d (1B, *J* 162), –25.5 d (1B, *J* 160), –26.9 d (1B, *J* 143), –40.4 d (1B, *J* 145).

Potassium 10-[4-(4-carboxyphenoxy)butoxy]-9,11-diiodononahydro-7,8-dicarba-*nido*-undecaborate (VI). To the solution of 0.09 g (0.20 mmol) of **I** in 10 ml of methanol several drops of trifluoroacetic acid was added. The mixture was cooled to 0°C, and the solution of 0.50 g (2.00 mmol) of I$_2$ in 15 ml of methanol was added dropwise in the course of 15 min. The mixture was stirred for 15 min at 0°C and for another 30 min at room temperature. The solvent was removed under a reduced pressure. To the obtained precipitate 15 ml of water was added, the target product was extracted with CH$_2$Cl$_2$ (2×30 ml). Organic fractions were combined and the solvent was removed in a vacuum. The product was purified from iodine by column chromatography with silica. After removal of the solvent, 0.09 g (71%) of an oily product was obtained. ^{1}H NMR spectrum (CD$_3$OD), δ, ppm: 0.5–3.0 br.s (10H, BH), 1.77 m (4H, OCH$_2$C<u>H$_2$</u>C<u>H$_2$</u>CH$_2$O), 2.13 s (2H, CH$_{carb}$), 3.64 m (1H, OC<u>H$_2$</u>CH$_2$CH$_2$CH$_2$O), 3.96 m (1H, OC<u>H$_2$</u>CH$_2$CH$_2$CH$_2$O), 4.30 m (2H, OCH$_2$CH$_2$CH$_2$C<u>H$_2$</u>O), 6.83 d (2H, Ar), 7.90 d (2H,

Ar). ^{11}B NMR spectrum (CD_3OD), δ_B, ppm (*J*, Hz): –11.4 s (1B), –14.7 d (3B, *J* 140), –20.7 d (2B, *J* 144), –22.8 s (2B), –39.6 d (1B, *J* 141).

Potassium 10-{2-[2-(4-carboxyphenoxy)ethoxy] ethoxy}-9,11-diiodononahydro-7,8-dicarba-*nido*-undecaborate (VII). The synthesis was performed similar to **VI** using 0.06 g (0.14 mmol) of compound **II** and 0.35 g (1.40 mmol) of I_2. As a result 0.06 g (66%) of an oily product was obtained. ^{1}H NMR spectrum (CD_3OD), δ, ppm: 0.4–3.0 br.s (10H, BH), 1.99 s (2H, CH_{carb}), 3.61 m (2H, OCH_2), 3.74 m (2H, OCH_2), 3.78 m (1H, OCH_2), 3.86 m (1H, OCH_2), 4.32 m (2H, OCH_2), 6.73 d (2H, Ar), 7.78 d (2H, Ar). ^{11}B NMR spectrum (CD_3OD), δ_B, ppm (*J*, Hz): –11.2 s (1B), –14.9 d (3B, *J* 141), –20.8 d (2B, *J* 155), –22.8 s (2B), –39.7 d (1B, *J* 143).

Potassium 10-[4-(4-carboxyphenoxy)butoxy]-9,11-dibromononahydro-7,8-dicarba-*nido*-undecaborate (VIII). The synthesis was performed similar to **VI** using 0.10 g (0.22 mmol) of compound **I** and 0.35 g (2.20 mmol) of Br_2. In result 0.09 g (76%) of an oily product was obtained. ^{1}H NMR spectrum (CD_3OD), δ, ppm: 0.5–3.0 br.s (10H, BH), 1.73 m (4H, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$), 2.03 s (2H, CH_{carb}), 3.66 m (1H, $OC\underline{H}_2CH_2CH_2CH_2O$),3.93 m (1H, $OC\underline{H}_2CH_2CH_2\cdot CH_2O$), 4.31 m (2H, $OCH_2CH_2CH_2C\underline{H}_2O$), 6.84 d (2H, Ar), 7.88 d (2H, Ar). ^{11}B NMR spectrum (CD_3OD), δ_B, ppm (*J*, Hz): –7.9 s (2B), –13.3 s (1B), –16.4 d (2B, *J* 138), –23.2 d (2B, *J* 155), –24.8 d (1B, *J* 160), –41.3 d (1B, *J* 145).

Potassium 10-{2-[2-(4-carboxyphenoxy)ethoxy]-ethoxy}-9,11-dibromononahydro-7,8-dicarba-*nido*-undecaborate (IX). The synthesis was performed similar to **VI** using 0.12 g (0.27 mmol) of compound **II** and 0.43 g (2.70 mmol) of Br_2. In result 0.10 g (67%) of an oily product was obtained. ^{1}H NMR spectrum (CD_3OD), δ, ppm: 0.5–3.0 br.s (10H, BH), 1.96 s (2H, CH_{carb}), 3.59 m (2H, OCH_2), 3.72 m (2H, OCH_2), 3.75 m (1H, OCH_2), 3.3 m (1H, OCH_2), 4.1 m (2H, OCH_2), 6.72 d (2H, Ar), 7.75 d (2H, Ar). ^{11}B NMR spectrum (CD_3OD), δ_B, ppm (*J*, Hz): –7.9 s (2B), –13.3 s (1B), –16.5 d (2B, *J* 138), –23.3 d (2B, *J* 154), –24.8 d (1B, *J* 161), –41.1 d (1B, *J* 145).

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