Synthesis of some functional derivatives of *o*- and *m*-carboranes

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Amides, amines, and alcohols were synthesized from 9-*o*- and 9-*m*-carboranecarboxylic chlorides. It follows from comparison of the ^{1}H NMR spectra of *N,N*-dimethyl-1-*o*- and -1-*m*-carboranecarboxamides and *N,N*-dimethyl-9-*o*- and -9-*m*-carboranecarboxamides that π-bonding of the carborane polyhedron with the carbonyl group in 1-carboranyl dimethylamides is stronger than that in 9-carboranyl dimethylamides. Oxidation of 9-hydroxymethyl-*m*-carborane with pyridinium chlorochromate gives 9-*m*-carboranylmethyl 9-*m*-carboranecarboxylate.

Key words: B-substituted carboranes: amides, amines, alcohols.

In the series of *o*- and *m*-carborane derivatives bearing functional groups at boron atoms of the carborane polyhedron, mainly 3-*o*- and 2-*m*-substituted carboranes are studied.[1] *o*-Carboranes and *m*-carboranes substituted at other positions of the polyhedron are studied only to a small extent.

In continuation of our studies of 9-substituted *o*- and *m*-carboranes, in this work *N,N*-dimethyl-9-*o*- and 9-*m*-carboranecarboxamides, 9-dimethylaminomethyl-, and 9-hydroxymethyl-*o*-, and 9-hydroxymethyl-*m*-carboranes, which are of interest as initial compounds for synthesis of medicinals for boron-neutron capture therapy for cancer, were obtained.

9-(*N,N*-Dimethylcarbamyl)-*o*- (**2a**) and 9-(*N,N*-dimethylcarbamyl)-*m*-carboranes (**2b**) are readily formed in the reactions of 9-*o*- and 9-*m*-carboranecarboxyl chlorides **1a,b** with dimethylamine at −10 °C in ether.

$$o\text{-},m\text{-}C_2H_2B_{10}H_9COCl\text{-}9 \xrightarrow{i} o\text{-},m\text{-}C_2H_2B_{10}H_9CONMe_2\text{-}9$$

o-**1a**, *m*-**1b**   *o*-**2a**, *m*-**2b**

i. Me_2NH, ether

Synthesis of amides **2a,b** is of additional interest, because this synthesis and ^{1}H NMR spectroscopy provide a possibility of comparing the barriers of rotation around C—N bonds in these amides containing the system of B—C—N bonds with that of rotation around the C—N bond in 1-(*N,N*-dimethylcarbamyl)-*o*- and -*m*-carboranes, in which the amide group is related to the carbon atoms of *o*- and *m*-carboranes possessing the system of C—C—N bonds.

It turned out that in the ^{1}H NMR spectra of amides **2a,b** at 20 °C the *N*-methyl groups manifest themselves as two narrow singlets, δ 3.09 and 2.73 ppm for **2a** and δ 3.20 and 2.81 ppm for **2b**, while in 1-(*N,N*-dimethylcarbamyl)-*o*- and -*m*-carboranes the *N*-methyl groups at 20 °C exhibit singlet signals with δ 2.91 and 3.09 ppm, respectively.[2] In the ^{1}H NMR spectrum of 1-(*N,N*-dimethylcarbamyl)-2-(phenyl)-*o*-carborane, the methyl groups of amide are also manifested as a singlet signal with δ 3.01 ppm despite the presence of the phenyl group at position 2. Since in the ^{1}H NMR spectra of amides **2a** and **2b** the *N*-methyl groups exhibit two singlets, we synthesized 1,2-(dimethyl)-3-(*N,N*-dimethylcarbamyl)-*o*-carborane (**3**), in which the Me_2NCO group is bonded to the boron atom at position 3, and established that in this compound the *N*-methyl groups are also manifested as two singlets with δ 3.05 and 2.92 ppm. Thus, in the Me_2NCO groups bonded to the boron atom at various positions of the carborane polyhedron, *N*-methyl groups are manifested in the ^{1}H NMR spectra as two singlets, which testifies to the retarded rotation around the C—N bond in these amides.

It is commonly accepted[3] that the reason for the difficult rotation around the C—N bond in *N,N*-dimethylamides of acids is the partially double character of this bond, and the presence of the π-bonded substituent at the carbonyl group results in a decrease in the order of the C—N bond and, as a consequence, in a decrease in the barrier of rotation around this bond. These groups are aromatic systems reacting with the CO group due to π-electrons, which results in the fact that the barrier of rotation around the C—N bond in $ArCONMe_2$ is lower than in $MeCONMe_2$.[4]

The authors of Ref. 5 used the methods based on the topology and theory of graphs to show that carboranes $C_2B_{n-2}H_n$ ($6 \le n \le 12$) can be considered as three-dimensional delocalized aromatic systems, in which the surface bonding and framework bonding correspond to the σ- and π-bonding in planar monocyclic hydrocarbons $C_nH_n^{(n-6)+}$ (n = 5 to 7), for example, in benzene. This agrees with the data of Refs. 2 and 3, in which it is assumed that *o*- and *m*-carborane rings are able to

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π-bonding with the carbonyl carbon atom of amide and are highly aromatic systems. This assumption is based on a decrease in the barrier of rotation in dimethyl-*o*- and -*m*-carboranecarboxamides compared to that in *N,N*-dimethylacetamide.

The data obtained show that the barrier of rotation around the C—N bond in amides **2a,b** and **3** is higher than in amides *o*- and *m*-$C_2B_{10}H_{11}$—1-$CONMe_2$ and, hence, the bond order of C—N in amides **2a,b** and **3** is higher than those in amides *o*-$C_2B_{10}H_{11}$—1-$CONMe_2$ and *m*-$C_2B_{10}H_{11}$—1-$CONMe_2$. This allows one to draw the conclusion that π-bonding of the 1-*o*- and 1-*m*-carboranyl groups with the CO group of amide in amides *o*- and *m*-$C_2B_{10}H_{11}$—1-$CONMe_2$ is stronger than those of the 9-*o*-, 9-*m*-, and 3-*o*-carboranyl groups in amides **2a,b** and **3**. The difference in π-bonding of the 1-*o*- and 1-*m*-carboranyl groups and 9-*o*-, 9-*m*-, and 3-*o*-carboranyl groups with the dimethylamide group, *i.e.*, with the systems of the C—C—N and B—C—N bonds, respectively, testifies, in our opinion, to the difference in the π-character of the framework bonding in *o*- and *m*-carboranes, which depends on the atom entering the framework of the polyhedron and its position in it.

Reduction of amides **2a,b** by H_2AlCl in ether results in the corresponding 9-(dimethylaminomethyl)-*o*- (**4a**) and -*m*-carboranes (**4b**).

$$\mathbf{2a,b} \xrightarrow{i} o\text{-},m\text{-}C_2H_2B_{10}H_9CH_2NMe_2\text{-}9$$
$$o\text{-}\mathbf{4a},\ m\text{-}\mathbf{4b}$$

i. H_2AlCl, ether

Amines **4a,b** are stable crystalline compounds.

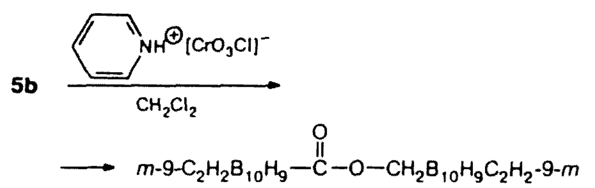
Reduction of acid chlorides **1a,b** and 9-*o*- and 9-*m*-carboxylic acids by $LiAlH_4$ in ether results in the smooth formation of crystalline 9-hydroxymethyl-*o*- (**5a**) and 9-hydroxymethyl-*m*-carboranes (**5b**):

$$\left.\begin{array}{l}\mathbf{1a,b}\\ o\text{-},m\text{-}C_2H_2B_{10}H_9COOH\text{-}9\end{array}\right\} \xrightarrow{i} \begin{array}{c}o\text{-},m\text{-}C_2H_2B_{10}H_9CH_2OH\text{-}9\\ o\text{-}\mathbf{5a},\ m\text{-}\mathbf{5b}\end{array}$$

i. $LiAlH_4$, ether

The IR spectra of compounds **5a,b** exhibit two absorption bands of the OH group: a broad band at 3100 to 3580 cm^{-1} (**5a**) or 3120 to 3590 cm^{-1} (**5b**) and a narrow band at 3610 cm^{-1} (**5a**) and 3604 cm^{-1} (**5b**), which are typical of associated and nonassociated alcohols, respectively. It should be mentioned that the IR spectra of 3-hydroxymethyl-*o*-carborane[1] and 1-hydroxymethyl-*o*-carborane[6] contain absorption bands at 3200 to 3600 and 3200 to 3500 cm^{-1}, respectively, related to the vibrations of the OH groups of associated alcohols.

We tried to obtain 9-formyl-*m*-carborane by oxidation of 9-hydroxymethyl-*m*-carborane; however, the known procedure of oxidation of primary alcohols to aldehydes by pyridinium chlorochromate resulted in the formation of 9-*m*-carboranylmethyl 9-*m*-carboranecarboxylate (**6**) from alcohol **5b** instead of expected 9-formyl-*m*-carborane:



6

We are unable yet to explain this unusual run of the reaction. The structure of **6** was confirmed by IR and mass spectra as well as by the independent synthesis from compounds **5b** and **1b** in the presence of pyridine.

Experimental

IR spectra were recorded on a UR-20 spectrophotometer in KBr pellets. ^1H NMR spectra were recorded on a Bruker WP-200SY instrument in $(CD_3)_2CO$ solutions relative to HMDS. Reactions and purity of compounds were controlled by TLC on Silufol plates. 9-*o*- and 9-*m*-Carboranecarboxylic acids and their chlorides were obtained by the described procedure.[7]

9-(*N,N*-Dimethylcarbamyl)-*o*-carborane (2a). A solution of acid chloride **1a** (3.5 g, 17 mmol) in 10 mL of anhydrous ether was added to a solution of dimethylamine (2.3 g, 50 mmol) in 25 mL of anhydrous ether at −10 °C in an argon atmosphere, and the mixture was stirred for 1 h at 20 °C. Then the reaction mass was poured into water (50 mL), NaOH was added until an alkaline medium was achieved, and the reaction mass was extracted with ether (2×30 mL). The ether extracts were washed with water and dried over Na_2SO_4. After distilling off the ether, amide **2a** was obtained (2.7 g, 74 %), m.p. 178 °C (benzene—THF). ^1H NMR, δ: 4.57 (br.s, 2 H, CH of carborane), 3.09 (s, 3 H, CH_3), 2.74 (s, 3 H, CH_3). Found (%): B, 50.02; N, 6.85. $C_5H_{17}B_{10}NO$. Calculated (%): B, 50.21; N, 6.51.

9-(*N,N*-Dimethylcarbamyl)-*m*-carborane (2b). Amide **2b** was obtained similarly from dimethylamine (1.43 g, 31.8 mmol) and acid chloride **1b** (2.18 g, 10.6 mmol), m.p. 135—136 °C (benzene—THF). ^1H NMR, δ: 3.71 (br.s, 2 H, CH of carborane), 3.20 (s, 3 H, CH_3), 2.81 (s, 3 H, CH_3). Found (%): B, 49.94; N, 6.76. $C_5H_{17}B_{10}NO$. Calculated (%): B, 50.21; N, 6.51.

1-(*N,N*-Dimethylcarbamyl)-2-phenyl-*o*-carborane (2.6 g, 90 %) was obtained similarly from dimethylamine (1.4 g, 31 mmol) and 2-phenyl-1-*o*-carboranecarboxyl chloride (2.82 g, 10 mmol), m.p. 122 °C. ^1H NMR, δ: 7.30—7.74 (m, 5 H, C_6H_5), 3.01 (s, 6 H, 2 CH_3). Found (%): C, 45.75; H, 7.34; B, 36.97. $C_{11}H_{21}B_{10}NO$. Calculated (%): C, 45.35; H, 7.21; B, 37.11.

1,2-(Dimethyl)-3-(*N,N*-dimethylcarbamyl)-*o*-carborane (3). Amide **3** (0.85 g, 70 %) was obtained similarly from dimethylamine (0.7 g, 15 mmol) and 1,2-dimethyl-3-*o*-carboranecarboxyl chloride (1.17 g, 5 mmol), m.p. 152 °C. ^1H NMR, δ: 3.05 (s, 3 H, B—CH_3), 2.92 (s, 3 H, B—CH_3), 1.38 (s, 6 H, C—CH_3).

9-(Dimethylaminomethyl)-*o*-carborane (4a). An ether solution of H_2AlCl (7.4 mmol, obtained from $AlCl_3$ (0.99 g) and $LiAlH_4$ (0.28 g) in 15 mL of anhydrous ether) was added to a solution of compound **2a** (1.6 g, 7.4 mmol) in 20 mL of ether in an argon atmosphere at 20 °C. The mixture was stirred for 1 h and poured into water with ice, and NaOH was added to obtain an alkaline medium. An ether layer was separated, and an aqueous layer was extracted with ether (2×15 mL). United ether extracts were washed with water and dried over Na_2SO_4. After removal of ether *in vacuo*, amine **4a** (1.4 g, 93 %) was obtained, m.p. 123—124 °C (benzene—heptane). Found (%): C, 30.07; H, 9.54; B, 53.25; N, 7.11. $C_5H_{19}B_{10}N$. Calculated (%): C, 29.83; H, 9.51; B, 53.70; N, 6.96.

9-(Dimethylaminomethyl)-*m*-carborane (4b) was synthesized similarly to the previous compound from compound **2b** (1 g, 4.6 mmol) and H_2AlCl (4.6 mmol, obtained from $AlCl_3$ (0.63 g) and $LiAlH_4$ (0.18 g)) in 30 mL of anhydrous ether. Amine **4b** was obtained in an 89 % yield (0.84 g), m.p. 83—84 °C (benzene—heptane). Found (%): C, 29.70; H, 9.54; B, 53.79. $C_5H_{19}B_{10}N$. Calculated (%): C, 29.83; H, 9.51; B, 53.70. Amine **4b** was also identified as oxalate with m.p. 117—118 °C. Found (%): N, 4.84. $C_7H_{21}B_{10}NO_4$. Calculated (%): N, 4.81.

9-(Hydroxymethyl)-*o*-carborane (5a). a. A solution of **1a** (2.1 g, 10.6 mmol) in 25 mL of anhydrous ether was added to a suspension of $LiAlH_4$ (0.8 g, 20 mmol) in 15 mL of anhydrous ether at 20 °C in an argon flow, and the mixture was stirred for 1 h. Then the reaction mass was poured into water and extracted with ether. The ether extracts were washed with a 5 % solution of HCl and water and dried over Na_2SO_4. After the ether was distilled off *in vacuo*, compound **5a** (1.5 g, 82 %) was obtained, m.p. 215—217 °C (benzene—heptane). IR spectrum, ν/cm^{-1}: 2600 (BH), 3060 (CH of carborane), 3390 (OH associated), 3610 (OH nonassociated). Found (%): C, 20.47; H, 7.99; B, 61.84. $C_3H_{14}B_{10}O$. Calculated (%): C, 20.68; H, 8.10; B, 62.04.

b. A solution of 9-*o*-carboranecarboxylic acid (0.94 g, 5 mmol) in 10 mL of anhydrous ether was added to a suspension of $LiAlH_4$ (0.15 g, 4 mmol) in 10 mL of anhydrous ether in an argon flow at 20 °C, and the mixture was stirred for 1 h. Then water (10 mL) was added to the reaction mixture, which was acidified with 10 % HCl. The organic layer was separated, and the aqueous layer was extracted with ether. The ether extracts were washed with water and dried over Na_2SO_4. After removal of the ether *in vacuo* and crystallization, compound **5a** (0,74 g, 85 %) was obtained.

9-(Hydroxymethyl)-*m*-carborane (5b). a. Compound **5b** was obtained similarly to the previous compound from $LiAlH_4$ (0.2 g, 5 mmol) and compound **1b** (1.6 g, 8 mmol) in 20 mL of anhydrous ether in a yield of 89 % (1.2 g), m.p. 175—176 °C (from a benzene—heptane mixture). IR, ν/cm^{-1}: 2600 (BH), 3056 (CH of carborane), 3390 (OH associated), 3604 (OH nonassociated). Found (%): C, 20.80; H, 7.98; B, 62.13. $C_3H_{14}B_{10}O$. Calculated (%): C, 20.68; H, 8.10; B, 62.04.

b. Compound **5b** (0.8 g, 91 %) was obtained similarly to the previous compound from $LiAlH_4$ (0.15 g) and 9-*m*-carboranecarboxylic acid (0.94 g) in 20 mL of anhydrous ether.

9-*m*-Carboranylmethyl 9-*m*-carboranecarboxylate (6). a. Alcohol **5b** (1.4 g, 8 mmol) in 15 mL of CH_2Cl_2 was added with intense stirring to a suspension of pyridinium chlorochromate (3.4 g, 16 mmol) in 35 mL of CH_2Cl_2 at 20 °C, and a mixture was stirred for 2 h. Then 50 mL of ether was added to the reaction mixture, and the ether solution was decanted from a black precipitate and filtered. The ether was distilled off, a residue was chromatographed on a column with silica gel (2×15 cm, 40×100 mm, benzene as eluent). Ester **6** was obtained in a 71 % yield (1 g), m.p. 225 °C (from a benzene—heptane mixture). IR, ν/cm^{-1}: 1250 (C—O—), 1680 (CO), 2600 (BH), 2875, 2940 (CH_2), 3070 (CH of carborane). Mass spectrum, *m/z*: 339 M^+. Found (%): C, 20.66; H, 7.14; B, 62.46. $C_6H_{24}B_{20}O_2$. Calculated (%): C, 20.93; H, 7.01; B, 62.77.

b. A solution of **1b** (1 g, 5 mmol) in 3 mL of anhydrous benzene was added to a mixture of compound **5b** (0.87 g, 5 mmol), pyridine (3 mL), and benzene (15 mL) at 5 °C. A mixture was stirred for 1 h. When the reaction was ceased, the mixture was poured into 10 % HCl (25 mL) and extracted with benzene (2×5 mL). Benzene extracts were washed with water and dried over Na_2SO_4. After distilling off the benzene, ester **6** (1.23 g, 72 %) was obtained, m.p. 224—225 °C.

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