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Synthesis of new *nido*-carborane based carboxylic acids and amines

Svetlana A. Erokhina, Marina Yu. Stogniy *, Kyrill Yu. Suponitsky, Irina D. Kosenko, Igor B. Sivaev, Vladimir I. Bregadze

A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov Str., 119991 Moscow, Russia

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ABSTRACT

A series of new *nido*-carborane based carboxylic acids 10-HOOC$(CH_2)_n$(Me)S-7,8-$C_2B_9H_{11}$ (n = 1–4) was prepared by alkylation of tetrabutylammonium salt of 10-methylthio-7,8-dicarba-*nido*-caborane with ω-halogenoalkyl esters or nitriles followed by acid hydrolysis. Likewise *nido*-carborane based amines 10-$H_2N(CH_2)_n$(Me)S-7,8-$C_2B_9H_{11}$ (n = 2, 3) were obtained using ω-bromoalkylphthalimides as alkylating agents followed by removal of the protecting group with hydrazine. Structure of 10-$C_6H_4(CO)_2NCH_2CH_2$(Me)S-7,8-$C_2B_9H_{11}$ was determined by single crystal X-ray diffraction.

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1. Introduction

Boron neutron capture therapy (BNCT) is a binary method for the treatment of cancer, which is based on the nuclear reaction of two essentially nontoxic species, non-radioactive ^{10}B and low-energy thermal neutrons. The neutron-capture reaction by ^{10}B produces α-particle, $^4He^{2+}$, and $^7Li^{3+}$ ion. These high-linear-energy transfer ions dissipate their kinetic energy before traveling one cell diameter (5–9 μm) in biological tissues, ensuring their potential for precise tumor cell-killing and sparing healthy tissues. Clinical interest in BNCT has focused primarily on the treatment of high-grade gliomas, and specifically glioblastoma multiforms, which are extremely resistant to all current forms of therapy, including surgery, chemotherapy, radiotherapy, immunotherapy, and gene therapy [1]. The initial step of development of the BNCT development was connected with use of nuclear reactors as the neutron sources [2,3]. The main advantage of using nuclear reactors is the lack of the need for large financial investments (only modification of the primary spectrum of the neutron beam for medical purposes using an appropriate beam shaping assembly (moderator, thermal neutron and gamma filters and collimator) is required). However, in this case, the medical treatment is strongly dependent on the operating cycle of the reactor and the reactor shutdown results in the stop of BNCT program. Therefore today's efforts to use BNCT as a routine radiotherapy focus on accelerator-based neutron sources which can be placed in a hospital environment [4–6]. At the same time, we should not forget that the accelerators are only one face of the problem and even more important for the BNCT establishment as a routine treatment procedure is development of new BNCT agents and better drug delivery systems [7–10].

Since BNCT is the binary therapy, the selective delivery of sufficiently large amount of ^{10}B nuclei to tumor cells (20–35 μg per gram of tumor tissue) is one of the most important requirements. This problem can be solved with the help of targeted liposomal delivery systems or by the attachment of a large number of boron-containing moieties to various biomolecules which will provide their targeted delivery to the tumor. One of the most widely used methods of modification of biomolecules is the reaction of their amino and carboxy groups with boron-containing acids and amines, respectively, to form an amide bond. Therefore, the synthesis of carborane-containing acids and amines has attracted the attention of researchers for more than fifty years [11]. Earlier we described the synthesis of a series of *nido*-carborane containing acids [12,13] and amines [13,14] with a terminal functional group attached to the carborane cage through sulfur atom. However, introduction of substituent at positions 7 or 9 of the *nido*-carborane cage results in the goal products as enantiomeric [12,14] or diastereomeric [13] mixtures. In this contribution we describe the synthesis of symmetrically substituted *nido*-carborane based carboxylic acids and amines 10-X$(CH_2)_n$(Me)S-7,8-$C_2B_9H_{11}$ (X = COOH, NH_2).

* Corresponding author.
E-mail address: stogniymarina@rambler.ru (M.Yu. Stogniy).

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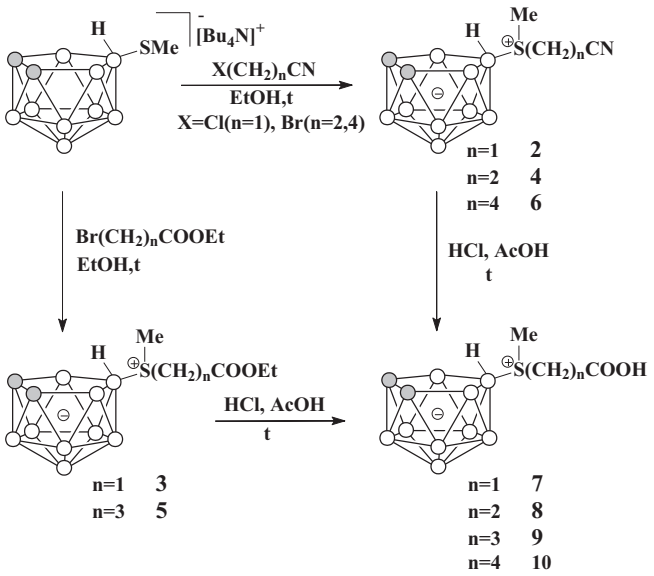
2. Results and discussion

Synthesis of functional derivatives of *closo*-decaborate $[B_{10}H_{10}]^{2-}$ [15–17] and *closo*-dodecaborate $[B_{12}H_{12}]^{2-}$ [15,18] anions by alkylation of their methylsulfide derivatives is well known. These reactions result in chiral BS(Me)R sulfonium derivatives, nevertheless due low activation energy (ΔG_{298} = 0.4–0.8 kcal/mol) the epimerization at sulfur atom was found to proceed much easier than for trialkylsulfonium salts and occurs rather fast at room temperature [19]. However, in some cases, for example in the case of 9-alkyl(methyl)sulfonium derivatives of *nido*-carborane 9-R$(CH_2)_n$(Me)S-7,8-$C_2B_9H_{11}$ [13,20,21], the epimerization barrier is much higher due to strong interaction of the sulfur lone pair electrons with the B(9)–B(10) antibonding orbital of the *nido*-carborane cage [22]. As a result, these derivatives exist as mixtures of diastereomers which are not very suitable for medical applications. To overcome this problem, we synthesized a series of new *nido*-carborane based acids by alkylation of the symmetrical 10-methylsulfide derivative $[10\text{-MeS-7,8-}C_2B_9H_{11}]^-$. The 10-methylsulfide derivative was prepared by partial demethylation of well known 10-dimethylsulfonium derivative [10-Me_2S-7,8-$C_2B_9H_{11}$] [23] with sodium amide in refluxing toluene [24].

Alkylation of the tetrabutylammonium salt of 10-methylthio-7,8-dicarba-*nido*-caborane $(Bu_4N)^+[10\text{-MeS-7,8-}C_2B_9H_{11}]^-$ (**1**) with ω-halogenoalkyl nitriles or esters in refluxing ethanol gives the corresponding nitriles **2**, **4**, **6** and esters **3**, **5** (Scheme 1). Compounds **2**–**6** were purified by column chromatography on silica with CH_2Cl_2 as eluent. In all cases small amount of the 10-dimethylsulfonium derivative 10-Me_2S-7,8-$C_2B_9H_{11}$ was isolated. The subsequent acidic hydrolysis of nitriles and esters with the mixture of glacial acetic and hydrochloric acids lead to a series of *nido*-carborane based carboxylic acids with different spacer length between the carborane cage and terminal carboxylic group **7**–**10** (Scheme 1).

The synthesized compounds were characterized by ^{1}H, ^{13}C and ^{11}B NMR spectroscopy, IR spectroscopy and mass spectrometry. The ^{1}H NMR spectra of compounds **2**, **3** and **7** demonstrate magnetically non-equivalent signals of the S-CH_2 protons with J_2(H-H) geminal coupling constants ~16 Hz, whereas in the spectra of the compounds with longer spacers these signals are observed as multiplets. The ^{11}B{^{1}H} NMR spectra of compounds **3**–**10** contain a set of signals with 2:2:1:2:1:1 intensity ratio, indicating the expected



Scheme 1. Synthesis of *nido*-carborane based carboxylic acids.

mirror symmetry. However, in the spectrum of 10-N≡CCH_2(Me)S-7,8-$C_2B_9H_{11}$ (**2**) all three pair of signals are splitted giving 1:1:1:2:1:1:1:1 pattern (Fig. 1) that practically exactly (with the measurement error) coincides with the spectrum of the related propargyl derivative 10-HC≡CCH_2(Me)S-7,8-$C_2B_9H_{11}$ [24]. The signals of the B(5) and B(6) atoms in *nido*-carborane derivatives are known to be very sensitive to the position of the "extra" hydrogen atom which can migrate over two bridge positions B(9)–H–B(10) and B(10)–H–B(11) (so-called "μ-H rule") [25]. In the symmetrical dimethylsulfonium derivative 10-Me_2S-7,8-$C_2B_9H_{11}$ the "extra" hydrogen is located equally over the B(9)–H–B(10) and B(10)–H–B(11) positions, that results in the mirror plane passing through the B(1), B(3) and B(10) atoms. In asymmetrical alkylmethylsulfonium derivatives 10-R(Me)S-7,8-$C_2B_9H_{11}$, the presence of nonequivalent substituents at the sulfur atom could shift slightly the equilibrium position, producing in such a way splitting of the B(5/6) signal in the ^{11}B NMR spectra. This splitting (Δ) is incomplete (less than the signal linewidth) and rather small and varies from 0 to 0.8 ppm [24,26]. However, in the case of **2** this splitting arises to 3.3 ppm with simultaneous splitting of the B(9/11) and B(2,4) signals (Δ = 1.1–1.2 ppm) indicating strong shift of the "extra" hydrogen equilibrium resulting in its fixation over one B-B edge of the open pentagonal face of *nido*-carborane ("frozen" migration). The similar pattern was found earlier for the alkyne derivatives RC≡CCH_2(Me)S-7,8-$C_2B_9H_{11}$ (R = H, Ph, $SiMe_3$) where intramolecular B–H···π(C≡C) hydrogen bonding between the BHB hydrogen and alkyne group was revealed by single crystal X-ray diffraction and quantum chemical calculations [24]. Unfortunately, we were unable to obtain good quality crystals of **2**, however it is reasonable to suppose that similar intramolecular interaction between the BHB hydrogen and the nitrile group exists in this case as well.

The reaction of **1** with ω-bromoalkylphthalimides in refluxing ethanol gives the corresponding carboranyl alkylphthalimides **11**–**13**. The subsequent treatment of **12** and **13** with hydrazine hydrate results in the removal of phthalimide protection leading to the corresponding amines **14** and **15** (Scheme 2).

The ^{11}B NMR spectra of compounds **13**–**15** are similar to those of compounds **3**–**10**, whereas the spectra of compounds **11** and **12** were found unexpectedly to display practically the same pattern as in the spectrum of nitrile **2** indicating the "frozen" migration of the "extra" hydrogen. It is worth noting that increase of the spacer length results in the absence of such effect in phthalimide **13** and the removal of the phthalimide protection produces the disappearance of this effect in amine **14**. On the other hand, the presence of carboxyl (carboxyethyl) group in compounds **3**, **5**, **7**–**10** with different spacer length produces no effect in the ^{11}B NMR spectra. This let us to assume that fixation of the "extra" hydrogen is caused by its interaction with the phthalimide group. To clarify the nature of these interactions we performed X-ray diffraction study of compound **12**. However, in the solid state the substituent is oriented outward the carborane cage (the torsion angle B10-S1-C2-C3 is equal to −173.49(9)°) and there are no intramolecular interactions between the "extra" hydrogen atom and the phthalimide group (Fig. 2). Instead of this, numerous intermolecular contacts including intermolecular C–H···O hydrogen bonds and head-to-tail π-stacking between the phthalimide rings which are well known for phthalimide derivatives [27,28] were found. Thus, the formation of numerous weak intermolecular interactions in the solid state is preferable than the formation of one stronger intramolecular hydrogen bond. A similar situation was observed earlier in the case of Me_3SiC≡CCH_2(Me)S-7,8-$C_2B_9H_{11}$ [24].

Assuming that intramolecular interactions between the "extra" hydrogen atom and the phthalimide group can exist in solution, we calculated dependence of conformational energy upon rotation of the heterocyclic fragment around the S1-C2 bond (from 0 to 360°

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