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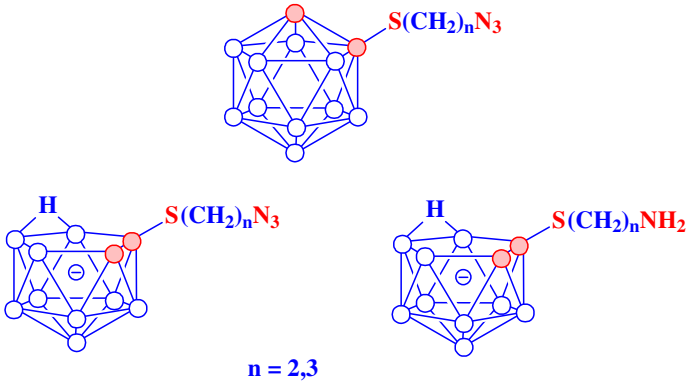
A series of new carboranyl azides and amines were synthesized by alkylation of 1-mercapto-*ortho*-carborane.



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LETTER

Synthesis of new ω-amino- and ω-azidoalkyl carboranes†,‡

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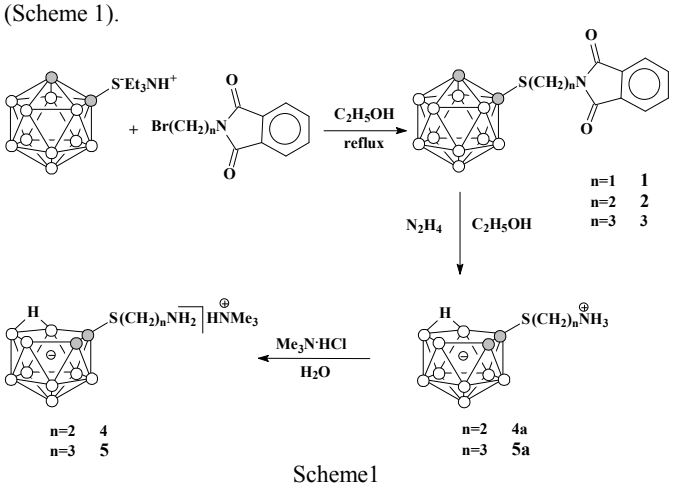
Novel carboranyl amines [7-$NH_2(CH_2)_nS$-7,8-$C_2B_9H_{11}$]$^-$ were synthesized by alkylation of 1-mercapto-*ortho*-carborane with the ω-bromoalkylphthalimides followed by removal of the protecting group with hydrazine. *closo*-Carboranyl azides 1-$N_3(CH_2)_nS$-1,2-$C_2B_{10}H_{11}$ were prepared by reaction of the corresponding carboranyl alcohol/iodide with sodium azide and converted to water soluble *nido*-form [7-$N_3(CH_2)_nS$-7,8-$C_2B_9H_{11}$]$^-$ with ammonium formate in refluxing methanol.

The development of new functional derivatives of carboranes for potentional use in the boron neutron capture therapy (BNCT),[1] radionuclide diagnostics[2] and drug design[3] remains an active area of research. Simple functional groups like amine or azide can be used for conjugation of carborane moiety with biomolecules that act as tumor-targeting vectors[4]. There are three main approaches to the synthesis of ω-aminoalkyl carboranes 1-$NH_2(CH_2)_n$-1,2-$C_2B_{10}H_{11}$. The first one is based on the reaction of decaborane(14) with protected ω-aminoalkylacetylenes followed by removal of protecting groups.[5-8] The similar approach includes alkylation of *ortho*-carborane with protected ω-halogenalkylamines.[9-11] The *N*-phthalimide protecting group is the most typical for these two synthetic schemes.[5-10] Another approach includes preliminary synthesis of ω-carboranylalkyl halides or triflates 1-$X(CH_2)_n$-1,2-$C_2B_{10}H_{11}$ (X = Cl, Br, I, OTf) followed by their treatment with various *N*-nucleophiles.[5,12] This synthetic scheme requires more steps, however, it is more universal and can be used for synthesis of ω-carboranylalkyl azides as well.[7,13,14] The same approach can be used for introduction of the amino group into related carborane systems.[15-17]

The common problem in the carborane chemistry is synthesis of their monosubstituted derivatives. It is caused by the tendency of monolithio carborane to disproportionate to dilithio carborane and the parent carborane that often results in mixtures of mono- and disubstituted derivatives.[18,19] This problem can be solved by introduction of *tert*-butyldimethylsilyl protecting group[20] or, sometimes, by using specific reaction conditions for different types of derivatives[21-24]. Some later, the introduction of mercapto group followed by their alkylation was proposed as a route to monosubstituted carboranes[25]. Recently this approach was used for synthesis of various functional derivatives of carboranes, including carboxylic acids[26], aminoacids[27], and carbohydrates[28]. In this contribution we describe synthesis of carborane based amines and azides from 1-mercapto-*ortho*-carborane.

The reaction of the triethylammonium salt of mercapto carborane (Et_3NH)[1-S-1,2-$C_2B_{10}H_{11}$] with commercially available ω-bromoalkylphthalimides in refluxing ethanol gives the corresponding carboranyl alkylphthalimides **1**-**3**. The ^1H and ^{13}C NMR spectra of **1**-**3** contain characteristic signals of the phthalimide protecting group. The reaction of **2** and **3** with hydrazine hydrate in refluxing ethanol results in deprotection of amino group and partial degradation of the *closo*-carborane cage to the *nido*-carborane one giving the corresponding amines **4a** and **5a** isolated as solvates with hydrazine (Scheme 1).



Scheme1

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Removal of the protecting group results in disappearance of characteristic signals in aromatic regions of the ^{1}H and ^{13}C NMR spectra of **4a** and **5a**. The carborane decapitation produces a high field shift and splitting of the $CarbSCH_2$-group in the ^{1}H NMR spectra. The high field shift is caused by the reduction of electron-withdrawal effect of carborane on its transformation from the *closo*- to the *nido*-form,[29] whereas the signal splitting can be ascribed to transformation of two primarily enantiotopic $CarbSCH_2$- methylene protons into magnetically nonequivalent diastereotopic ones on the degradation of achiral 1-R-*closo*-$C_2B_{10}H_{11}$ carborane to chiral 7-R-*nido*-$C_2B_9H_{11}$ carborane.[26] The carborane decapitation results in the corresponding changes in the ^{11}B NMR spectra as well.

The structure of **5a** was determined by single crystal X-ray diffraction (Fig. 1). The amino group of *nido*-carborane in **5a** is protonated forming the inner ammonium salt. The ammonium hydrogen atoms form hydrogen bonds with three solvate molecules of hydrazine (Fig. S1). The hydrazine molecules are connected by hydrogen bonds to form associates including a pair of the carborane molecules (Figs. S2 and S3). A similar pattern of hydrogen bonds between the protonated amino groups and solvate hydrazine molecules was found earlier in the structure of closely related aminocarborane 7-$NH_3CH_2CH_2CH_2$-7,8-$C_2B_9H_{11}$*N_2H_4.[10]

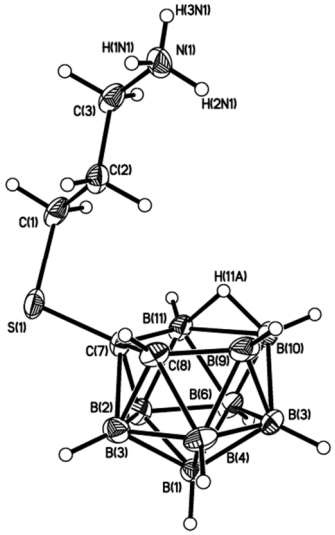
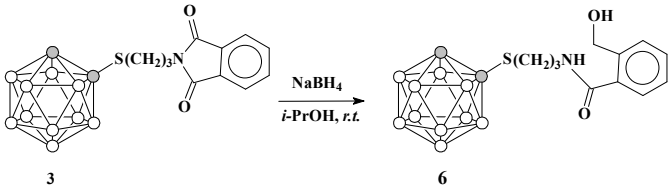


Fig.1. Molecular structure and numbering scheme of 7-$NH_3CH_2CH_2CH_2$S-7,8-*nido*-$C_2B_9H_{11}$. Selected bond lengths [Å]: C(7)-C(8) 1.562(3), C(7)-B(11) 1.628(3), C(8)-B(9) 1.600(3), C(7)-S(1) 1.781(2), N(1)-C(3) 1.483(3), H(11A)-B(11) 1.18(3), H(11A)-B(10) 1.43(3).

In aqueous solution there is equilibrium between the protonated inner ammonium salts **4a** and **5a** and hydrazinium salts of deprotonated amines **4** and **5**. The deprotonated amines were isolated by the treatment with trimethylamine hydrochloride in aqueous solution. The driving force of this process is formation of the water-insoluble trimethylammonium salts of *nido*-carboranes **4** and **5**.

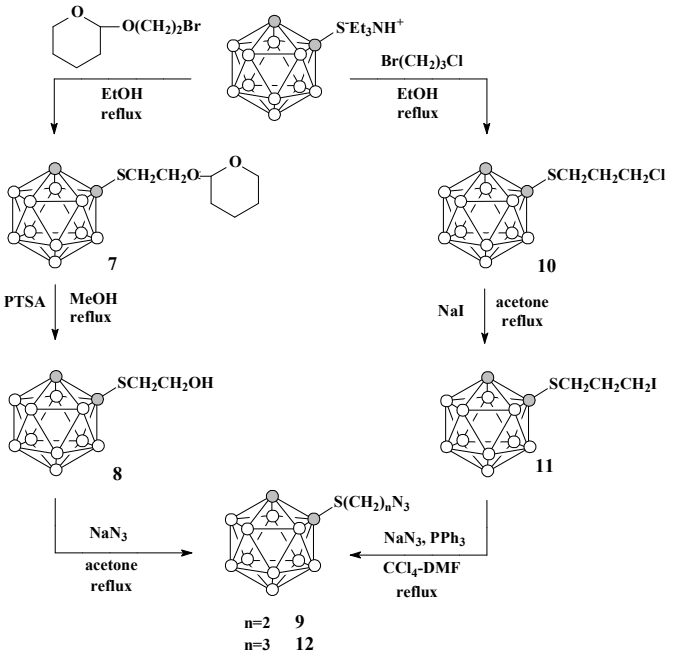
Our attempt to prevent degradation of the *closo*-carborane cage by carrying out the reaction of **3** with hydrazine hydrate in ethanol at room temperature[10] resulted in the formation of 3-phthalmidopropyl derivative of 7-mercapto-*nido*-carborane in 15 min. It means that the transformation of 1-RS-*closo*-$C_2B_{10}H_{11}$ to [7-RS-*nido*-$C_2B_9H_{11}$]$^-$ proceeds faster than the removal of phthalyl group. The reaction of **3** with sodium tetrahydroborate in isopropanol[7] gave the corresponding *ortho*-(hydroxymethyl)benzoyl derivative **6** in a low yield (Scheme 2).



Scheme 2

However, acidic hydrolysis of **6** after standard workup[7,30] unexpectedly resulted in *nido*-carborane **5a**. The decreased stability of the 1-RS-1,2-$C_2B_{10}H_{11}$ fragment can be explained by donation of electron density from the sulfur atom to the carborane LUMO orbital[31] that favors the cage degradation.

The synthesis of the corresponding carboranyl azides was carried out. To obtain 1-(2-azidoethylthio)-*ortho*-carborane **9** the triethylammonium salt of mercapto carborane (Et_3NH)[1-S-1,2-$C_2B_{10}H_{11}$] was treated with 2-(2-tetrahydropyranyloxy)ethyl bromide in refluxing ethanol giving compound **7**. The hydrolysis of the last one with *para*-toluenesulfonic acid in methanol gave the corresponding alcohol **8**. The reaction of alcohol **8** with sodium azide in a mixture of carbon tetrachloride and dimethylformamide in the presence of PPh_3 resulted in desired azide **9** (Scheme 3).



Scheme 3

1-(3-Azidopropylthio)-*ortho*-carborane **12** was prepared using other synthetic scheme. At first the reaction of the triethylammonium salt of mercapto carborane (Et_3NH)[1-S-1,2-$C_2B_{10}H_{11}$] with 1-bromo-3-chloropropane in refluxing ethanol resulted in 1-(3-chloro-propylthio)-*ortho*-carborane **10**. The last one was converted to the corresponding iodide **11** by the exchange reaction with sodium iodide. Next, the compound **11** also was converted to azide **12** by the reaction with NaN_3 in refluxing acetone (Scheme 3).

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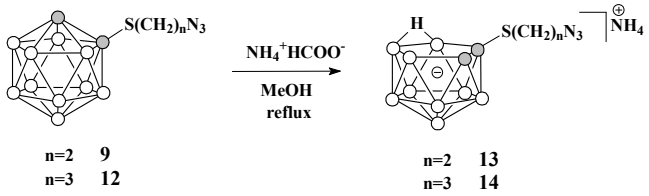
The *closo*-carboranyl azides **9** and **12** were converted into water soluble *nido*-carboranyl azides **13** and **14**, respectively, by the treatment with ammonium formate in refluxing methanol (Scheme 4). Similar degradation of the *closo*-carborane cage upon refluxing ammonium salt of 1,2-dimercapto-*ortho*-carborane in ethanol was described earlier.[32]



Scheme 4

Conclusions

A series of new carborane based amines [7-$H_2N(CH_2)_nS$-*nido*-7,8-$C_2B_9H_{11}$]$^-$ (n = 2, 3) azides 1-$N_3(CH_2)_nS$-*closo*-1,2-$C_2B_{10}H_{11}$ (n = 2, 3) and [7-$N_3(CH_2)_nS$-*nido*-7,8-$C_2B_9H_{11}$]$^-$ (n = 2, 3) were synthesized by alkylation of 1-mercapto-*ortho*-carborane followed by functional group interconversions. The compounds prepared can be used for conjugation with tumor seeking biomolecules for cancer diagnostics and therapy. The presence of alkylthio group attached to carbon atom of the carborane cage decreases dramatically the stability of *closo*-carborane derivatives and facilitates their degradation to the *nido*-form.

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Notes and references

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† Dedicated to the memory of Dr. Victor Brattsev, one of the fathers of the carborane chemistry.

‡ Electronic Supplementary Information (ESI) available: Experimental details and hydrogen bonds in the structure of 7-$NH_3CH_2CH_2CH_2$S-7,8-*nido*-$C_2B_9H_{11}$*1.5N_2H_4. See DOI: 10.1039/c3nj000x/

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