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Synthesis of novel derivatives of *closo*-dodecaborate anion with azido group at the terminal position of the spacer

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Two novel azido-derivatives of *closo*-dodecaborate anion with hydrophobic and hydrophilic spacers were prepared by reaction of tetrabutylammonium azide with cyclic oxonium derivatives of the *closo*-dodecaborate anion. The compounds prepared can be regarded as precursors of derivatives of *closo*-dodecaborate anion with amino group at the terminal position of a spacer or as building blocks for 'click chemistry', which are useful for preparation of various conjugates with targeting molecules. A concentration dependence of the ^{11}B NMR spectra of functionalized derivatives of *closo*-dodecaborate anion was discovered, which is of great importance for analytical purposes. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: *closo*-dodecaborate; oxonium derivatives; boron neutron capture therapy; functional derivative; azido derivative; spacer

INTRODUCTION

Derivatives of the *closo*-dodecaborate anion[1] are promising agents for boron neutron capture therapy of cancer (BNCT).[2] The selectivity of BNCT agents may be substantially increased by attachment of the *closo*-dodecaborate anion to tumor-specific targeting molecules (peptides, proteins, carbohydrates and other biomolecules). Derivatives of the *closo*-dodecaborate anion are also attractive pendant groups for attachment of radioactive halogens to targeting agents because of their solubility in water, the high thermodynamic stability of the halogen-boron bond in such compounds, their facile radiohalogenation chemistry and their stability to enzymatic degradation.[3] Radioactive nuclides attached to the targeting agents may be used for detection (radionuclide diagnostics) as well as for destruction of tumor cells (radionuclide therapy).[3] In order to link the *closo*-dodecaborate anion to a targeting molecule, functionalized derivatives of this compound are required. Several ways to introduce functional groups into the *closo*-dodecaborate anion have already been proposed and used for its conjugation with various targeting molecules.[1,3] At present, azide-containing compounds are of great interest in bioconjugate chemistry since mild conditions for the reaction of azides with alkynes have recently been found and this reaction has been used for the rapid assembly of a variety of conjugates by so-called 'click chemistry'.[4,5] For this reason, azido derivatives of the *closo*-dodecaborate anion would be potentially useful precursors for further functionalization (e.g. to amino derivatives and amide-linked conjugates) or direct conjugation to carrier molecules using a 'click chemistry' approach.

RESULTS AND DISCUSSION

We report a simple and convenient synthesis of azido-derivatives of the *closo*-dodecaborate anion. Known cyclic oxonium derivatives **1** and **2**, which can be easily prepared by reaction of the *closo*-dodecaborate anion with THF or 1,4-dioxane,[6] were selected as starting compounds, since these derivatives are known to react with nucleophiles to

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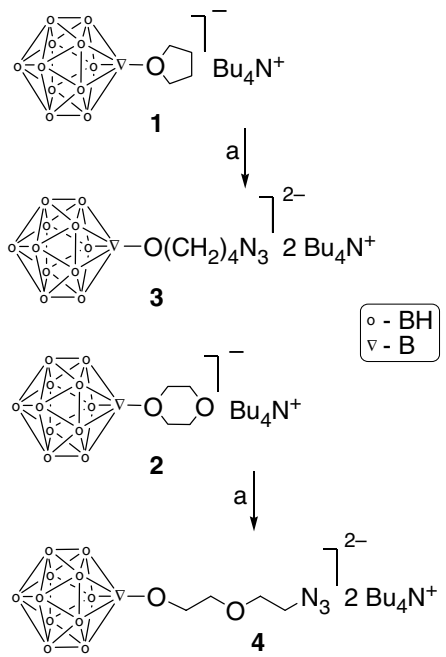

Figure 1. Reagents and conditions: *a*, Bu_4NN_3, CH_2Cl_2, 20 °C, 24 h.

give the respective adducts.[6] We reasoned that a similar reaction with azide anion would lead to azido-functionalized derivatives of the *closo*-dodecaborate anion. Since the reaction should be performed in a non-aqueous solvent to prevent hydrolysis of the starting complexes, tetrabutylammonium azide (Bu_4NN_3)[7] was chosen as a suitable azidation reagent (Fig. 1).

The reagent was prepared by reaction of Bu_4NHSO_4 with NaN_3 followed by extraction of the product from the reaction mixture with dichloromethane and subsequent evaporation.[7] Tetrabutylammonium azide can be introduced into a reaction with an oxonium derivative either as a dichloromethane extract (before evaporation) or as a dichloromethane solution of the compound isolated in the individual state, the latter procedure ensuring the correct amount of the reagent being added. Reactions of **1** and **2** with Bu_4NN_3 were complete within 24 h; no starting material was present in the reaction mixtures according to TLC. An excess of Bu_4NN_3 was removed by washing the reaction mixture with water to give the target azides **3** and **4** in high yield (69 and 92%, respectively). The absence of Bu_4NN_3 in the products was confirmed by IR spectroscopy (a characteristic band of the azide anion at 2040 cm^{-1} was absent). Data for ^1H, ^{13}C and ^{11}B NMR and IR spectroscopy and mass spectrometry were in full accord with the proposed structures of the compounds. ^{11}B NMR spectra of **3** and **4** contained the set of signals (δ_B − 22.8; −18.1; −16.8; 6.5) characteristic[6] of the *closo*-dodecaborate anion. Their IR spectra contained the characteristic absorption bands [2469 or 2465 cm^{-1} (BH) and 2099 or 2106 cm^{-1} (N_3), respectively in **3** and **4**]. The presence of the respective spacers in **3** and **4** was evident from their ^1H and ^{13}C NMR spectra, which contained signals of C_4 alkyl chain or diethylene glycol fragment, respectively. We have to stress that, although according to the spectroscopic data the compounds **3** and **4** were isolated in pure form, satisfactory elemental analyses could not be obtained notwithstanding our efforts.

When analyzing the products by ^{11}B NMR we made an interesting observation. The ^{11}B NMR pattern of compound **4** (unlike compound **3**) in $CDCl_3$ does depend on the concentration of the solution. Thus, for example, while only one signal (δ_B 6.5) was observed in the low-field region for the 0.12 M solution of **4** (giving the spectrum expected for the *closo*-dodecaborate anion[6]), two signals were observed in the low field region (δ_B 6.6 and 8.3) for slightly more concentrated (0.22 M) solution. Such concentration dependence of the ^{11}B NMR spectra was not observed in the case of compound **3**. The ^1H and ^{13}C NMR spectra of both **3** and **4** do not depend on concentration. This phenomenon is apparently related to the aggregation of solute molecules and may have great importance for the interpretation of ^{11}B NMR spectra of derivatives of the *closo*-dodecaborate anion, identification of compounds and assessment of their purity by ^{11}B NMR.

In conclusion, we have described the synthesis of two novel azido-derivatives **3** and **4** of *closo*-dodecaborate anion with hydrophobic and hydrophilic spacers, respectively. These compounds can be regarded as precursors of derivatives of *closo*-dodecaborate anion with amino group at the terminal position of a spacer or as ready-to-use building blocks for 'click chemistry', which are useful for preparation of various conjugates with targeting molecules. A concentration dependence of the ^{11}B NMR spectra of functionalized derivatives of *closo*-dodecaborate anion was discovered, which is of importance for analytical purposes.

EXPERIMENTAL

General

The reactions were performed with the use of commercial reagents (Aldrich and Fluka) and solvents purified according to standard procedures. Compounds **1** and **2** were synthesized according to the published procedures.[6] Thin-layer chromatography was carried out on plates with silica gel 60 on aluminum foil (Merck). Spots of compounds containing boron hydride fragments were visualized with solution of $PdCl_2$ (1.256 g) in 10% aqueous HCl (25 ml) and MeOH (250 ml). The ^1H, ^{13}C, and ^{11}B NMR spectra were recorded on Bruker AC-200 instrument (200.13, 50.32 and 64.21 Hz, respectively). The ^1H NMR chemical shifts are referred to the residual $CHCl_3$ signal (δ_H 7.27), the ^{13}C NMR to the $CDCl_3$ signal (δ_C 77.0), and the ^{11}B NMR to the $BF_3 \cdot Et_2O$ signal (δ_B 0.0, external standard). The assignment of the signals in the ^{13}C NMR spectra was made based on the DEPT-135

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experiments. IR spectra were recorded in KBr disks in the 3700–400 cm^{-1} range on a Carl-Zeiss M-82 IR spectrometer. Mass spectra (electrospray ionization, ESI) were recorded on a Finnigan LCQ mass spectrometer for 2×10^{-5} M solutions in MeOH in negative ions detection mode; m/z values and relative abundance [I_{rel} (%)] for monoisotopic peaks are quoted. The observed isotopic patterns in mass spectra of compounds **3** and **4** fit well the expected ones for boron-containing compounds with the respective structures. In the description of mass spectra, M denotes the exact mass of the dianion.

Tetrabutylammonium azide[7]

To a solution of Bu_4NHSO_4 (778 mg, 2 mmol) in water (1 ml) 10 M NaOH (0.3 ml) was added, followed by a solution of NaN_3 (260 mg, 4 mmol) in water (1 ml). Then H_2O (4 ml) was added and the resulting mixture was extracted with CH_2Cl_2 (3×5 ml). Combined organic extracts were concentrated to dryness and dried *in vacuo* to give crude Bu_4NN_3 (596 mg), which was used without any additional purification. IR (cm^{-1}): 2040 [ν (N_3)].

Bis(tetrabutylammonium) (4-azidobutyloxy)-*closo*-dodecaborate (3)

To a solution of compound **1** (135.2 mg, 0.296 mmol) in CH_2Cl_2 (1 ml), the solution of Bu_4NN_3 (145.4 mg, 0.511 mmol) in CH_2Cl_2 (1 ml) was added. The reaction mixture was stirred for 24 h then washed with water (3×10 ml). The aqueous layer was extracted with CH_2Cl_2 (3×5 ml) and organic extracts were concentrated to dryness to give **3** (153.2 mg, 69%) as a colorless oil, R_f 0.53 (toluene–acetone, 2 : 1).

^{1}H NMR ($CDCl_3$): δ0.99 (t, 24H, CH_3, $J = 7.1$ Hz); 1.30–1.80 (m, 36H, CH_2CH_2); 3.15–3.40 (m, 18H, $CH_3CH_2CH_2C\underline{H}_2N$, $C\underline{H}_2N_3$); 3.56–3.68 (m, 2H, $B_{12}H_{11}OC\underline{H}_2$).

^{13}C NMR ($CDCl_3$): δ13.7 (CH_3); 19.7 ($\underline{C}H_2CH_3$); 24.1 ($NCH_2\underline{C}H_2CH_2CH_3$); 25.9 ($\underline{C}H_2CH_2N_3$); 29.2 ($\underline{C}H_2CH_2OB_{12}H_{11}$); 51.9 ($\underline{C}H_2N_3$); 58.8 ($N\underline{C}H_2CH_2CH_2CH_3$); 68.2 ($B_{12}H_{11}O\underline{C}H_2$).

^{11}B{^{1}H} NMR ($CDCl_3$): δ − 22.8 (1B), −18.1 (5B), −16.8 (5B), 6.5 (1B).

MS, m/z [I_{rel} (%)] 497.3 [M + Bu_4N] (73). $C_{20}H_{55}N_4B_{12}O$. Calculated: m/z 497.4 [M + Bu_4N].

IR (cm^{-1}): 2469 [ν (BH)], 2099 [ν (N_3)].

Bis(tetrabutylammonium) (4-azidoethoxy-ethoxy)-*closo*-dodecaborate (4)

A reaction of compound **2** (100 mg, 0.212 mmol) with Bu_4NN_3 (120.7 mg, 0.424 mmol) was performed essentially as described for **3** to give **4** (147.4 mg, 92%) as colorless oil, R_f 0.64 (toluene–acetone, 2 : 1).

^{1}H NMR ($CDCl_3$, δ, J/Hz): 0.90 (t, 24H, CH_3, $J =$ 7.1 Hz); 1.32–1.52 (m, 16H, $CH_3C\underline{H}_2$); 1.52–1.72 (m, 16H, $CH_3CH_2C\underline{H}_2$); 3.15–3.30 (m, 18H, $CH_3CH_2CH_2C\underline{H}_2N$, $C\underline{H}_2N_3$); 3.55–3.67 (m, 6H, $OC\underline{H}_2CH_2N_3$, $B_{12}H_{11}OCH_2C\underline{H}_2O$, $B_{12}H_{11}OC\underline{H}_2$).

^{13}C NMR ($CDCl_3$): δ13.5 (CH_3); 19.4 ($\underline{C}H_2CH_3$); 23.8 ($NCH_2\underline{C}H_2CH_2CH_3$); 50.8 ($CH_2N_3$); 58.5 ($N\underline{C}H_2CH_2CH_2CH_3$); 67.9 ($B_{12}H_{11}O\underline{C}H_2$); 69.1, 72.2 ($B_{12}H_{11}OCH_2\underline{C}H_2O$, $O\underline{C}H_2CH_2N_3$).

^{11}B{^{1}H} NMR ($CDCl_3$, 0.22 M): δ − 23.2 (1B), −18.2 (5B), −16.7 (5B), 6.6, 8.3 (total 1B).

^{11}B{^{1}H} NMR ($CDCl_3$, 0.12 M): δ − 23.2 (1B), −18.2 (5B), −16.7 (5B), 6.5 (1B).

MS, m/z [I_{rel} (%)]: 513.3 [M + Bu_4N] (44). $C_{20}H_{55}N_4B_{12}O$. Calculated: m/z 513.6 [M + Bu_4N]; 1269.2 [M_2 + 3 Bu_4N] (74). $C_{88}H_{218}N_{11}B_{24}O$. Calculated: m/z 1269.4 [M_2 + 3 Bu_4N].

IR (cm^{-1}): 2465 [ν (BH)], 2106 [ν (N_3)].

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REFERENCES

1. Sivaev IB, Bregadze VI, Sjoberg S. *Collect. Czech. Chem. Commun.* 2002; **67**: 679.
2. Soloway AH, Tjarks W, Barnum BA, Rong FG, Barth RF, Codogni IM, Wilson JG. *Chem. Rev.* 1998; **98**: 1515.
3. Tolmachev V, Sjöberg S. *Collect. Czech. Chem. Commun.* 2002; **67**: 913.
4. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. *Angew. Chem., Int. Edn* 2002; **41**: 2596.
5. Tornoe CW, Christensen C, Meldal M. *J. Org. Chem.* 2002; **67**: 3057.
6. Sivaev IB, Semioshkin AA, Brellochs B, Sjoberg S, Bregadze VI. *Polyhedron* 2000; **19**: 627.
7. Brandstrom A, Lamm B, Palmertz J. *Acta Chem. Scand., Ser. B* 1974; **28**: 699.

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