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Reactions of oxonium derivatives of $[B_{12}H_{12}]^{2-}$ with amines: Synthesis and structure of novel B_{12}-based ammonium salts and amino acids

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Abstract

The reactions of oxonium derivatives of $[B_{12}H_{12}]^{2-}$ with various amines were studied. A series of novel B_{12}-species with ammonium group on the side chain was synthesized in high yield. A structure of tetrabutylammonium-[2-(2-morpholinium-ethoxy)-ethoxy]-undecahydro-*closo*-dodecaborate was determined and the existence of intramolecular N–H···O–B bond was shown. Using these reactions, novel boronated piperazines and amino acids were prepared.

Keywords: *closo*-Dodecaborate; Ammonium salts; Piperazine; Amino acids; X-ray structure

1. Introduction

Water-soluble functionalized derivatives of the dodecahydro-*closo*-dodecaborate anion $[B_{12}H_{12}]^{2-}$ are promising candidates for boron neutron capture therapy (BNCT) [1]. Synthesis of their oxonium derivatives (tetrabutylammonium 1-tetramethyleneoxonium-*closo*-undecahydrododecaborate (**1**) and tetrabutylammonium 1-tetramethylene-(3-oxa)-oxonium-*closo*-undecahydrododecaborate (**2**)) directly from $[B_{12}H_{12}]^{2-}$ is one of the most powerful way of introduction of reaction centre into B_{12} moiety [2]. Their reactions with various O- and C-nucleophiles gave rise to a rich variety of $[B_{12}H_{12}]^{2-}$-derivatives with different functional groups. B_{12}-based amino acid [2], phthalocyanines [3] and natural porphyrines [4] were prepared using this method.

However, reactions of **1** and **2** with nitrogen based nucleophiles were practically not described. In the present paper we would like to present data on interaction of oxonium derivatives of $[B_{12}H_{12}]^{2-}$ **1** and **2** with various amines and preparation of novel B_{12}-containing piperazines and amino acids based on these reactions.

2. Experimental

2.1. Materials and equipment

Chemicals were reagent grade and used as received from standard commercial vendors. THF and 1,4-dioxane were distilled from Na/benzophenone. Oxonium derivatives **1** and **2** were prepared by the described methods [2]. The ^{1}H, ^{13}C and ^{11}B NMR spectra were recorded at 400.13, 100.61 and 128.38 MHz respectively on a BRUKER-Avance-400 spectrometer either in DMSO-d_6 (NBu_4-salts) or in D_2O (Cs-salts). Mass spectra were recorded on a Finnigan MAT 8222 spectrometer. Melting points were measured in open capillary and are not corrected. IR spectra were recorded on Infralum FT-801 FTIR spectrometer in Nujol. Elemental analysis were performed in Microanalytical

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2.2. Reactions of **1** and **2** with amines

2.2.1. General procedure for **3(a–c)** and **4(a–i)**

The mixture of 1.1 mmol of **1** or **2** and 10 mmol of the corresponding amine (in case of **4a** and **4b** the corresponding amounts of 25% ammonia and 33% methylamine were used respectively) was refluxed for 12 h in 10 ml of 96% ethanol. After precipitation the desired products were filtered off, washed with 3–4 ml of ethanol and air dried.

2.2.2. Tetrabutylammonium-[4-(2-hydroxyethylammonium)-butoxy]-undecahydro-closo-dodecaborate **3a**

Prepared from **1** and monoethanolamine. Yield 76%, m.p. = 168 °C. Anal. Calc. for $C_{22}H_{62}B_{12}N_2O_2$: C, 51.16; H, 12.10; N, 5.42; B, 25.12. Found: C, 51.26; H, 12.21; N, 5.45; B, 25.05%. ^{1}H NMR (ppm): 8.81 (2H, broad s NH_2^+); 3.64 (2H, t, CH_2OB_{12}); 3.45 (2H, t, CH_2OH); 3.12 (8H, m, $NCH_2CH_2CH_2CH_3$); 2.94 (2H, m, CH_2N); 2.86 (2H, m, CH_2N); 1.63 (2H, m, $OCH_2CH_2CH_2CH_2N$); 1.56 (10H, m, $OCH_2CH_2CH_2CH_2N$ and $NCH_2CH_2CH_2CH_3$); 1.30 (8H, m, $NCH_2CH_2CH_2CH_3$); 0.91 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 68.3 (CH_2OB_{12}); 58.0 ($NCH_2CH_2CH_2CH_3$); 57.1 (CH_2OH); 49.8 (CH_2N); 47.9 (CH_2N); 30.3 ($OCH_2CH_2CH_2CH_2N$); 25.8 ($OCH_2CH_2CH_2CH_2N$); 23.5 ($NCH_2CH_2CH_2CH_3$); 19.6 ($NCH_2CH_2CH_2CH_3$); 13.9 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.5 (1B, s, B(1)); −16.9 (5B, d, B(2–6)); −17.8 (5B, d, B(7–11)); −22.3 (1B, d, B(12)). IR (cm^{-1}): 3425 (OH), 3134 (NH_2^+), 2480 (BH).

2.2.3. Tetrabutylammonium-(4-morpholinium-buthoxy)-undecahydro-closo-dodecaborate **3b**

Prepared from **1** and morpholine. Yield 67%, m.p. = 210 °C. Anal. Calc. for $C_{24}H_{64}B_{12}N_2O_2$: C, 53.14; H, 11.89; N, 5.16; B, 23.91. Found: C, 52.91; H, 11.81; N, 5.11; B, 23.05%. ^{1}H NMR (ppm): 10.62 (1H, broad s NH^+); 3.91 (2H, d, OCH_2 of morpholine); 3.76 (2H, t, CH_2OB_{12}); 3.54 (2H, m, NCH_2 of morpholine); 3.37 (2H, d, OCH_2 of morpholine); 3.12 (8H, m, $NCH_2CH_2CH_2CH_3$); 3.03 (2H, m, NCH_2 of morpholine); 2.94 (2H, m, $NCH_2CH_2CH_2CH_2OB_{12}$); 1.68 (2H, m, $OCH_2CH_2CH_2CH_2N$); 1.56 (10H, m, $CH_2CH_2CH_2CH_2N$ and $NCH_2CH_2CH_2CH_3$); 1.28 (8H, m, $NCH_2CH_2CH_2CH_3$); 0.89 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 68.4 (CH_2OB_{12}); 63.3 (OCH_2 of morpholine); 58.0 ($NCH_2CH_2CH_2CH_3$); 53.4 ($NCH_2CH_2CH_2CH_2OB_{12}$); 50.8 (NCH_2 of morpholine); 29.7 ($OCH_2CH_2CH_2CH_2N$); 23.5 ($NCH_2CH_2CH_2CH_3$); 22.8 ($OCH_2CH_2CH_2CH_2N$); 19.7 ($NCH_2CH_2CH_2CH_3$); 14.0 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.6 (1B, s, B(1)); −16.8 (5B, d, B(2–6)); −17.8 (5B, d, B(7–11)); −22.1 (1B, d, B(12)). IR (cm^{-1}): 3200 (NH_2^+), 2476 (BH).

2.2.4. Tetrabutylammonium-[4-(4-ethoxycarbonyl-piperazinium)-buthoxy]-undecahydro-closo-dodecaborate **3c**

Prepared from **1** and ethyl 1-piperazinecarboxylate. Yield 87%, m.p. = 116 °C. Anal. Calc. for $C_{27}H_{69}B_{12}N_3O_3$: C, 52.85; H, 11.33; N, 6.85; B, 21.14. Found: C, 52.59; H, 11.20; N, 6.81; B, 21.09%. ^{1}H NMR (ppm): 10.89 (1H, broad s NH^+); 4.05 (2H, q, $CH_2(OCH_2CH_3)$); 3.88 (2H, t, CH_2OB_{12}); 3.50 (2H, m, N^+CH_2 of piperazine); 3.40 (4H, m, $(CH_2)_2NCOOEt$); 3.13 (8H, m, $NCH_2CH_2CH_2CH_3$); 3.01 (2H, m, N^+CH_2 of piperazine); 2.92 (2H, m, $NCH_2CH_2CH_2OB_{12}$); 1.70 (2H, m, $OCH_2CH_2CH_2CH_2N$); 1.57 (10H, m, $OCH_2CH_2CH_2CH_2N$ and $NCH_2CH_2CH_2CH_3$); 1.26 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.17 (3H, t, $CH_3(OEt)$); 0.89 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 154.8 (CO); 77.6 ($CH_2(OEt)$); 68.5 (CH_2OB_{12}); 61.8 ($CH_2NCOOEt$); 58.0 ($NCH_2CH_2CH_2CH_3$); 55.9 ($NCH_2CH_2CH_2OB_{12}$); 50.2 (N^+CH_2 of piperazine); 30.0 ($OCH_2CH_2CH_2CH_2N$); 23.5 ($NCH_2CH_2CH_2CH_3$); 23.2 ($OCH_2CH_2CH_2CH_2N$); 19.7 ($NCH_2CH_2CH_2CH_3$); 14.9 (OCH_2CH_3); 14.0 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.6 (1B, s, B(1)); −16.9 (5B, d, B(2–6)); −17.7 (5B, d, B(7–11)); −22.1 (1B, d, B(12)). IR (cm^{-1}): 3183 (NH^+), 2477 (BH), 1695 (CO).

2.2.5. Tetrabutylammonium-[2-(2-ammonium-ethoxy)-ethoxy]-undecahydro-closo-dodecaborate **4a**

Prepared from **2** and 25% aq ammonia. Yield 77%, m.p. = 194 °C. Anal. Calc. for $C_{20}H_{58}B_{12}N_2O_2$: C, 49.18; H, 11.97; N, 5.74; B, 26.56. Found: C, 48.95; H, 11.91; N, 5.76; B, 26.61%. ^{1}H NMR (ppm): 8.03 (3H, broad s NH_3^+); 3.62 (2H, t, CH_2O); 3.51 (4H, m, CH_2O); 3.16 (8H, m, $NCH_2CH_2CH_2CH_3$); 2.92 (2H, q, CH_2NH_3); 1.56 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.31 (8H, m, $NCH_2CH_2CH_2CH_3$); 0.92 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 70.5, 68.4, 66.6 (CH_2O); 57.9 ($NCH_2CH_2CH_2CH_3$); 56.8 (CH_2NH_3); 23.3 ($NCH_2CH_2CH_2CH_3$); 19.4 ($NCH_2CH_2CH_2CH_3$); 13.4 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.6 (1B, s, B(1)); −16.9 (5B, d, B(2–6)); −17.8 (5B, d, B(7–11)); −22.2 (1B, d, B(12)). IR (cm^{-1}): 3178 (NH_3^+), 2484 (BH).

2.2.6. Tetrabutylammonium-[2-(2-methylammonim-ethoxy)-ethoxy]-undecahydro-closo-dodecaborate **4b**

Prepared from **2** and 33% aq methylamine. Yield 85%. m.p. = 208 °C. Anal. Calc. for $C_{21}H_{60}B_{12}N_2O_2$: C, 50.20; H, 12.04; N, 5.58; B, 25.82. Found: C, 49.83; H, 12.11; N, 5.52; B, 25.64%. ^{1}H NMR (ppm): 8.81 (2H, broad s, NH_2^+); 3.71 (2H, t, OCH_2); 3.53 (4H, m, OCH_2); 3.20 (8H, m, $NCH_2CH_2CH_2CH_3$); 3.01 (2H, m, CH_2NH_2); 2.65 (3H, t, CH_3NH_2); 1.60 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.35 (8H, m, $NCH_2CH_2CH_2CH_3$); 0.96 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 70.6, 68.8, 65.1 (OCH_2); 58.0 ($NCH_2CH_2CH_2CH_3$); 47.7 (CH_2NH_2); 32.9 (CH_3NH_2); 23.5 ($NCH_2CH_2CH_2CH_3$); 19.6 ($NCH_2CH_2CH_2CH_3$); 13.9 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.6 (1B, s, B(1)); −17.0 (5B, d, B(2–6)); −17.8 (5B,

d, B(7–11)); −22.1 (1B, d, B(12)). IR (cm^{-1}): 3223 (NH_2^+), 2478 (BH).

2.2.7. Tetrabutylammonium-{2-[2-(2-hydroxyethylamonium)-ethoxy]-ethoxy}-undecahydro-closo-dodecaborate **4c**

Prepared from **2** and monoethanolamine. Yield 72%, m.p. = 190 °C. Anal. Calc. for $C_{22}H_{62}B_{12}N_2O_3$: C, 49.53; H, 11.90; N, 5.25; B, 24.32. Found: C, 49.61; H, 11.86; N, 5.29; B, 24.35. ^{1}H NMR (ppm): 8.62 (1H, broad s, OH); 7.69 (2H, broad s, NH_2^+); 3.66 (4H, m, OCH_2); 3.54 (4H, m, OCH_2); 3.12 (8H, m, $NCH_2CH_2CH_2CH_3$); 3.07 (2H, m, CH_2NH_2); 2.83 (2H, m, CH_2NH_2); 1.53 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.22 (8H, m, $NCH_2CH_2CH_2CH_3$); 0.90 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 70.6, 68.3, 64.9, 56.5 (OCH_2); 57.4 ($NCH_2CH_2CH_2CH_3$); 48.3, 46.0 ($CH_2N^+H_2CH_2$); 23.1 ($NCH_2CH_2CH_2CH_3$); 19.2 ($NCH_2CH_2CH_2CH_3$); 13.4 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.6 (1B, s, B(1)); −16.9 (5B, d, B(2–6)); −17.8 (5B, d, B(7–11)); −22.2 (1B, d, B(12)). ESI-MS: *m*/*z* 242 $[C]^+$, 289 $[A]^-$. IR (cm^{-1}): 3420 (OH), 3128 (NH_2^+), 2485 (BH).

2.2.8. Tetrabutylammonium-[2-(2-cyclohexylammonium-ethoxy)-ethoxy]-undecahydro-closo-dodecaborate **4d**

Prepared from **2** and cyclohexylamine. Yield 71%, m.p. = 195 °C. Anal. Calc. for $C_{26}H_{67}B_{12}N_2O_2$: C, 54.83; H, 11.86; N, 4.92; B, 22.78. Found: C, 54.50; H, 11.96; N, 4.76; B, 22.63%. ^{1}H NMR (ppm): 8.62 (2H, broad s, NH_2^+); 3.72 (2H, t, OCH_2); 3.52 (4H, m, OCH_2); 3.16 (8H, m, $NCH_2CH_2CH_2CH_3$); 3.08 (3H, m, CH_2NH_2CH); 2.02 (2H, m, NH_2CHCH_2); 1.53 (2H, m, NH_2CHCH_2); 1.72 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.29 (14H, m, $NCH_2CH_2CH_2CH_3 + 3CH_2$ of cyclohexyl); 0.93 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 70.9, 68.5, 65.4 (CH_2O); 57.6 ($NCH_2CH_2CH_2CH_3$); 55.5 (CH_2N); 52.3 (CHN); 28.2, 24.6, 24.0 (CH_2 of cycloxehyl); 23.0 ($NCH_2CH_2CH_2CH_3$); 19.1 ($NCH_2CH_2CH_2CH_3$); 13.2 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.6 (1B, s, B(1)); −16.9 (5B, d, B(2–6)); −17.9 (5B, d, B(7–11)); −22.2 (1B, d, B(12)). ESI-MS: *m*/*z* 242 $[C]^+$, 165 $[A-H]^{2-}$. IR (cm^{-1}): 3220 (NH_2^+), 2470 (BH).

2.2.9. Tetrabutylammonium-[2-(2-morpholinium-ethoxy)-ethoxy]-undecahydro-closo-dodecaborate **4e**

Prepared from **2** and morpholine. Yield 82%, m.p. = 185 °C. Anal. Calc. for $C_{24}H_{64}B_{12}N_2O_3$: C, 51.61; H, 11.55; N, 5.02; B, 23.23; O 8.59. Found: C, 50.47; H, 11.62; N, 4.86; B, 23.24%. ^{1}H NMR (ppm): 9.89 (1H, broad s, NH^+); 3.93 (2H, m, CH_2O of morpholine); 3.79 (2H, t, CH_2O); 3.73 (2H, m, CH_2O of morpholine); 3.66 (2H, m, CH_2O); 3.58 (2H, m, CH_2N of morpholine); 3.55 (2H, m, CH_2O); 3.33 (2H, m, CH_2N); 3.16 (8H, m, $NCH_2CH_2CH_2CH_3$); 3.11 (2H, m, CH_2N of morpholine); 1.55 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.30 (8H, m, $NCH_2CH_2CH_2CH_3$); 0.93 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 71.6, 68.6, 63.9, 63.4 (OCH_2); 58,1 ($NCH_2CH_2CH_2CH_3$); 55.3, 51.8 (NCH_2); 23.6 ($NCH_2CH_2CH_2CH_3$); 19.8 ($NCH_2CH_2CH_2CH_3$); 14.0 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.6 (1B, s, B(1)); −16.9 (5B, d, B(2–6)); −17.8 (5B, d, B(7–11)); −22.2 (1B, d, B(12)). ESI-MS: *m*/*z* 242 $[C]^+$, 158 $[A-H]^{2-}$. IR (cm^{-1}): 3180 (NH^+), 2481 (BH).

2.2.10. Tetrabutylammonium-[2-(2-piperidinium-ethoxy)-ethoxy]-undecahydro-closo-dodecaborate **4f**

Prepared from **2** and piperidine. Yield 82%, m.p. = 218 °C. Anal. Calc. for $C_{24}H_{64}B_{12}N_2O_3$: C, 53.95; H, 11.95; N, 5.03; B, 23.31. Found: C, 52.40; H, 12.02; N, 4.85; B, 23.24%. ^{1}H NMR (ppm): 9.35 (1H, broad s, NH^+); 3.79 (2H, t, OCH_2); 3.55 (4H, m, OCH_2); 3.47 (2H, m, NCH_2 of piperidine); 3.24 (2H, m, NCH_2 of piperidine); 3.14 (8H, m, $NCH_2CH_2CH_2CH_3$); 2.94 (2H, m, NCH_2); 1.74 (6H, m, CH_2 of piperidine); 1.54 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.33 (8H, m, $NCH_2CH_2CH_2CH_3$); 0.92 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 70.6, 68.4, 64.2 (OCH_2); 57.6 ($NCH_2CH_2CH_2CH_3$); 54.5, 52.4 ($NHCH_2$); 23.1 ($NCH_2CH_2CH_2CH_3$); 21.9, 21.3 (CH_2 of piperidine); 19.2 ($NCH_2CH_2CH_2CH_3$); 13.5 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.5 (1B, s, B(1)); −16.9 (5B, d, B(2–6)); −17.8 (5B, d, B(7–11)); −22.2 (1B, d, B(12)). ESI-MS: *m*/*z* 242 $[C]^+$, 157 $[A-H^+]^{2-}$. IR (cm^{-1}): 3180 (NH^+), 2479 (BH).

2.2.11. Tetrabutylammonium-{2-[2-(4-ethoxycarbonyl-piperazinium)-ethoxy]-ethoxy}-undecahydro-closo-dodecaborate **4g**

Prepared from **2** and ethyl 1-piperazinecarboxylate. Yield 42%, m.p. = 164 °C. Anal. Calc. for $C_{27}H_{69}B_{12}N_3O_4$: C, 51.51; H, 11.05; N, 6.67; B, 20.60; O, 10.17. Found: C, 49.96; H, 11.10; N, 6.57; B, 20.62. ^{1}H NMR (ppm): 10.01 (1H, broad s NH^+); 4.06 (2H, q, OCH_2CH_3); 3.93 (2H, m, CH_2O); 3.78 (2H, m, CH_2O); 3.55 (6H, m) and 3.31 (4H, m) (CH_2O and CH_2N of piperazine); 3.15 (8H, m, $NCH_2CH_2CH_2CH_3$); 3.03 (2H, m, NCH_2); 1.55 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.29 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.27 (3H, t, OCH_2CH_3); 0.91 (12H, t, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR (ppm): 154.5(CO); 71.1, 68.4, 63.5, 61.6 (CH_2O); 57.6 ($NCH_2CH_2CH_2CH_3$); 54.5, 52.4 ($NHCH_2$); 55.5, 52.0, 51.8 (CH_2N); 23.3 ($NCH_2CH_2CH_2CH_3$); 19.2 ($NCH_2CH_2CH_2CH_3$); 14.7 (OCH_2CH_3); 13.7 ($NCH_2CH_2CH_2CH_3$), 1.9–0.1 (11H, broad m, BH). ^{11}B NMR (ppm): 5.6 (1B, s, B(1)); −16.9 (5B, d, B(2–6)); −17.8 (5B, d, B(7–11)); −22.2 (1B, d, B(12)). ESI-MS: *m*/*z* 242 $[C]^+$, 193 $[A]^{2-}$. IR (cm^{-1}): 3180 (NH^+), 2478 (BH), 1696 (CO).

2.2.12. Tetrabutylammonium-[2-(2-pyridinium-ethoxy)-ethoxy]-undecahydro-closo-dodecaborate **4h**

Prepared from **2** and pyridine. Yield 83%, m.p. = 270°C. Anal. Calc. for $C_{25}H_{60}B_{12}N_2O_2$: C, 54.55; H, 10.99; N, 5.09; B, 5.81. Found: C, 54.63; H, 10.81; N,

5.12; B, 5.89%. ^{1}H NMR (ppm): 9.21 (2H, d, *o*-Py); 8.60 (1H, t, *p*-Py); 8.11 (2H, t, *m*-Py); 4.79 (2H, t, CH_2N); 3.87 (2H, t, CH_2O); 3.55 (4H, m, CH_2O); 3.16 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.56 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.31 (8H, m, $NCH_2CH_2CH_2CH_3$); 0.92 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 146.0, 142.1, 128.0(Py); 71.6, 69.0, 67.8 (CH_2O); 60.7 (CH_2N); 57.9 ($NCH_2CH_2CH_2CH_3$); 23.4 ($NCH_2CH_2CH_2CH_3$); 19.5 ($NCH_2CH_2CH_2CH_3$); 13.8 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.6 (1B, s, B(1)); −16.9 (5B, d, B(2–6)); −17.8 (5B, d, B(7–11)); −22.2 (1B, d, B(12)). IR (cm^{-1}): 3151, 3053 (CH Py), 2481 (BH).

2.2.13. Tetrabutylammonium-[2-(2-triethylammonium-ethoxy)-ethoxy]-undecahydro-closo-dodecaborate **4i**

Prepared from **2** and triethylamine. Yield 66%, m.p. = 270 °C. Anal. Calc. for $C_{26}H_{70}B_{12}N_2O_2$: C, 54.54; H, 12.32; N, 4.89; B, 22.66. Found: C, 54.60; H, 12.23; N, 4.93; B, 22.72%. ^{1}H NMR (ppm): 3.84 (2H, m, CH_2O); 3.56 (2H, m, CH_2O); 3.51 (2H, m, CH_2O); 3.37 (2H, m, CH_2N); 3.31 (6H, q, NCH_2CH_3); 3.17 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.57 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.32 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.20 (9H, t, NCH_2CH_3); 0.94 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 70.6, 68.3, 63.8 (CH_2O); 57.6 ($NCH_2CH_2CH_2CH_3$); 56.1 (CH_2N); 53.0 (NCH_2CH_3); 23.1 ($NCH_2CH_2CH_2CH_3$); 19.2 ($NCH_2CH_2CH_2CH_3$); 13.5 ($NCH_2CH_2CH_2CH_3$); 7.4 (NCH_2CH_3). ^{11}B NMR (ppm): 5.6 (1B, s, B(1)); −16.9 (5B, d, B(2–6)); −17.8 (5B, d, B(7–11)); −22.2 (1B, d, B(12)). IR (cm^{-1}): 2465 (BH).

2.3. Synthesis of B_{12}-based piperazines

2.3.1. Dicesium-[(4-piperazine-1-yl)-buthoxy]-undecahydro-closo-dodecaborate **5a**

0.41 g (0.7 mmol) of **3c** and 0.22 g (4.2 mmol) of KOH were refluxed in 4 ml of 96% EtOH for 48 h. Then EtOH was evaporated, the rest was treated with water (10 ml) and extracted with CH_2Cl_2 (3 × 5 ml), the organic layers were combined and dried over Na_2SO_4. CH_2Cl_2 was evaporated and the rest was dissolved in 5 ml of MeOH. To the resulting solution 0.2 g (1.4 mmol) of CsF in 5 ml of MeOH were added, the precipitated product was filtered, washed with CH_2Cl_2 (3 ml) and air dried. Yield −0.36 g of **5a** (97%), m.p. = 150 °C (dec). Anal. Calc. for $C_8H_{28}B_{12}N_2OCs_2$: C, 17.04; H, 5.01; N, 4.97; B, 23.01. Found: C, 16.98; H, 4.96; N, 4.81; B, 23.09. ^{1}H NMR (ppm): 3.38 (2H, t, CH_2–O); 2.65 (10H, m, CH_2–N); 1.41 (4H, m, $OCH_2CH_2CH_2CH_2N$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 71.4 (CH_2O); 60.0, 53.2, 45.5 (CH_2–N); 30.9 (OCH_2CH_2); 24.0 (CH_2CH_2–N). ^{11}B NMR (ppm): 6.4 (1B, s, B(1)); −16.4 (5B, d, B(2–6)); −18.2 (5B, d, B(7–11)); −23.1 (1B, d, B(12)). IR (cm^{-1}): 3338 (NH), 2477 (BH).

2.3.2. Dicesium-{2-[(2-piperazine-1-yl)-ethoxy]-ethoxy}-undecahydro-closo-dodecaborate **5b**

The compound was prepared the same way as **5a** from 0.4 g (0.6 mmol) of **4g**. Yield 0.32 g of **5b** (87%), m.p. = 250 °C (dec). Anal. Calc. for $C_8H_{27}B_{12}N_2O_2Cs_2$: C, 16.60; H, 4.70; N, 4.84; B, 22.41. Found: C, 16.55; H, 4.64; N, 4.76; B, 22.49%. ^{1}H NMR (ppm): 3.52 (2H, t, CH_2–O); 3.47 (4H, m, CH_2–O); 2.65 (6H, m, CH_2–N); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 71.0, 67.6, 66.6 (CH_2O); 56.6, 50.8, 43.2 (CH_2–N). ^{11}B NMR (ppm): 6.4 (1B, s, B(1)); −16.3 (5B, d, B(2–6)); −18.2 (5B, d, B(7–11)); −23.2 (1B, d, B(12)). IR (cm^{-1}): 3325 (NH), 2482 (BH).

2.4. Synthesis of amino acids

2.4.1. Dicesium-{2-[2-((1-carbomethoxy-2-methyl)-propylamino)-ethoxy]-ethoxy}-undecahydro-closo-dodecaborate **6a**

The mixture of 0.36 g (0.76 mmol) of **2**, 0.19 g (1.1 mmol) of valine methyl ester hydrochloride and 0.2 g (2.4 mmol) of $NaHCO_3$ was refluxed in 5 ml of dry CH_3CN for 24 h. Then inorganic materials were filtered off, CH_3CN was evaporated and the rest was dissolved in 5 ml of MeOH. The product was precipitated by the addition of 0.116 g (1.5 mmol) of CsF in 5 ml MeOH. It was filtered, washed with MeOH (5 ml), CH_2Cl_2 (5 ml) and air dried. Yield 0.295 g of **6a** (62%), m.p. = 286 °C (dec). Anal. Calc. for $C_{10}H_{31}B_{12}NO_4Cs_2$: C, 19.22; H, 5.00; N, 2.24; B, 20.76. Found: C, 18.99; H, 4.93; N, 2.09; B, 20.59%. ^{1}H NMR

Table 1
Crystal data and structure refinement parameters for **4e**

Compound	**4e**
Empirical formula	$C_{24}H_{64}B_{12}N_2O_3$
Formula weight	557.48
Crystal colour, habit	Colourless, prism
Crystal size (mm)	0.50 × 0.35 × 0.25
Temperature (K)	120(2) K
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	10.7978(11)
b (Å)	14.9677(16)
c (Å)	21.201(2)
V (Å^3)	3426.5(6)
Z(*Z*′)	4(1)
F(000)	1220
D_{calc} (g cm^{-1})	1.081
Linear absorption, μ (cm^{-1})	0.62
Scan type	ω
θ Range (°)	3.57–29.00
Completeness of dataset (%)	99.0
Reflections measured	24061
Independent reflections	4523 [R_{int} = 0.0512]
Observed reflections [$I > 2\sigma(I)$]	3941
Parameters	374
Final $R(F_{hkl})$: R_1	0.0402
wR_2	0.0877
GOF	0.940
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.209, −0.236

(ppm): 3.62 (3H, s, CH_3–O); 3.48 (6H, m, CH_2–O); 3.11 (1H, d, CH–N); 2.56 (2H, m, CH_2–N); 1.88 (1H, m, C*H*–$(CH_3)_2$); 0.81 (3H, d, CH_3); 0.77 (3H, d, CH_3); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 176.5 (CO); 70.8, 67.5, 66.9 (CH_2O); 69.2 (CH_3–O); 52.2 (CH–N); 46.6 (CH_2–N); 30.8 (*C*H–$(CH_3)_2$); 18.3, 17.6 (CH_3). ^{11}B NMR (ppm): 6.5 (1B, s, B(1)); −16.4 (5B, d, B(2–6)); −18.2 (5B, d, B(7–11)); −23.2 (1B, d, B(12)). IR (cm^{-1}): 3348 (NH), 2482 (BH); 1732 (CO).

2.4.2. Dicesium-{2-[2-(L-(1-carbomethoxy-2-phenyl)-ethylamino)-ethoxy]-ethoxy}-undecahydro-closo-dodecaborate **6b**

The compound was prepared the same way as **6a** from 0.3 g (0.64 mmol) of **2** and 0.205 g (0.95 mmol) of L-phenylalanine methyl ester hydrochloride. Yield 0.232 g of **6b** (68%), m.p. = 280 °C (dec). Anal. Calc. for $C_{14}H_{31}B_{12}NO_4Cs_2$: C, 24.99; H, 4.64; N, 2.08; B, 19.28. Found: C, 24.87; H, 4.62; N, 2.11; B, 19.39. ^{1}H NMR (ppm): 7.26 (5H, m, Ph); 3.60 (3H, s, CH_3–O); 3.5 (7H, m, CH_2–O and CH–N); 3.03 (2H, q, CH_2–N); 2.75 (2H, m, CH_2-Ph); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 174.7 (CO); 136.1, 129.2, 128.9, 127.3 (Ph); 70.7, 67.6, 62.2 (CH_2O); 68.3 (CH_3–O); 52.6 (CH–N); 46.0 (CH_2–N); 37.7 (CH_2Ph). ^{11}B NMR (ppm): 6.5 (1B, s, B(1)); −16.3

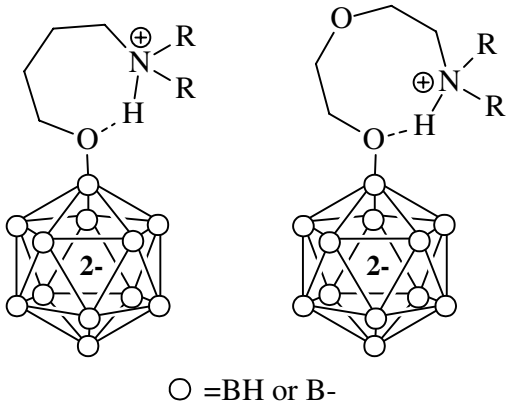
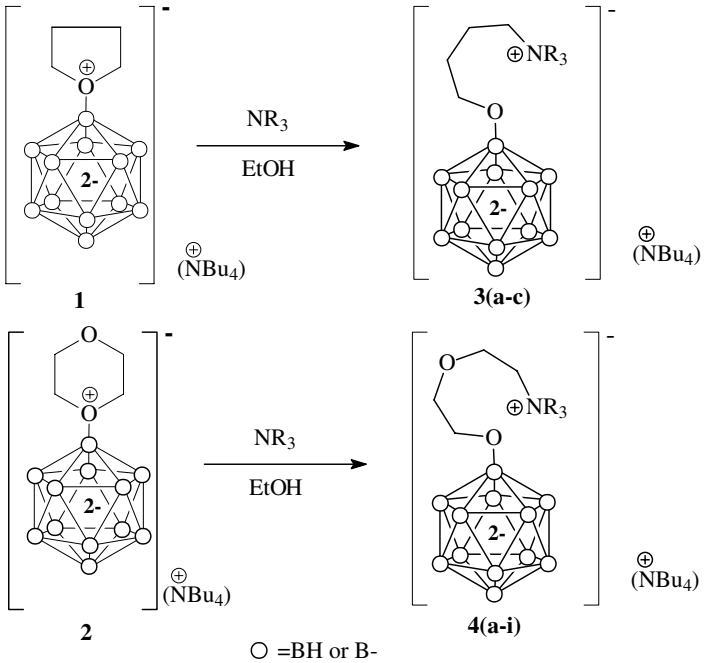


Fig. 1.



Scheme 1.

(5B, d, B(2–6)); −18.2 (5B, d, B(7–11)); −23.1 (1B, d, B(12)). IR (cm^{-1}): 3351 (NH), 2482 (BH); 1726 (CO).

2.4.3. Tetrabutylammonium-{2-[2-((1-carboxy-2-methyl)-propylammonium)-ethoxy]-ethoxy}-undecahydro-closo-dodecaborate 7a

0.295 g (0.5 mmol) of **6a** was refluxed in 10 ml of 15% HCl for 24 h. Then 0.15 g (0.5 mmol) of NBu_4Br in 2 ml of water was added and the precipitated product was filtered and vacuum dried. Yield 0.270 g of **7a** (97%), m.p. = 226 °C (dec). Anal. Calc. for $C_{25}H_{66}B_{12}N_2O_4$: C, 51.02; H, 11.30; N, 4.76; B, 22.04. Found: C, 50.89; H, 11.31; N, 4.79; B, 21.98%. ^{1}H NMR (ppm): 3.86 (1H, m, CH–N); 3.69 (2H, t, CH_2–O); 3.62 (2H, t, CH_2–O); 3.51 (2H, t, CH_2–O); 3.14 (10H, m, $NCH_2CH_2CH_2CH_3$ and CH_2–N); 2.29 (1H, m, CH–$(CH_3)_2$); 1.53 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.28 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.02 (3H, d, CH_3); 0.89 (15H, m, $NCH_2CH_2CH_2CH_3$ and CH_3); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 169.8 (CO); 72.0, 68.5, 65.9 (CH_2O); 64.8 (CH–N); 58.9 ($NCH_2CH_2CH_2CH_3$); 46.8 (CH_2–N); 29.0 (CH–$(CH_3)_2$); 23.5 ($NCH_2CH_2CH_2CH_3$); 19.7 ($NCH_2CH_2CH_2CH_3$); 17.6 (CH_3); 13.9 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 6.1 (1B, s, B(1)); −16.8 (5B, d, B(2–6)); −18.0 (5B, d, B(7–11)); −22.4 (1B, d, B(12)). IR (cm^{-1}): 3150 (NH_2^+), 2485 (BH); 1736 (CO).

2.4.4. Tetrabutylammonium-{2-[2-(L-(1-carboxy-2-phenyl)-ethylammonium)-ethoxy]-ethoxy}-undecahydro-closo-dodecaborate 7b

The compound was prepared the same way as **7a** from 0.23 g (0.4 mol) of **6b**. Yield 0.26 g of **7b** (98%), m.p. = 280 °C (dec). Anal. Calc. for $C_{29}H_{66}B_{12}N_2O_4$: C, 54.72; H, 10.45; N, 4.40; B, 20.38. Found: C, 54.55; H, 10.46; N, 4.20; B, 20.34%. ^{1}H NMR (ppm): 9.35 (3H, broad s, NH_2^+ and OH); 7.28 (5H, m, Ph); 4.21 (1H, m, CH–N); 3.67 (2H, t, CH_2O); 3.63 (2H, t, CH_2O); 3.54 (2H, t, CH_2O); 3.29 (1H, dd, CH_2Ph); 3.12 (10H, m, $NCH_2CH_2CH_2CH_3$ and CH_2–N); 3.05 (1H, dd, CH_2Ph); 1.53 (8H, m, $NCH_2CH_2CH_2CH_3$); 1.28 (8H, m, $NCH_2CH_2CH_2CH_3$); 0.89 (12H, t, $NCH_2CH_2CH_2CH_3$); 1.9–0.1 (11H, broad m, BH). ^{13}C NMR (ppm): 170.1 (CO); 135.4, 130.2, 128.9, 127.5 (Ph); 71.8, 68.6, 66.2 (CH_2O); 60.7 (CH–N); 58.0 ($NCH_2CH_2CH_2CH_3$); 46.3 (CH_2–N); 35.8 (CH_2Ph); 23.5 ($NCH_2CH_2CH_2CH_3$); 19.7 ($NCH_2CH_2CH_2CH_3$); 13.9 ($NCH_2CH_2CH_2CH_3$). ^{11}B NMR (ppm): 5.5 (1B, s, B(1)); −16.8 (5B, d, B(2–6)); −17.6 (5B, d, B(7–11)); −21.8 (1B, d, B(12)). IR (cm^{-1}): 3110 (NH_2^+), 2485 (BH); 1738 (CO), 1573 (Ph).

2.5. X-ray diffraction data

X-ray diffraction experiment was carried out with a Bruker SMART 1000 CCD area detector, using graphite monochromated Mo Kα radiation ($\lambda l = 0.71073$ Å, ω-scans) at 120 K. The structure was solved by direct method and refined by the full-matrix least-squares against F^2 in anisotropic approximation for no-hydrogen atoms. All polyhedron hydrogen atoms were located from the Fourier density synthesis and refined in isotropic approximation. Crystal data and structure refinement parameters for **4e** are given in Table 1. All calculations were performed using the SHELXTL software [5].

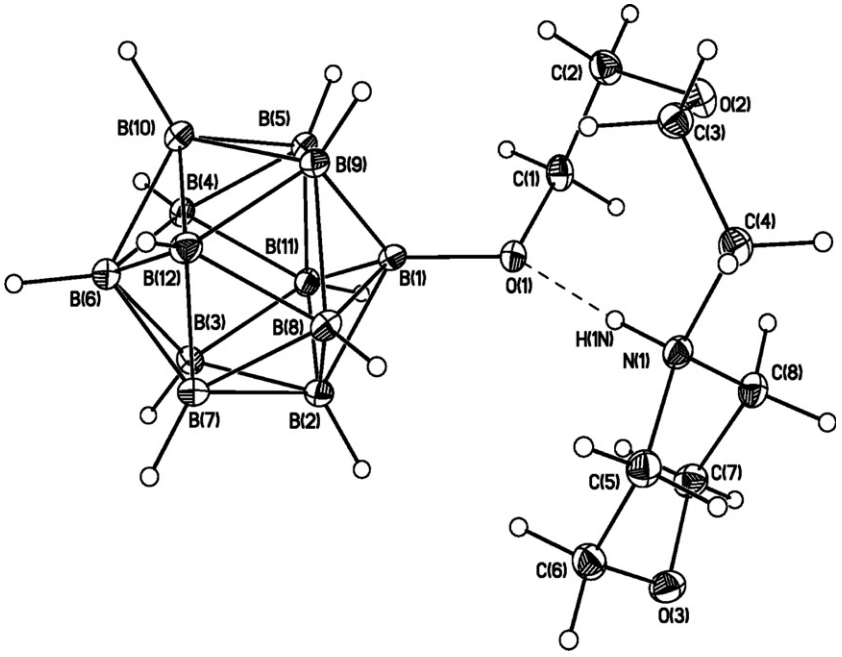


Fig. 2. The general view of anion **4e** in representation of atom by thermal ellipsoids ($p = 50\%$).

3. Results and discussion

We have found, that oxonium derivatives **1** and **2** react with ammonia, primary, secondary and tertiary amines resulting in novel ammonium derivatives **3**(**a**–**c**) and **4**(**a**–**i**) with excellent yields (Scheme 1).

It was amazing, that when **1** and **2** react with ammonia, primary and secondary amines, ammonium salts instead of free amines were formed, despite the huge excess of amine was used. It is to be noticed, that **1**, **2** react only with rather strong amines. For example, reactions with inactive amines (aniline, ethylisonicotinate) resulted in recovery of starting materials after 24 h heating in EtOH. Changing of EtOH to DMFA and heating at 150 °C led to starting materials as well.

The structure of **3**, **4** was proved by ^{1}H, ^{1}H–^{1}H COSY, ^{13}C, ^{1}H–^{13}C HMQC-gs and ^{11}B NMR spectra. In the ^{11}B NMR of **3**, **4** the signal of the substituted boron atom is

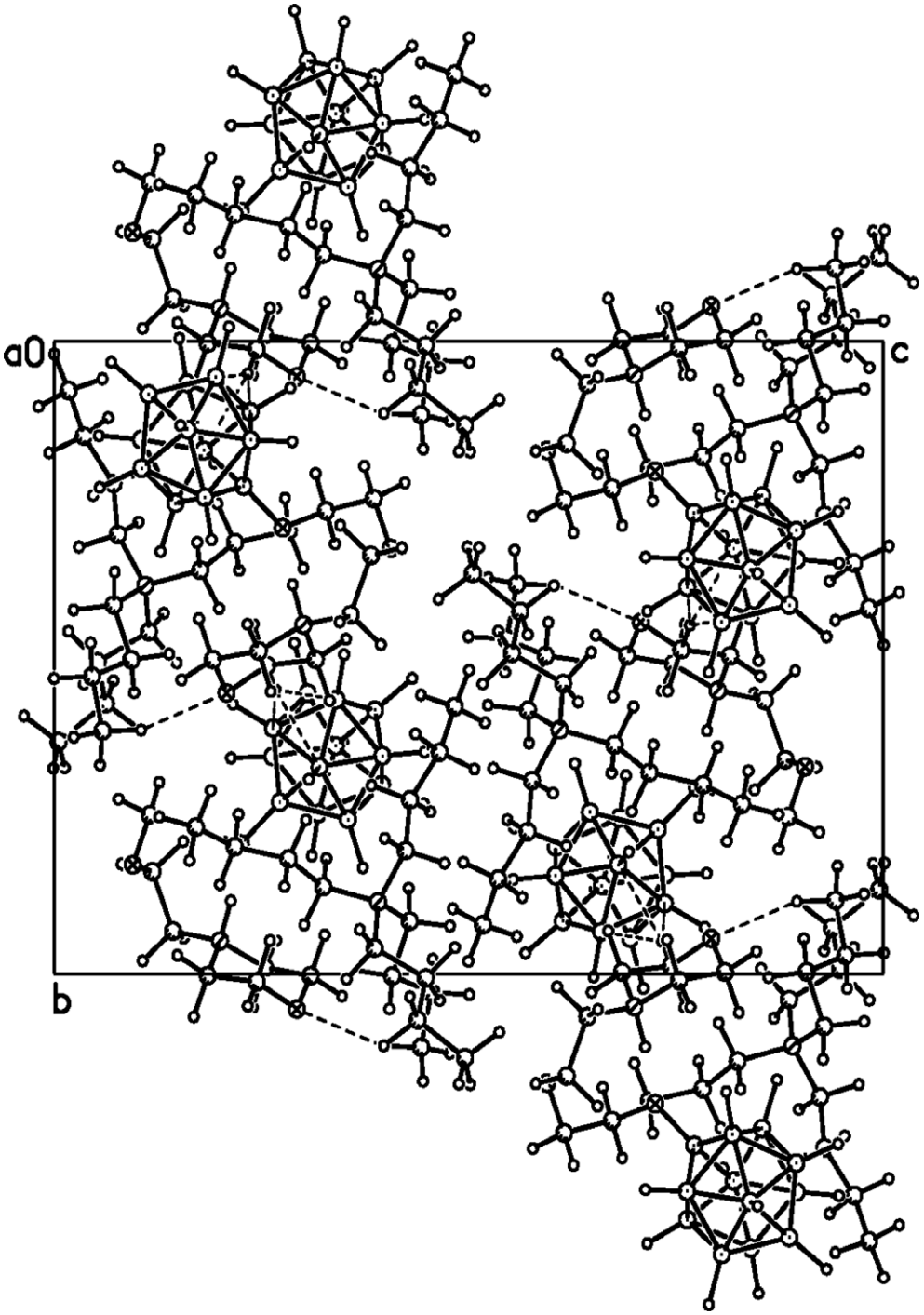
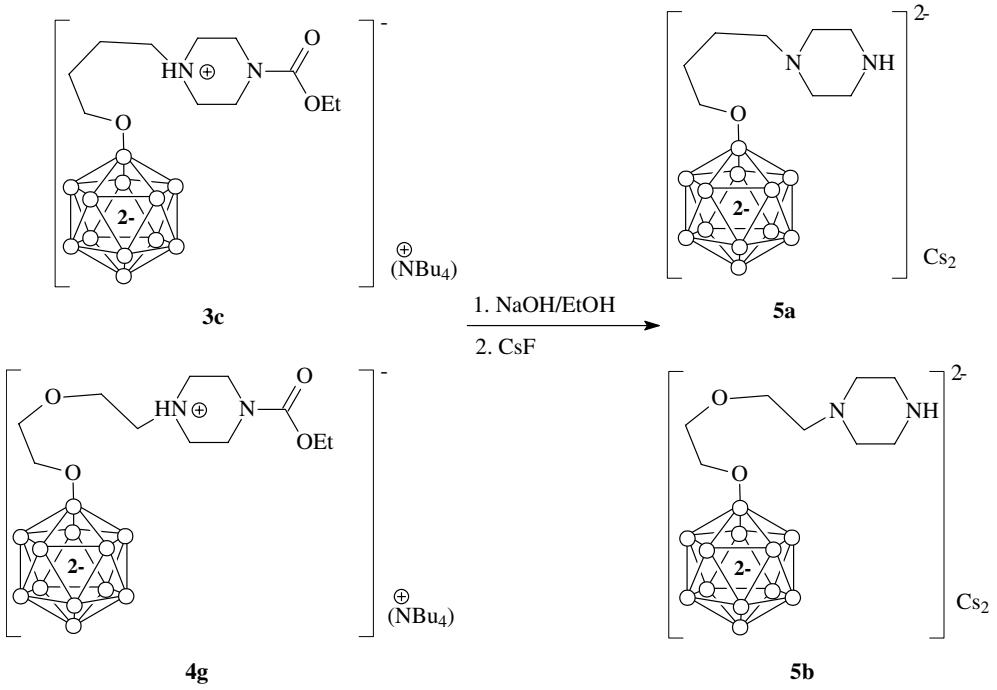


Fig. 3. The projection of crystal packing in **4e**.

shifted ca 2 ppm downfield compared to the starting materials **1**, **2** [2]. This is typical for the transformation of BO^+R_2 system to B-OR. In the ^1H NMR spectra of **3**, **4** (except **4h** and **5i**) the lowfield signals of NH_3^+ (**4a**), NH_2^+ (**3a**, **4**(**b**–**d**)) and NH^+ (**3**(**b**–**c**), **4**(**e**–**g**)) protons were observed at a range of 7–9 ppm.

In the IR spectra of prepared compounds the absorption bands of NH_3^+ (**4a**), NH_2^+ (**3a**, **4**(**b**–**d**)) and NH^+ (**3**(**b**–**c**), **4**(**e**–**g**)) groups were observed at the range of 3200–3100 cm^{-1}, indicating formation of hydrogen bonds including NH^+ proton. This permits us to propose the formation of intramolecular hydrogen bond between hydrogen of ammonium group and oxygen atom attached to the boron cage (Fig. 1). The formation of such intramolecular hydrogen bond was confirmed by X-ray diffraction analysis on the example of **4e** (Fig. 2).

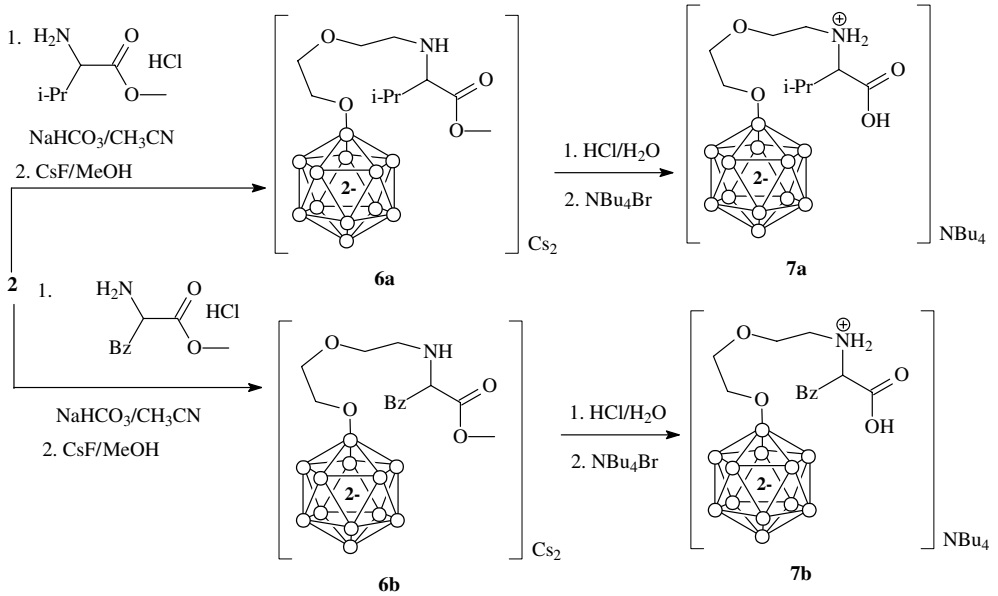
According to the XRD data the amino group in the crystal participates in rather strong intramolecular interaction with O(1) atom (N(1)···O(1) 2.705(2) Å, H(1N)···O(1) 1.78 Å, N(1)H(1N)O(1) 171°).



3c **5a**

4g **5b**

Scheme 2.



2 **6a** **7a**

6b **7b**

Scheme 3.

The geometrical parameters of the anion in salt **4e** are close to the corresponding values in bis(pyridinium)methylene [6] and bis(tetra-*n*-butylammonium) ethoxyundecahydro-*closo*-dodecaborate [7]. In particular B–B bond lengths vary in the narrow range of 1.776(3)–1.793(3) Å with slight elongation of the bonds formed by B(1) atom. It is noteworthy that C(1)O(1)B(1) angle (119.4(2)°) and B(1)–O(1) bond length (1.456(2) Å) are slightly differ from the corresponding values in ethoxyundecahydro-*closo*-dodecaborate (115.9(3)° and 1.442(1) Å) that is probably the consequence of N–H···O–B bond formation.

In the crystal anion is surrounded by four ammonium cations and form rather weak intermolecular B–H···H–C contacts with H···H distance being in the range of 2.0–2.2 Å (Fig. 3).

Probably, formation of this H-bond stabilizes prepared compounds. This can explain formation of ammonium salts and not free amines in the studied reactions.

Different piperazine derivatives are widely used in medicine. These are impotence drugs (Viagra®, Levitra®), recreational stimulants (mCPP, MeOPP), anti-angina drug (Trimetazidine®), etc. Imatinib® is known to be leukaemia drug [8]. Till now the piperazine-containing dodecaborates were not described. Thus, we have carried out the reaction of **1** and **2** with ethyl 1-piperazinecarboxylate under standard conditions, leading to ammonium derivatives **3c** and **4g** respectively with excellent yield. Hydrolysis of **3c** and **4g** (Scheme 2) by KOH/EtOH afforded novel B_{12}-based piperazines **5 a**, **b**. These compounds were isolated as Cs-salts and characterized by NMR spectra and element analysis. These data have shown that in both compounds amino groups are deprotonated. For example, the signals of N–CH_2 protons in **5**(**a**–**b**) were observed at $\delta =$ 2.65 ppm. This is ca 0.5 ppm upfield compared to starting materials (**3c**, **4g**), isolated as ammonium salts. The prepared compounds are the first examples of dodecaborate derivatives, containing piperazine fragment. Free amino-group of the piperazine ring in **5a**,**b** is ready for the further modification.

Preparation of boronated amino acids is of great importance because 4-dihydroxyborylphenylalanine (*p*-BPA) is one of two BNCT agents used clinically. Therefore, a large amount of amino acids with –$B(OH)_2$ group and amino acid-based carboranes were synthesized [9]. However, only one example of $B_{12}H_{12}$-anion containing amino acid group is reported till now [2]. Thus, we have tried to apply our method on the reactions with amino acids and their esters. We have found that amino acids do not react with **1** and **2** at the conditions, found for regular amines. Reaction of **2** with alanine in boiling EtOH in the presence of KOH or K_2CO_3 resulted in recovery of starting materials. Contrary, α-amino acid esters react with **2** in boiling EtOH in the presence of the same bases, as regular amines. But after boiling in EtOH for 48 h only ca. 30% conversion took place according to the ^{1}H NMR-spectrum of the reaction mixture. Finally we have found that heating of methyl esters of valine or L-phenylalanine (hydrochloride forms) with **2** in CH_3CN for 24 h in the presence of $NaHCO_3$ resulted in formation of the esters **6 a**,**b** in good yield.

The acidic hydrolysis of **6a**,**b** resulted in corresponding novel B_{12}-aminoacids **7a**,**b** (Scheme 3), which are rather interesting compounds as precursors for potential BNCT drugs.

Acknowledgements

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Appendix A. Supplementary material

CCDC 255386 contains the supplementary crystallographic data for **4e**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2007.06.001.

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