Synthesis of Schiff bases and benzylamino derivatives containing $[1\text{-}B_{10}H_9NH_3]^-$ anion

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Reactions of an amino derivative of the *closo*-decaborate anion $[1\text{-}B_{10}H_9NH_3]^-$ with aromatic aldehydes afforded Schiff bases $[1\text{-}B_{10}H_9NH{=}CHAr]^-$ (Ar = Ph, C_6H_4-2-OMe, or C_6H_4-4-NHCOMe). The reduction of the latter with sodium borohydride gave the corresponding benzylamino derivatives $[1\text{-}B_{10}H_9NH_2CH_2Ar]^-$.

Key words: decahydro-*closo*-decaborate anion $[B_{10}H_{10}]^{2-}$; Schiff bases; benzylamino derivatives.

The development of the chemistry of polyhedral boron hydrides is closely related to their promising use in medicine, primarily in boron neutron capture therapy (BNCT) of cancer[1,2]. In this aspect, derivatives of carboranes $C_2B_{10}H_{12}$ [3] and the *closo*-dodecaborate anion $[B_{12}H_{12}]^{2-}$ have been studied in most detail.[4,5] In contrast, the chemistry of compounds based on the *closo*-decaborate anion $[B_{10}H_{10}]^{2-}$, which experienced a violent surge of research activity in the 1960s [6] has not been properly developed later. During the last few years, there was a growing interest in the use of *closo*-decaborate derivatives in the BNCT,[7,8] which in turn gave a new impetus to the studies into the chemistry of *closo*-decaborate derivatives.[9—13]

The development of the BNCT requires the synthesis of a new generation of agents that should accumulate highly selectively in tumor cells. According to modern concepts of ways of targeted drug delivery to tumor cells, such agents can be created by, *e.g.*, attachment of boron compounds to various macromolecules with a high affinity for tumor cells such as monoclonal antibodies, growth factors, *etc.*[2,14,15] Earlier, we synthesized a number of benzylamino-*closo*-dodecaborate derivatives $[B_{12}H_{11}NH_2CH_2C_6H_4\text{-}4\text{-}Z]^-$ containing various functional groups in the benzene ring[16] and showed that they can be employed in the preparation of boron-containing monoclonal antibodies.[17,18] Using this approach, we obtained and characterized[10] the Schiff bases and benzylamino derivatives based on the anion $[2\text{-}B_{10}H_9NH_3]^-$. In this study, Schiff bases and benzylamino compounds were derived from the isomeric amino derivative $[1\text{-}B_{10}H_9NH_3]^-$.

Earlier,[19] the Schiff base $[1\text{-}B_{10}H_9NH{=}CHPh]^-$ has been synthesized by the reaction of a sodium salt of $[1\text{-}B_{10}H_9NH_3]^-$ with benzaldehyde. In the present work, Schiff bases were obtained by reactions of the tetrabutylammonium salt $(Bu_4N)[1\text{-}B_{10}H_9NH_3]$ with aldehydes ArC(O)H (Ar = Ph, 2-C_6H_4OMe, and 4-C_6H_4NHCOMe) in methanol in the presence of a catalytic amount of NaOH as previously described for the synthesis of Schiff bases from the anions $[B_{12}H_{11}NH_3]^-$ and $[2\text{-}B_{10}H_9NH_3]^-$. The presence of a base is required to deprotonate the ammonium N atom. A methanolic solution of $(Bu_4N)[1\text{-}B_{10}H_9NH_3]$ (**1**) and aldehyde turned yellow upon the addition of a solution of NaOH; stirring at room temperature for 20 to 120 min gave a precipitate of the corresponding Schiff base $(Bu_4N)[1\text{-}B_{10}H_9NH{=}CHAr]$ (Ar = Ph (**2**), 2-C_6H_4OMe (**3**), and 4-C_6H_4NHCOMe (**4**)). The resulting Schiff bases are colored from light yellow to lemon.

The ^{1}H NMR spectra of the Schiff bases in DMSO-d_6 show signals for the protons of the imino group at δ 12.9—13.9 (N—H) and 9.0—9.5 (C—H). Both signals are doublets ($J \approx 16$—19 Hz), which corresponds to the *trans*-arrangement of the substituents relative to the double bond of the imine. The signal from the N—H hydrogen atom rapidly disappears upon the addition of D_2O, while the doublet for the C—H hydrogen atom of the imino group changes to a singlet. The ^{13}C NMR spectra show a signal for the imino C atom at δ 163—169. The IR

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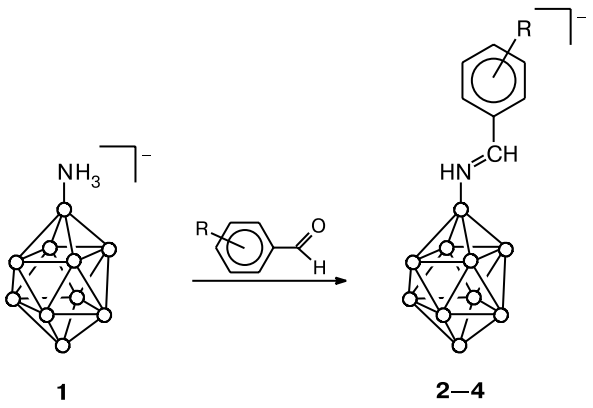
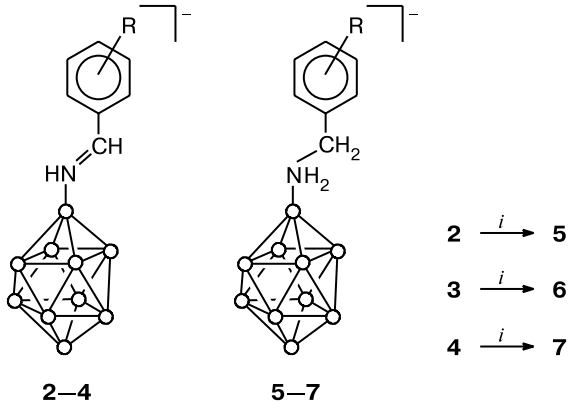


1 **2—4**

R = H (**2**), 2-OMe (**3**), 4-NHCOMe (**4**)

spectra of the Schiff bases contain an intense band at 1630—1640 cm^{-1} for the C=N stretching vibrations and bands at 3240—3340 cm^{-1} relating to the N—H stretching vibrations.

Schiff bases **2—4** were reduced with sodium borohydride in aqueous methanol as described earlier.[10,16] A suspension of the Schiff base in aqueous methanol containing three equivalents of $NaBH_4$ (4 : 1) was stirred at room temperature to complete decoloration to give the corresponding benzylamino derivatives $(Bu_4N)[1\text{-}B_{10}H_9NH_2CH_2Ar]$ (Ar = Ph (**5**), $2\text{-}C_6H_4OMe$ (**6**), and $4\text{-}C_6H_4NHCOMe$ (**7**)) in virtually quantitative yields.



2—4 **5—7**

R = H, 2-OMe, 4-NHCOMe *i*. $NaBH_4$, $MeOH—H_2O$

The ^1H NMR spectra of products **5—7**, contain no signals corresponding to the —NH=CH— group but contain signals at δ 4.3—4.5 and 7.8—8.0 for the benzyl and amino groups, respectively. The ^{13}C NMR spectra show no signal for the imino C atom; instead, a signal for the benzyl C atom appears at δ 54—55. The IR spectra of the benzylamino derivatives obtained no longer contain the band of the C=N stretching vibrations.

Note that the benzylamino derivative $[1\text{-}B_{10}H_9NH_2CH_2Ph]^-$ was obtained earlier[9] by the reaction of the diazo compound $[1\text{-}B_{10}H_9N_2]^-$ with benzylamine at 120 to 130 °C; however, our procedure allows the room-temperature synthesis of this compound under milder conditions.

The proposed approach can be used to obtain functionalized benzylamino derivatives based on the *closo*-decaborate anion, which are promising for medical use.

Experimental

^1H, ^{13}C, and ^{11}B NMR spectra were recorded on a Varian Unity 400 spectrometer. The chemical shifts are referenced to Me_4Si and $BF_3 \cdot Et_2O$. IR spectra were recorded on a Perkin Elmer 1760 FTIR spectrometer. The salt $(Bu_4N)[1\text{-}B_{10}H_9NH_3]$ (**1**) was prepared as described earlier.[20]

Synthesis of the Schiff bases containing $[1\text{-}B_{10}H_9NH_3]^-$ (general procedure). A solution of the corresponding aldehyde (1.1 mmol) in 5—6 mL of methanol was added to a stirred solution of complex **1** (0.37 g, 1.0 mmol) in 6 mL of methanol (when a liquid aldehyde was used, it was added as such to the reaction mixture). Then 5% aqueous NaOH (5—6 drops) was added and the reaction mixture turned yellow-orange. After 20 to 120 min, the yellow-orange precipitate that formed was filtered off and dried in air.

Tetrabutylammonium 1-benzylideneammoniononahydro-*closo*-decaborate $(Bu_4N)[1\text{-}B_{10}H_9NH{=}CHPh]$ (2) was synthesized from benzaldehyde as described above. The yield of product **2** was 0.41 g (88%). Found (%): C, 58.97; H, 11.37; N, 5.91; B, 21.08. $C_{23}H_{52}B_{10}N_2$. Calculated (%): C, 59.44; H, 11.28; N, 6.03; B, 21.23. ^1H NMR (DMSO-d_6), δ: 13.42 (d, 1 H, J = 16.0 Hz); 9.29 (d, 1 H, J = 16.0 Hz); 8.36 (d, 2 H, J = 7.2 Hz); 7.75 (t, 1 H); 7.70 (t, 2 H); 3.17, 1.56, 1.32 (all m, 8 H each, Bu_4N^+); 1.27 (t, 12 H, Bu_4N^+). ^{13}C NMR (DMSO-d_6), δ: 168.4, 134.8, 130.6, 130.5, 129.9, 57.9 (Bu_4N^+); 23.3 (Bu_4N^+); 19.4 (Bu_4N^+); 13.8 (Bu_4N^+). ^{11}B NMR (CD_3OD), δ: 11.0 (s, 1 B); 5.0 (d, 1 B, J = 141 Hz); –24.1 (d, 4 B, J = 115 Hz); –27.3 (d, 4 B, J = 120 Hz). IR (CH_2Cl_2), ν/cm^{-1}: 3324, 3266, 3233, 2995, 2965, 2932, 2877, 2476, 1633, 1599, 1482, 1473, 1454, 1420, 1382, 1346, 1319, 1219, 1184, 1153, 1043, 1024, 1005, 928, 884, 750, 683, 666.

Tetrabutylammonium 1-(2-methoxybenzylidene)ammonio-nonahydro-*closo*-decaborate $(Bu_4N)[1\text{-}B_{10}H_9NH{=}CHC_6H_4\text{-}2\text{-}OMe]$ (3) was synthesized from 2-methoxybenzaldehyde as described above. The yield of product **3** was 0.33 g (67%). Found (%): C, 57.86; H, 10.76; N, 5.57; B, 22.06. $C_{24}H_{54}B_{10}N_2O$. Calculated (%): C, 58.26; H, 11.00; N, 5.66; B, 21.85. ^1H NMR (DMSO-d_6), δ: 12.92 (d, 1 H, J = 19.0 Hz); 9.43 (d, 1 H, J = 19.0 Hz); 8.34 (d, 1 H, J = 8.0 Hz); 7.73 (t, 1 H, J = 7.7 Hz); 7.32 (d, 1 H, J = 8.2 Hz); 7.20 (t, 1 H, J = 7.4 Hz); 4.02 (s, 3 H); 3.15, 1.55, 1.29 (all m, 8 H each, Bu_4N^+); 0.92 (t, 12 H, Bu_4N^+). ^{13}C NMR (DMSO-d_6), δ: 163.5, 160.1, 136.8, 130.2, 121.4, 118.2, 112.8, 57.5 (Bu_4N^+); 56.5, 23.0 (Bu_4N^+); 19.2 (Bu_4N^+); 13.5 (Bu_4N^+). ^{11}B NMR (CD_3OD), δ: 11.3 (s, 1 B); 1.8 (d, 1 B, J = 141 Hz); –25.7 (d, 4 B, J = 128 Hz); –29.2 (d, 4 B, J = 115 Hz). IR (CH_2Cl_2), ν/cm^{-1}: 3310, 2994, 2964, 2876, 2472, 1628, 1602, 1576, 1495, 1480, 1469, 1438, 1381, 1348, 1314, 1270, 1249, 1218, 1180, 1166, 1129, 1107, 1038, 1009, 879, 842, 754, 665.

Tetrabutylammonium 1-(4-acetamidobenzylidene)ammonio-nonahydro-*closo*-decaborate (Bu_4N)[1-$B_{10}H_9NH{=}CHC_6H_4$-4-NHCOMe] (4) was synthesized from 4-acetamidobenzaldehyde as described above. The yield of product **4** was 0.41 g (78%). Found (%): C, 57.30; H, 10.21; N, 7.83; B, 21.02. $C_{25}H_{55}B_{10}N_3O$. Calculated (%): C, 57.54; H, 10.62; N, 8.05; B, 20.72. ^{1}H NMR (DMSO-d_6), δ: 12.99 (d, 1 H, J = 17.2 Hz); 10.48 (s); 9.07 (d, 1 H, J = 17.2 Hz); 8.26, 7.80 (both d, 2 H each, J = 8.8 Hz); 3.13 (m, 8 H, Bu_4N^+); 2.11 (s, 3 H); 1.54, 1.28 (both m, 8 H each, Bu_4N^+); 0.91 (t, 12 H, Bu_4N^+). ^{13}C NMR (DMSO-d_6), δ: 169.4, 166.8, 144.7, 131.8, 124.3, 118.9, 57.6 (Bu_4N^+); 24.4, 23.1 (Bu_4N^+); 19.3 (Bu_4N^+); 13.6 (Bu_4N^+). ^{11}B NMR (acetone-d_6), δ: 9.7 (s, 1 B); 5.4 (d, 1 B, J = 147 Hz); −24.6 (d, 4 B, J = 128 Hz); −28.0 (d, 4 B, J = 131 Hz). IR (CH_2Cl_2), ν/cm^{-1}: 3335, 3263, 3209, 3020, 2994, 2963, 2939, 2876, 2524, 2483, 2456, 1692, 1634, 1606, 1589, 1516, 1471, 1422, 1370, 1323, 1262, 1216, 1181, 1052, 1005, 881, 825, 755, 668.

Reduction of the Schiff bases containing the *closo*-decaborate anion to benzylamino derivatives (general procedure). Sodium borohydride (0.06 g, 1.5 mmol) was added to the Schiff base (**2**—**4**) (0.5 mmol) in 5 mL of water—methanol (4 : 1). The reaction mixture was stirred for 30 to 60 min to decoloration, acidified to pH 5 with 1 *M* HCl, and stirred again for 30 min. The resulting solution was evaporated to dryness. The residue was treated with water (15 mL) and dichloromethane (15 mL). The organic phase was separated. The product was additionally extracted from the aqueous phase with dichloromethane (20 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness.

Tetrabutylammonium 1-benzylammoniononahydro-*closo*-decaborate (Bu_4N)[1-$B_{10}H_9NH_2CH_2Ph$] (5) was obtained from (Bu_4N)[1-$B_{10}H_9NH{=}CHPh$]. The yield of product **5** was 0.22 g (94%). Found (%): C, 58.76; H, 11.28; N, 6.20; B, 22.78. $C_{23}H_{54}B_{10}N_2$. Calculated (%): C, 59.18; H, 11.66; N, 6.00; B, 23.16. ^{1}H NMR (DMSO-d_6), δ: 7.99 (m, 2 H); 7.58, 7.38 (both d, 2 H each, J = 7.6 Hz); 7.32 (d, 1 H, J = 7.2 Hz); 4.42 (m, 2 H); 3.12, 1.53, 1.28 (all m, 8 H each, Bu_4N^+); 0.90 (m, 12 H, Bu_4N^+). ^{13}C NMR (DMSO-d_6), δ: 136.6, 129.3, 128.6, 128.1, 57.9 (Bu_4N^+); 54.2, 23.3 (Bu_4N^+); 19.5 (Bu_4N^+); 13.8 (Bu_4N^+). ^{11}B NMR (CD_3OD), δ: 11.2 (s, 1 B); −3.2 (d, 1 B, J = 143 Hz); −28.5 (d, 4 B, J = 128 Hz); −31.0 (d, 4 B, J = 122 Hz). IR (CH_2Cl_2), ν/cm^{-1}: 3519, 3281, 3182, 3113, 2992, 2965, 2876, 2472, 1603, 1570, 1497, 1480, 1458, 1382, 1348, 1319, 1265, 1218, 1184, 1155, 1108, 1058, 1024, 976, 923, 882, 798, 755, 700, 665.

Tetrabutylammonium 1-(2-methoxybenzylammonio)nonahydro-*closo*-decaborate (Bu_4N)[1-$B_{10}H_9NH_2CH_2C_6H_4$-2-OMe] (6) was obtained from (Bu_4N)[1-$B_{10}H_9NH{=}CHC_6H_4$-2-OMe]. The yield of product **6** was 0.46 g (93%). Found (%): C, 57.91; H, 11.50; N, 5.51; B, 21.08. $C_{24}H_{56}B_{10}N_2O$. Calculated (%): C, 58.02; H, 11.36; N, 5.61; B, 21.76. ^{1}H NMR (DMSO-d_6), δ: 7.78 (s, 2 H); 7.62 (d, 1 H, J = 7.0 Hz); 7.35 (t, 1 H, J = 14.5 Hz); 7.06 (d, 1 H, J = 8.0 Hz); 6.99 (t, 1 H, J = 14.3 Hz); 4.47 (s, 2 H); 3.87 (s, 3 H); 3.17, 1.57 (both m, 8 H each, Bu_4N^+); 1.33 (m, 8 H); 0.94 (t, 12 H, J = 14.6 Hz). ^{13}C NMR (DMSO-d_6), δ: 157.4, 130.1, 129.6, 124.4, 120.5, 110.9, 57.8 (Bu_4N^+); 55.8, 49.2, 23.3 (Bu_4N^+); 19.5 (Bu_4N^+); 13.8 (Bu_4N^+). ^{11}B NMR (CD_3OD), δ: 10.7 (s, 1 B); −0.7 (d, 1 B, J = 139 Hz); −27.1 (d, 8 B, J = 115 Hz); −29.0 (d, 8 B, J = 148 Hz). IR (CH_2Cl_2), ν/cm^{-1}: 3527, 3289, 3252, 3195, 2992, 2965, 2876, 2467, 1605, 1580, 1495, 1483, 1466, 1439, 1381, 1309, 1292, 1247, 1218, 1180, 1164, 1118, 1049, 1029, 981, 933, 882, 753, 665.

Tetrabutylammonium 1-(4-acetamidobenzylammonio)nonahydro-*closo*-decaborate (Bu_4N)[1-$B_{10}H_9NH_2CH_2C_6H_4$-4-NHCOMe] (7) was obtained from (Bu_4N)[1-$B_{10}H_9NH{=}CHC_6H_4$-4-NHCOMe]. The yield of product **7** was 0.24 g (92%). Found (%): C, 57.14; H, 10.47; N, 7.98; B, 20.70. $C_{25}H_{57}B_{10}N_3O$. Calculated (%): C, 57.32; H, 10.97; N, 8.02; B, 20.64. ^{1}H NMR (DMSO-d_6), δ: 9.98 (s, 1 H); 7.93 (m, 2 H); 7.55, 7.50 (both d, 2 H each, J = 8.8 Hz); 4.35 (m, 2 H); 3.13 (m, 8 H, Bu_4N^+); 2.03 (s, 3 H), 1.54, 1.28 (both m, 8 H each, Bu_4N^+); 0.91 (m, 12 H, Bu_4N^+). ^{13}C NMR (CD_3OD), δ: 171.7, 139.2, 133.2, 130.6, 121.3, 59.6 (Bu_4N^+); 55.1, 24.9 (Bu_4N^+); 23.9, 20.7 (Bu_4N^+); 14.0 (Bu_4N^+). ^{11}B NMR (CD_3OD), δ: 11.1 (s, 1 B); −3.1 (d, 1 B, J = 131 Hz); −28.4 (d, 4 B, J = 122 Hz); −30.9 (d, 4 B, J = 119 Hz). IR (CH_2Cl_2), ν/cm^{-1}: 3516, 3338, 3284, 3188, 3108, 2993, 2965, 2876, 2471, 1673, 1600, 1568, 1526, 1481, 1415, 1380, 1319, 1260, 1218, 1184, 1152, 1108, 1025, 982, 926, 882, 836, 757, 666.

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