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$B_{12}H_{11}$-containing guanidinium derivatives by reaction of carbodiimides with H_3N–$B_{12}H_{11}(1-)$. A new method for connecting boron clusters to organic compounds

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Abstract

The reaction of $B_{12}H_{11}NH_3(1-)$ with carbodiimides can form guanidinium salts containing the boron cluster. Depending on the side chains of the carbodiimide, these derivatives of the $B_{12}H_{12}(2-)$ cluster can be uncharged or can carry an overall positive or negative charge. This reaction allows the preparation of $B_{12}H_{11}NH_3^-$ derivatives with aliphatic side chains, in contrast to the acylation reaction of $B_{12}H_{11}NH_3^-$ and the formation of Schiff bases, both of which are successful only with aromatic acid chlorides or aromatic, respectively, α,β-unsaturated aldehydes. The acylation of $B_{12}H_{11}NH_3^-$ with benzoyl chloride gives an N-protonated form of an imidoacid, carrying a single overall charge.

Keywords: Borates; Boron neutron capture therapy; Carbodiimides; Guanidinium salts; Imido acid

1. Introduction

For the use of cluster-containing compounds in boron neutron capture therapy (BNCT) [1], the charge of the compounds plays an important role. Carborane-containing organic compounds are often water-insoluble. In contrast, the (negative) charge of the $B_{12}H_{12}(2-)$ cluster conveys water solubility to the sodium salts of the substances, which is often required. Nevertheless, the negative charge of $B_{12}H_{12}(2-)$ might hinder the transport to and the passage into the target cells. $Na_2B_{12}H_{11}SH$, which is used successfully in BNCT, is found intracellularly [2,3]; the uptake mechanism, however, is still not known. We are interested in preparing water-soluble compounds containing the $B_{12}H_{12}(2-)$ cluster, in which one or both of the negative charges are compensated by substituents, thereby possibly enabling transport and passage into target cells.

The $B_{12}H_{12}^{2-}$ cluster can be connected to organic compounds through exoskeletal substituents (S, O, N) linking the cluster and an organic moiety [4–7]. Of these substituents, N is of special interest as the nitrogen is usually positively charged, thereby reducing to overall charge to (1−). The preparation and alkylation of $B_{12}H_{11}NH_3^-$ (**1**), which was first described by Hertler and Raasch [8], leads to mixtures of mono-, di- and trialkylated products [5]. The degree of alkylation is governed by the steric demand of the alkyl chain. The formation of a Schiff base, and subsequent reduction to a primary amine, has been reported for **1** with aromatic and α,β-unsaturated aldehydes [9]. This reaction fails for aliphatic aldehydes. Acylation of N with aliphatic acid chlorides also fails; with aromatic acid chlorides we obtained imidoacids. Interestingly **1** reacts readily with aliphatic carbodiimides to guanidium salts. Depending on the choice of side chains of the

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carbodiimide, the resulting structures can be neutral or even positively charged.

2. Results and discussion

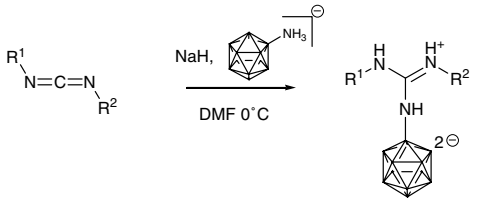
2.1. Acylation of $B_{12}H_{11}NH_3^-$

Acylation of the nitrogen atom is limited to aromatic carboxylic acids; aliphatic carboxylic acids did not react. The resulting product carries a single negative charge, as the product exists in its protonated tautomeric imidoacid form, as in the case of the benzoyl derivate **2** (see Fig. 1). The increased basicity of the imidoacid might be seen as the result of the strong electron-donating power of the cluster, which manifests itself also in increased pK_A-values of the SH group in $B_{12}H_{11}SH(2-)$ [4] and of the $-NH_3(1+)$ group of **1**. The double bond character of the N–C bond is also reflected in the bond length of 1.293 Å (see Table 2) (**2** crystallizes with two molecules in the asymmetric unit and therefore the mean distances are given), which is substantially shorter than the standard amide bond length of 1.46 Å. The length of the C–O bond is 1.313 Å, slightly longer than the bond length in a standard amide bond. The bond length of the B–N bond is 1.53 Å and does not indicate a double bond character.

Due to the low acidity of **1**, the reaction with chlorocarbonyl derivatives requires the use of a strong base such as NaH.

2.2. Formation of guanidinium derivatives of $B_{12}H_{11}NH_3^-$

The reaction of amines with carbodiimides [10–13] offers a convenient approach for connecting **1** to organic moieties. When we reacted equimolar amounts of **1** with DCC (dicyclohexylcarbodiimide) **3** and a double molar amount of NaH in DMF, we obtained the corresponding guanidinium compound **4** carrying a single negative charge. With EDC (1-ethyl-3-3-(dimethylamino)propylcarbodiimide) **5**, we obtained the guanidinium compound **6**, which is neutral at pH 7. When isolated from the basic reaction mixture, one molecule of TMA is associated with **6**. At neutral pH, the amino group is protonated, resulting in a neutral molecule. With DAPC (bis(*N*,*N*-dimethylaminopropyl)carbodiimide) **7** prepared according to the general method described by Appel et al. [14,15] from *N*,*N*′-bis(dimethylaminopropyl)urea, which can easily be prepared from *N*,*N*-dimethylaminopropylamine and urea in a one step synthesis [16,17], we obtained **8**, which again is isolated together with one molecule of TMA; it carries, however, one positive charge at pH 7. For recovery of the final compounds, the solvent was evaporated and the product was washed. Recrystallization was also possible, but usually not necessary. The yields of the reactions were between 83% and 95% (Scheme 1).



$R^1=R^2=cycloC_6H_{11}$	**3**	**4**
R^1=Et $R^2=Me_2NPr$	**5**	**6**
$R^1=R^2=Me_2NPr$	**7**	**8**

Scheme 1.

Compounds **6** and **8** are protonated on the amino group when dissolved in buffer of neutral pH; at physiological pH, they represent a neutral and a positively charged compound, respectively. The water solubility of the neutral compound **6** is moderate, whereas **8** is freely water soluble. As expected, the tetramethylammonium (TMA) salt of **4** is not water-soluble. Additionally the compounds **5** and **7** can be alkylated at the terminal N atoms, resulting in permanent positive charges at these atoms, which will be pertained in the final compounds **6** and **8**.

The ease of the reaction and the high yield make this reaction attractive for the synthesis of water-soluble boron compounds with suitable characteristics for in vivo application for BNCT.

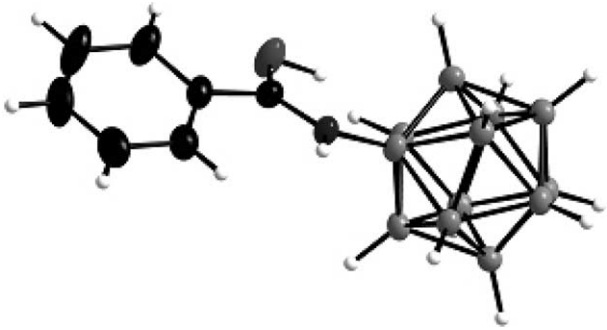


Fig. 1. View of **2** with vibrational ellipsoids.

3. Experimental

IR spectra were recorded on a Biorad FTS-IR 155 spectrometer. NMR spectra were recorded on a Bruker Avance DPX 200. For the boron atoms in positions 2 through 12 of the cluster occurring around −15.5 ppm, resolution was not sufficient to assign unique shifts and integrals. Integrals are given over the whole signal; when discernible peaks were found, their individual shifts are given, also when sufficient separation was not achieved. Signal forms for these peaks are not given.

Mass spectra were obtained on a Bruker MAT 95 or MAT 8200 (EI) and on a Bruker Esquire (ESI). For boron-containing compounds, the most intense peak of the pattern caused by the boron isotopes is indicated.

The carbodiimides **3** (DCC) and **5** (EDC) were obtained from Aldrich Chemical Co. Ammoniumundecahydro-*closo*-dodecaborate was prepared according to [8].

3.1. *N,N′-(ω-dimethylaminopropyl)-urea*

Dimethylamino-1-propylamine (Aldrich) (12.6 mL, 0.1 mol), 6 g (0.1 mol) urea and 3 mL water were refluxed for 4 h. The residue was cooled down to room temperature, diluted with $CHCl_3$ and filtered. The solvent was removed and the reaction product was distilled (b.p. 75 °C at 2×10^{-3} mbar). Yield: 15 g (65%). MS (EI) 70 eV *m/z* 230, 172, 159, 129, 58; IR (KBr) ν_{max} = 3327 (s) [ν(N–H)], 2940, 2864, 2773 (s) [$\nu(CH_2)$], 1643 (s) [ν(C=O)]; ^{1}H NMR $\delta_H(CDCl_3)$ = 1.38 (m, 4H, –CH_2–CH_2–CH_2–), 1.95 (s, 12H, (CH_3)$_2$N–), 2.06 (t, 4H, –CH_2–N(CH_3)$_2$), 2.92 (q, 4H, –CH_2–NH–CO–), 5.9 (s, 2H, –N*H*–CO–); ^{13}C{^{1}H} NMR $\delta_C(CDCl_3)$ = 28.21 (–CH_2–*C*H_2–CH_2–), 39.02 (–*C*H_2–N(CH_3)$_2$), 45.56 ((*C*H_3)$_2$N–), 57.47(–*C*H_2–NH–CO), 159.86 (–NH–*C*O–NH–).

3.2. *N,N′-(ω-dimethylaminopropyl)-carbodiimide (7)*

N,N′-(ω-dimethylaminopropyl)-urea (4 g, 17.4 mmol), 10 mL (0.105 mol) CCl_4, 5 g (19 mmol) triphenylphosphine and 3.56 mL (26.1 mmol) triethylamine were dissolved in 30 mL dry CH_2Cl_2 and refluxed under a N_2-atmosphere for 5 h. The solvent was removed to near dryness. The residue was extracted with 3×100 mL of dry pentane. The combined extracts were dried over anhydrous K_2CO_3. The solvent was removed to give a brownish oil. Yield: 300 mg (8%). MS (EI) 70 eV *m/z* 212, 197, 169, 154, 58; IR (KBr) ν_{max} = 3523, 3419, 3327 (s) [ν(N–H)], 2948, 2860, 2769 (s) [$\nu(CH_2)$], 2130 (s) [ν(–N=C=N–)]; ^{1}H NMR δ_H(benzene) = 1.49 (m, 4H, –CH_2–C*H*$_2$–CH_2–), 1.96 (s, 12H, (C*H*$_3$)$_2$N–), 2.11 (t, 4H, –C*H*$_2$–N(CH_3)$_2$), 2.92 (t, 4H, –C*H*$_2$–N=C=N–); ^{13}C{^{1}H} NMR δ_C(benzene) = 29.78 (–CH_2–*C*H_2–CH_2–), 45.19 (–*C*H_2–N(CH_3)$_2$), 45.95 ((*C*H_3)$_2$N–), 57.29 (–*C*H_2–N=C=N–), 140.54 (–N=*C*=N–).

3.3. *Benzoylimido-undecahydro-closo-dodecaborate(1-) (2)*

1 as tetramethylammonium salt (500 mg, 0.432 mmol) was dissolved in 10 mL dry DMF. The solution was cooled to 0 °C and 55.4 mg (0.83 mmol) NaH (60% suspension in oil) were added. The reaction mixture was stirred until no gas bubbles (H_2) could be observed. Then a solution of 1.6 mL (13.77 mmol) benzoylchloride in 10 mL DMF was dropped to the solution and the reaction mixture was stirred for 2 h. Then the solvent was removed and 50 mL of diethylether was added to the residue. After 20 min of stirring, the ether was decanted and the crude product was recrystallized from water. Yield: 458.3 mg (63%). m.p. 185 °C. MS (ESI) negative: *m/z* 261, positive 74; IR (KBr) ν_{max} = 3361 (w), 3073 (m), 3029 (m), 2478 (s) [ν(B–H)], 2368 (m), 1640 (s) [νC=N]; ^{1}H NMR δ_H(DMSO) = 0.4–1.9 (m, 12H, *H*–B), 3.1 (s, 12H, (CH_3)$_4$N$^+$), 7.55–7.9 (3 m, 5H, Aryl-*H*), 9.78 (s, 1H, N–*H*). ^{11}B {^{1}H} NMR δ_B^{11}(DMSO) = −6.88 (s, 1B, *B*–N), −14.90/−15.57 (11B).

The crystal data of **2** as *N,N*-bis(triphenylphosphonium)-ammonium salt are given in Table 1. Selected bond lengths and angles are given in Table 2.

3.4. *General method for preparation of guanidinium derivatives of 1*

1 as tetramethylammonium salt (100 mg, 0.432 mmol) was dissolved in 10 mL dry DMF. The

Table 1
Crystal data and structure refinement for **2**

Empirical formula	$C_{43}H_{48}B_{12}N_2OP_2$
Formula weight	800.49
Temperature (K)	173(2)
Wavelength (pm)	154.178
Crystal system	Monoclinic
Space group	*C*2/*c*
Unit cell dimensions	
a (pm)	5714.9(9)
b (pm)	1441.7(2)
c (pm)	2177.7(3)
α (°)	90
β (°)	103.39(2)
γ (°)	90
Volume (nm^3)	17.45(1)
Z	16
Density (calculated) (mg/m^3)	1.218
Absorption coefficient (mm^{-1})	1.174
F(000)	6688
Crystal size (mm^3)	0.4 × 0.3 × 0.2
Theta range for data collection (°)	3.17–76.49
Index ranges	$0 \leqslant h \leqslant 72$, $-18 \leqslant k \leqslant 0$, $-27 \leqslant l \leqslant 26$
Reflections collected	18,654
Independent reflections	18,320 [$R_{(int)}$ = 0.0237]
Completeness to theta = 76.49°	99.9%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	18,320/0/1100
Goodness-of-fit on F^2	1.036
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0495, wR_2 = 0.1304
R indices (all data)	R_1 = 0.0558, wR_2 = 0.1373
Extinction coefficient	0.000335(14)
Largest difference in peak and hole (e Å^{-3})	0.454 and −0.448
CCDC deposition number	252,153

Table 2
Selected bond lengths and bond angles for the two molecules of **2** in the asymmetric unit

B1		N1	1.534(4)
N1		C1	1.295(7)
C1		O1	1.314(11)
B13		N2	1.530(3)
N2		C11	1.291(8)
C11		O2	1.313(3)
B1	N1	C1	128.11(16)
N1	C1	O1	120.70(17)
N1	C1	C2	124.95(17)
B13	N2	C8	128.81(17)
N2	C7	O2	120.61(17)
N2	C7	C8	124.24(17)

solution was cooled to 0 °C and 55.4 mg (0.83 mmol) NaH (60% suspension in oil) was added. The reaction mixture was stirred until no gas bubbles (H_2) could be observed. Then, an equimolar amount of neat carbodiimide was added and the solution was stirred overnight at room temperature. The solvent was removed, and the crude reaction product was washed with CH_2Cl_2 and then with water. If necessary the product can be recrystallized from acetone/water.

As an alternative solvent for the reaction, THF can be used; this requires, however, the use of triethylammonium instead of tetramethylammonium as counter ion for **1**. Deprotonation was then carried out for 3 h at room temperature and subsequent 30 min of reflux, before the carbodiimide was added.

*3.5. N′-ethyl-N″-(ω-dimethylaminopropyl)-guanidinium-undecahydro-closo-dodecaborate (**6**)*

EDC–HCl salt, (**5**) was used. Yield: 112 mg (83%). m.p. 252 °C. MS (ESI) negative: *m/z* 314; IR (KBr) ν_{max} = 3443, 3375 (s) [(N–H)], 3028 (w), 2924 (s), 2860, 2821, 2777 (m) [*ν*(C–H)], 2485 (s) [*ν*(B–H)], 1619 (s) [*ν*(guanidinium)]; ^{1}H NMR δ_H(DMSO) = −0.5–2.0 (m, 11H, *H*–B), 1.08 (t, 3H, C*H*$_3$–CH$_2$–N), 1.26 (q, 2H, CH$_3$–C*H*$_2$–N), 1.56 (m, 2H, –CH$_2$–C*H*$_2$–CH$_2$–), 2.85 (s, 6H, (C*H*$_3$)$_2$N), 3.07 (s, 12H, TMA) 3.13 (m, 2H, –C*H*$_2$–N=C), 3.15 (m, 2H, –C*H*$_2$–N(CH$_3$)$_2$), 5.1 (s, 1H), 6.8, 9.3 (s, 1H)(N–*H*); ^{11}B{^{1}H} NMR δ_B^{11}(DMSO) = −6.27(s, 1B, *B*–N), −15.84 (11B); ^{13}C{^{1}H} NMR δ_C(DMSO) = 14.4 (*C*H$_3$–CH$_2$–N), 15.04 (–CH$_2$–*C*H$_2$–CH$_2$–), 20.09 (CH$_3$–*C*H$_2$–N), 23.91 (–*C*H$_2$–N(CH$_3$)$_2$), 43.26 ((*C*H$_3$)$_2$N), 55.22 (TMA), 58.45 (–*C*H$_2$–N=C), 156.43 (N$_2$=*C*=N).

*3.6. N′,N″-dicyclohexyl-guanidinium-undecahydro-closo-dodecaborate (**4**)*

Dicyclohexylcarbodiimide (**3**) was used. Yield: 135 mg (86%). m.p. 190 °C. MS (ESI) negative: *m/z* 364; IR (KBr) ν_{max} = 3347 (m) [*ν*(N–H)], 2924 (s), 2852 (m) [*ν*(C–H)], 2493 (s) [*ν*(B–H)], 1623 (s) [*ν*(guanidinium)]; ^{1}H NMR δ_H(DMSO) = −0.2–2.0 (m, 11H, *H*–B), 1.2 (m, 4H, CH$_2$–(C*H*$_2$)$_2$–(CH$_2$)$_2$–CH–N) 1.6 (m, 4H, CH$_2$–(CH$_2$)$_2$–(C*H*$_2$)$_2$–CH–N), 1.7 (m, 2H, C*H*$_2$–(CH$_2$)$_2$–(CH$_2$)$_2$–CH–N), 3.07 (s, 12H, TMA), 3.45 (m, 1H, –C*H*–N=C), 6.87 (d, 2H, *H*–N$^+$–*H*), ^{11}B{^{1}H} NMR δ_B^{11}(DMSO) = −5.89 (s, 1B, *B*–N), −15.92 (11B); ^{13}C{^{1}H} NMR δ_c(DMSO) = 25.06 + 25.35 (CH$_2$–(*C*H$_2$)$_2$–(CH$_2$)$_2$–CH–N), 25.91 + 26.19 (*C*H$_2$–(CH$_2$)$_2$–(CH$_2$)$_2$–CH–N), 33.26 + 34.22 (CH$_2$–(CH$_2$)$_2$–(*C*H$_2$)$_2$–CH–N), 48.37 + 50.05 (–*C*H–N=C), 55.27 (TMA), 154.83 (N$_2$=*C*=N).

*3.7. N′,N″-bis-(ω-dimethylaminopropyl)-guanidinium-undecahydro-closo-dodecaborate (**8**)*

N,*N*′-(ω-dimethylaminopropyl)-carbodiimide (**7**) was used. Yield: 155 mg (97%). m.p. 220 °C. MS (ESI) negative: *m/z* 371; IR (KBr) ν_{max} = 3367 (s) [*ν*(N–H)], 2952, 2821 (m) [*ν*(C–H)], 2481 (s) [*ν*(B–H)], 1631 (s) [*ν*(guanidinium)]; ^{1}H NMR δ_H(DMSO) = −0.5–2.0 (m, 11H, *H*–B), 0.73 (s, 2H, N–*H*), 1.46 (m, 4H, –CH$_2$–C*H*$_2$–CH$_2$–), 2.07 (s, 12H, C*H*$_3$–N–C*H*$_3$), 2.18 (t, 4H, –C*H*$_2$–N(CH$_3$)$_2$), 2.93 (m, 4H, –C*H*$_2$–N=C), 3.07 (s, 12H, TMA), 7.93 (s, 1H, N–*H*); ^{11}B{^{1}H} NMR δ_B^{11}(DMSO) = −5.71 (s, 1B, *B*–N), −15.40/−15,86 (11B); ^{13}C {^{1}H} NMR δ_C(DMSO) = 31.58 (–CH$_2$–*C*H$_2$−CH$_2$–), 45.59 (–*C*H$_2$–N(CH$_3$)$_2$), 44.67 ((*C*H$_3$)$_2$N), 55.25(–*C*H$_2$–N=C), 55.33 (TMA), 166.82 (N$_2$=*C*=N).

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