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Nucleophilic addition of amino acid esters to nitrilium derivatives of *closo*-decaborate anion

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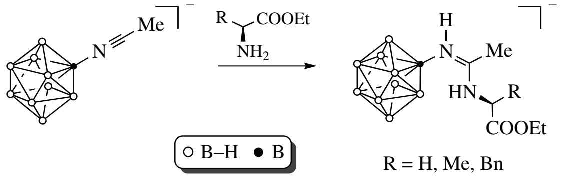
The addition of amino acid esters to $[2\text{-}B_{10}H_9\text{–}N{\equiv}CMe]^-$ Bu_4N^+ salt under mild conditions affords amidine *closo*-decaborates in high yields. The structure of compound $(PPh_4)[2\text{-}B_{10}H_9NH{=}C(Me)NHCH_2COOEt]$ was elucidated by single-crystal XRD analysis.



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Since the first synthesis of boronophenylalanine (BPA) was reported as early as 1958,[1] the use of transport amino acid groups to create BNCT agents has been actively developed since tumour cells require high quantity of amino acids to maintain metabolism. There are two general pathways to design boron-containing bioinorganic systems based on amino acids. The first approach is based on modification of boronophenylalanine and its structural analogues.[2–4] The second one involves the creation of conjugates from carboranes or boron cluster anions and amino acids or oligopeptides.[5,6] In addition, various ways of drug delivery were discovered (*e.g.* liposomes,[7] polypeptides,[8] and polymers[9–11]).

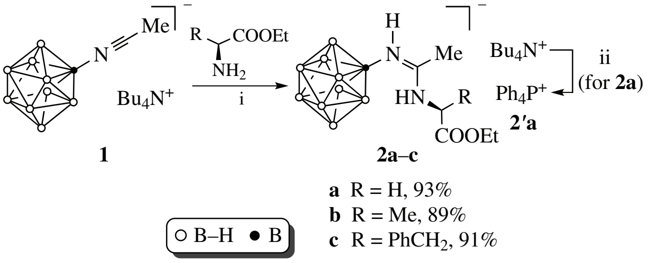
closo-Borate anions are attracting attention as platforms for drug design due to their stability, low toxicity, and significant hydrophilicity.[12–14] Methods based on the functionalization of *exo*-polyhedral substituents of the cluster are often used to modify boron cluster anions.[15–17] The nitrilium derivatives of *closo*-borates were known as convenient precursors for boron cluster modification.[18–20] The process of nucleophilic addition to nitrile substituent has been used for the modification of various functional groups under mild conditions.[21,22] The principal approaches to modifying such nitrilium derivatives are reviewed.[23] Previously, reactions between nitrilium derivatives of *closo*-borate anion and organic amines were investigated in our research group. The reactions with primary amines proceeded regio- and stereospecifically. During the reaction, only one nucleophile molecule was attached, and the resulting amidine possessed *Z*-configuration of the nitrogen–carbon double bond.

In the present work, we extended the elaborated approach for the preparation of conjugates based on nitrilium derivatives of the *closo*-decaborate anion and esters of some natural amino acids. Non-covalent interactions in the synthesized compounds were theoretically studied. The reaction of acetonitrile derivative of *closo*-decaborate anion **1** with glycine, alanine and phenylalanine ethyl esters is outlined in Scheme 1.

In the presence of slight excess of the nucleophilic reagent, the reaction is finished within 2 h in refluxing dichloromethane. The main features of amino acid ester addition are very similar to those observed in the case of ordinary amines.[23] According to NMR spectra, the yield of the target products **2a–c**, substituted amidines stabilized by the boron polyhedra, is close to quantitative. Acyclic amidines stabilized by the formation of coordination bonds can find a use as catalysts and components of drugs.[24,25] As in the case of amines, the amidine fragment is in the *Z*-configuration, which is stabilized by an intramolecular dihydrogen bond.

The reaction course was controlled using ^{11}B NMR spectroscopy. In the spectra of products, signals from apical boron atoms appear in the ranges of 3.1–2.9 ppm [B(10), $I = 1$] and –4.1 to –4.2 ppm [B(1), $I = 1$], which is typical of monosubstituted amidine borates.[26] We observed significant high frequency shift of signal B(1) compared to the signal found in the spectrum of the initial nitrilium derivative. The main reason of this phenomena is the presence of an intramolecular dihydrogen bond in the product. The signal from the substituted boron atom B(2) is observed at –15.0 to –15.1 ppm, signals from the unsubstituted equatorial vertices of the boron cluster resonate at –23.6, –23.7, –26.7 and –26.8 ppm.

The structure of the synthesized conjugates **2a–c** was determined using multinuclear NMR spectroscopy. In the ^{1}H NMR spectra of the obtained compounds, the amidine



Scheme 1 *Reagents and conditions*: i, CH_2Cl_2, reflux, 2 h; ii, $NaBPh_4$, H_2O, room temperature, then PPh_4Cl, H_2O, room temperature.

fragment is represented by two signals. The proton of the imino group is located in the region of 6.47–6.39 ppm, and the proton of the amino group is located at 8.81–8.60 ppm. Proton signals from the Me-substituent of the nitrile group resonate at 2.02–2.00 ppm. The amino acid residue is represented by signals from protons at the α-carbon atom in the region of 4.15–4.37 ppm, signals of substituents at the α-atom, and signals from the ethoxy group. Note that in the obtained borylated amidines **2a**–**c**, the substituent has a rigid spatial structure, which affects the shape of signals in the ^{1}H NMR spectra. Additional J_{NHCH} constants (~5–6 Hz) are obsreved for the protons at the α-carbon atom of the amino acid residue, which is characteristic of structurally rigid peptides and zwitterionic forms in a synclinal conformation (with values of dihedral angles H–N–C–H 30–60°).[27]

In the ^{13}C NMR spectra, the most characteristic signals are those from the carboxylic carbon atom at 171.3–168.8 ppm and signals for the amidine group at 166.2–164.8 ppm and carbon atoms for the methyl group at 19.5–18.5 ppm.

The crystal structure for compound **2′a** ($\mathrm{Bu_4N^+}$ cation was replaced by $\mathrm{Ph_4P^+}$) was established by X-ray diffraction analysis.[†] The structure consists of cations and anions; the anions are connected into infinite polymer chains and form channels with a square cross-section, inside which cations are located (for details, see Online Supplementary Materials, Figure S1). The $[2\text{-}\mathrm{B_{10}H_9NH{=}C(Me)NHCH_2COOEt}]^-$ anion is monosubstituted *closo*-decaborate with an equatorial position of the substituent. The geometry of the clusters in the crystal structure is slightly distorted relative to the unsubstituted anion $[\mathrm{B_{10}H_{10}}]^{2-}$.[28] The substituent is located in the equatorial position. The B(2)–N(1) bond length is 1.527 (3) Å, which corresponds to the length of an ordinary bond.[29,30] As stated above, the amidine fragment is *Z*-configured and is stabilized by an intramolecular dihydrogen bond (Figure 1).

The bond lengths N(1)–C(1) [1.308(3) Å] and C(1)–N(2) [1.318(3) Å] indicate the presence of conjugation and delocalization of the positive charge of the substituent.[31] These parameters are similar to those for analogous borylated amidines described previously.[26] The angles at amidine carbon are close to 120° [N(1)–C(1)–N(2) 120.7(2)°, N(2)–C(1)–C(2) 119.2(2)°, C(2)–C(1)–N(1) 120.1(2)°], which indicates its sp^2-hybridized character. The bond lengths and angles of the ester fragment are in good agreement with those for amino acid esters.

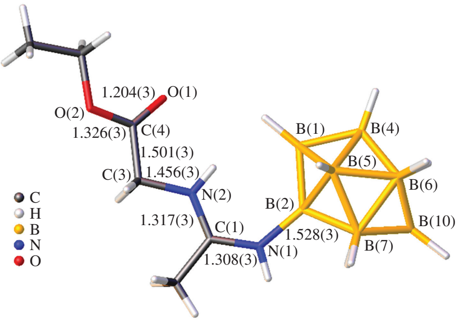


Figure 1 Structure of anion in salt **2′a**.

An essential feature of the structure is the presence of two types of dihydrogen bonds, intramolecular and intermolecular. The intramolecular contact between the apical hydrogen atom of the cluster and the proton of the amino group of glycine B(1)–H(1)···H(2D)–N(2) is 1.91 Å, which is significantly less than the sum of the van der Waals radii of hydrogen atoms (2.40 Å).[32–34] It is noteworthy that in case of borylated amidines previously described, the contacts B(1)–H(1)···H(2D)–N(2) are longer and lie in interval 2.04–2.07 Å.[26] Besides, this interaction determines the nucleophilic addition process stereospecificity and product formation with the *Z*-configuration of the substituent double bond. The existence of the dihydrogen bond causes the red shift and the broadening of the N–H stretching band in IR spectra.[35] The N–H mode which lies in region of 3250–3240 cm^{-1} can be ascribed to non-covalent interaction, while in the ethyl acetylglycinate similar absorption band appears at 3305 cm^{-1}.[36]

Another relatively short intermolecular contact C(3)–H(3A)···H(9)–B(9) is 2.45 Å (which is the boundary value for dihydrogen interactions) also characterizes the effects of crystalline packing. However, it causes the formation of infinite polymer chains from substituted anions (Figure 2). In addition, the C(1)–N(2)–C(3)–C(4) fragment possesses *anti*-conformation, in contrast to the synclinal conformations in solutions, according to NMR spectra.

Thus, the inspection of the crystallographic data reveals the presence of unusual short contact N–H···H–B (1.91 Å) in the solid-state XRD structure. In order to clarify whether the crystal packing effects explain short contact N–H···H–B of the studied compound, or this is a specific property of this molecule, quantum chemical calculations at the ωB97X-D3/6-31++G(d,p) level of theory were performed (for computational details and Cartesian atomic coordinates of model structure, see Online Supplementary Materials). Results of full geometry optimization of model structure $[2\text{-}\mathrm{B_{10}H_9NH{=}C(Me)NHCH_2COOEt}]^-$ using experimental XRD geometry as the starting point show that appropriate short contact N–H···H–B was elongated up to 2.50 Å during the geometry optimization procedure. Thus, these crystal packing induced non-covalent interactions are repulsive.

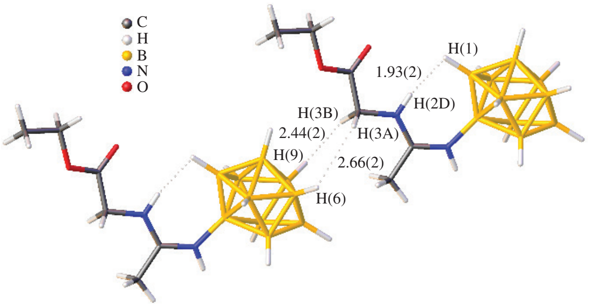


Figure 2 Dihydrogen bonds in the crystal structure of salt **2′a**.

[†] *Crystal data for* **2′a**. $\mathrm{C_{36}H_{55}B_{10}N_2O_3P}$ (M = 702.89), monoclinic, space group $P2_1/n$, 100 K, a = 9.9522(3), b = 18.0265(7) and c = 21.1420(8) Å, β = 93.556(2)°, V = 3785.6(2) Å^3, Z = 4, d_{calc} = 1.233 g cm^{-1}, μ(MoKα) = 0.112 mm^{-1}, F(000) = 1496.0. Total of 33729 reflections were collected (8651 independent reflections, R_{int} = 0.0860) and used in the refinement, which converged to wR_2 = 0.1501, GOOF = 1.022 for all independent reflections [R_1 = 0.0522 was calculated for 5933 reflections $I > 2\sigma(I)$].

X-ray diffraction experiments were conducted at the Center for collective use of physical methods of research of IPCE RAS on a Bruker KAPPA APEX II[40] automatic four-circle diffractometer with an area detector (MoKα radiation) at 20 °C. The unit cell parameters refined on all the data.[41] The structure was solved by the direct method[42] and refined by full-matrix least-squares on F^2 for all data in the anisotropic approximation for all non-hydrogen atoms.[43] H atoms of a borohydride cluster were located from difference Fourier map and refined with isotropic temperature factors equal to 1.2 U_{eq}(B). H atoms of the organic part of the structure were placed in geometrically calculated positions with isotropic temperature factors equal to 1.2 U_{eq}(C) for CH$_2$ groups and 1.5 U_{eq}(C) for the Me ones. The absolute structure was not determined. Images were created using a package OLEX2.[44]

CCDC 2008587 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

We studied the nature of intramolecular non-covalent interactions between the glycine ester moiety and the boron cluster in the optimized equilibrium model structure $[2\text{-}B_{10}H_9NH{=}C(Me)NHCH_2COOEt]^-$ using QTAIM analysis. Quantum theory of atoms in molecules (QTAIM) is useful in investigations of non-covalent interactions and provides information about electron density distribution straightforwardly and clearly.[37–39] Results of QTAIM analysis reveal that there is contact not between the H···H atoms, but between the H···B atoms in $[2\text{-}B_{10}H_9NH{=}C(Me)\ NHCH_2COOEt]^-$ (for details see Online Supplementary Materials, Figure S2). The appropriate N–H···B non-covalent interactions in the optimized equilibrium model structure are characterized by a small value of electron density $\rho(r)$ (0.021 e Å^{-3}) and positive value of Laplacian of electron density $\nabla^2\rho(r)$ (0.053 e Å^{-5}). The value of total electron energy in the corresponding bond critical point between H and B atoms is almost equal to zero; the value of ellipticity of electron density is relatively high (2.678), and the value of electron delocalization index is 0.010.

In summary, the reaction of nitrilium derivative $[2\text{-}B_{10}H_9\text{–}N{\equiv}C\text{–}Me]^-$ with amino acid esters was explored. The process was regio- and stereoselective to afford exclusively *Z*-configured amidine substituent in products **2a–c**. This selectivity is determined by the presence of a dihydrogen bond, which was also evaluated by QTAIM analysis.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.018.

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