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Investigation of zwitterionic 7-ammonium-7,9-*nido*-*m*-carborane

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Abstract—Zwitterionic ammonium-substituted *nido* *m*-carborane (7-NH$_3$-7,9-*nido*-carborane), a novel boron moiety for boron neutron capture therapy, was synthesized and its chemical properties were investigated. This boron cluster system showed unique properties by reacting with carbonyl groups of ketones and aldehydes to generate the corresponding iminium-substituted *nido* *m*-carboranes.

Closo and *nido* carboranes have been used in the design of boron-delivery agents for boron neutron capture therapy (BNCT) because of their high boron content.[1,2] More recently, *closo* carboranes have also found application in conventional drug design as replacements for hydrophobic aromatic groups.[3] However, the low water-solubility of *closo* carboranes and the low lipid-solubility of *nido* carboranes have limited their biological and medical applications. Recently, we reported that zwitterionic NH$_3^+$-substituted *nido* *m*-carboranyl thymidine derivatives had an unique hydrophilicity/hydrophobicity balance unlike those of hydrophobic *closo* carboranyl and hydrophilic *nido* carboranyl thymidine derivatives.[4] The basis for the unusual physicochemical properties of zwitterionic *nido* *m*-carborane is the intramolecular charge-compensation between the positively charged NH$_3^+$ group and the negatively charged carborane cage.

Nido *o*-carboranes substituted at a boron atom with charge-compensating ligands such as the sulfonium-, and phosphonium groups have been described previously.[5–7] In this report, we describe for the first time chemical features of *nido* *m*-carborane substituted at a carbon atom with a charge-compensating ammonium group.

Compound **1** was prepared from *m*-carborane (1,7-C$_2$B$_{10}$H$_{12}$) in three steps as described previously.[8] Deprotection of the *tert*-butoxycarbonyl (Boc) group of compound **1** was achieved by treatment with trifluoroacetic acid (TFA) at room temperature for 12 h to afford 1-amino-1,7-carborane (**2**) in 85% yield (Scheme 1). Reaction of compound **2** with tetrabutylammonium fluoride (TBAF) in THF at 70 °C for 1.5 h afforded zwitterionic *nido* *m*-carborane (**3**[†]) in 61% yield.

During ^{11}B NMR studies with compound **3** in acetone-d^6, we observed time-dependant disappearance and emergence of signals, as shown in Figure 1. The solution of **3** in acetone-d^6 at 180 min contained a UV-active compound that could be detected at 254 nm via

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[†] 7-Ammonium-7,9-*nido*-*m*-carborane (**3**): To a solution of TBAF hydrate (2.50 g, 7.94 mmol) in THF (25 mL) was slowly added a solution of compound **2** (420 mg, 2.64 mmol) in THF (5 mL) at 70 °C. The solution was stirred at the same temperature for 1.5 h. After cooling to room temperature, distilled water (10 mL) was added, followed by evaporation of excess THF. Aqueous 3 N hydrochloric acid (3 mL) was added to adjust the pH to 2–3. The solution was extracted with ethylacetate (30 mL × 2) and the combined ethylacetate layers were washed with brine and dried over magnesium sulfate. After filtration and evaporation, the residue was purified by silica gel column chromatography (hexanes/ethylacetate, 1:1) to give compound **3** in 61% (240 mg, 1.61 mmol) yield. R_f 0.24; ^{1}H NMR (CD$_3$CN) δ −1.99 (br s, 1H, bridging H), 1.43 (br s, 1H, H–C$_{\text{carborane}}$), 6.04 (br s, 3H, NH_3); ^{13}C NMR (CD$_3$CN) δ 32.83 (H–$C_{\text{carborane}}$), 53.77 (N–$C_{\text{carborane}}$); ^{11}B NMR (CD$_3$CN) δ −33.59, −31.95, −20.07, −19.53, −15.75, −3.60, −2.82, 0.82; IR (cm^{-1}) 3215 (s), 3189, 2535 (s), 1467 (s); MS (HR-ESI) C$_2$H$_{14}$B$_9$N$_1$ (M+Na)$^+$ calcd 173.1900, found: 173.1897.

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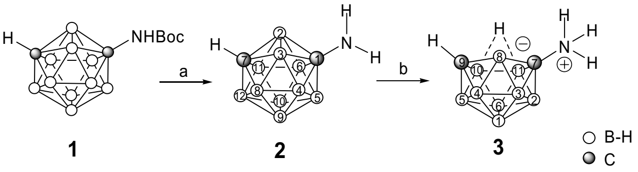
UV/TLC analysis. To explore potential solvent effects on ^{11}B NMR chemical shifts and the formation of an UV-active component, the capacity of various solvents (acetone, methylethylketone, acetonitrile, benzene, chloroform, diethylether, dimethylsulfoxide, ethylacetate, hexane, methanol, tetrahydrofuran, and water) to form an UV-active complex with **3** was studied by UV/TLC analysis. Only the ketones (acetone and methylethylketone) interacted with **3** to form UV-active species. Therefore, we carried out the reaction of **3** with acetone at room temperature for 6 h to yield the iminium-type compound **4**[‡] in quantitative yield (Scheme 2).



Scheme 1. Synthesis of zwitterionic *nido m*-carborane (**3**). Reagents and conditions: (a) CF_3COOH, dichloromethane, rt, 12 h, (b) TBAF, THF, 70 °C, 1.5 h.

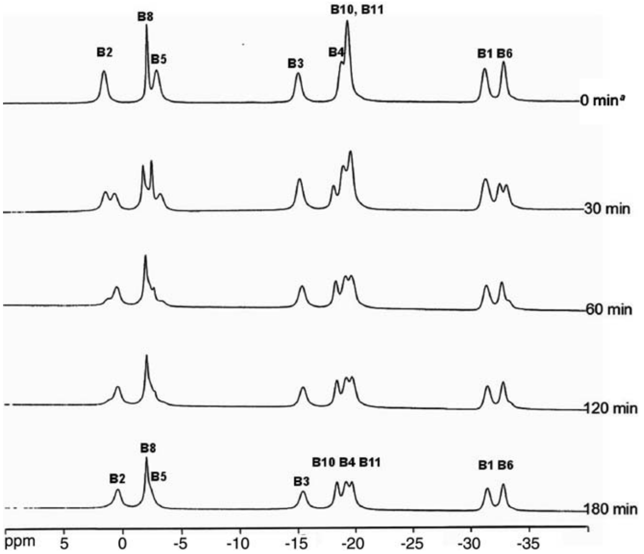
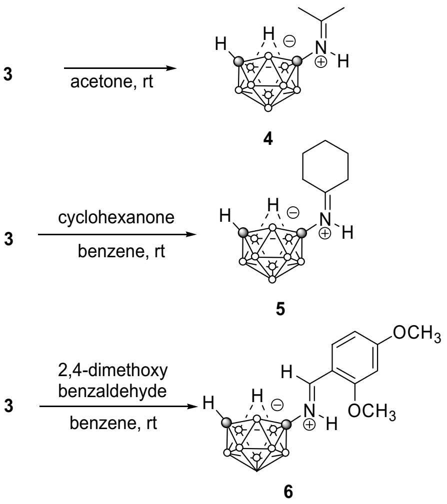


Figure 1. Proton-decoupled ^{11}B NMR spectra of compound **3** in acetone-d^6 solution recorded as a function of time. [a]The 0 min spectrum was recorded immediately after dissolving **3** in acetone-d^6.



Scheme 2. Generation of iminium-substituted *nido m*-carboranes (**4**–**6**).

Following this, we explored the reactivity of **3** with several ketones (e.g., acetophenone, cyclohexanone, benzophenone, methylethylketone) and aldehydes (e.g., acrolein, acetaldehyde, anisaldehyde and 2,4-dimethoxybenzaldehyde) in benzene without addition of any catalyst. With the exception of benzophenone, all of the tested ketones and aldehydes generated iminium-type compounds as demonstrated by UV/TLC inspection at 254 nm. However, carboxylic acids (e.g., benzoic acid, cinnamic acid) treated with **3** did not generate iminium-type compounds. Iminium compounds **5**[§] and **6**[¶] (Scheme 2), derived from cyclohexanone and 2,4-dimethoxybenzaldehyde, precipitated from benzene and their structures were fully confirmed by ^{1}H, ^{13}C NMR and HRMS. The iminium-substituted carboranes (**4**–**6**) were fairly stable in anhydrous solvents such as

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[‡] 7-Isopropylideneammonium-7,9-*nido-m*-carborane (**4**): Compound **3** (50 mg, 0.34 mmol) was dissolved in anhydrous acetone (5 mL) and stirred at room temperature for 6 h. After evaporation of excess acetone, the residue was purified by silica gel flash column chromatography (hexanes/ethylacetate, 1:1) to give compound **4** in quantitative yield. R_f 0.27; ^{1}H NMR (CD_3CN) δ −1.92 (br s, 1H, bridging H), 1.54 (br s, 1H, *H*–$C_{carborane}$), 2.35 (s, 3H, C*H*$_3$), 2.51 (s, 3H, C*H*$_3$), 10.37 (br s, 3H, C═N*H*); ^{13}C NMR (CD_3CN) δ 23.09 (*C*H$_3$), 25.56 (*C*H$_3$), 32.64 (H–$C_{carborane}$), 61.59 (N–$C_{carborane}$), 193.08 (*C*═N); ^{11}B NMR (CD_3CN) δ −32.93, −31.59, −19.75, −19.33, −18.47, −15.59, −2.48, −2.04, 0.21; IR (cm^{-1}) 3268 (s), 2529 (s), 1662 (s), 1424, 1003; MS (HR-ESI) $C_5H_{18}B_9N_1$ $(M+Na)^+$ calcd 213.2215, found: 213.2216.

[§] 7-Cyclohexylideneammonium-7,9-*nido-m*-carborane (**5**): Compound **3** (100 mg, 0.68 mmol) and cyclohexanone (0.13 mL, 1.36 mmol) were dissolved in anhydrous benzene (3 mL) and stirred at room temperature for 6 h. The precipitated solid was collected by filtration and washed with hexanes to give compound **5** in 68% yield. ^{1}H NMR (CD_3OD) δ −1.92 (br s, 1H, bridging H), 1.43 (br s, 1H, *H*–$C_{carborane}$), 1.72–1.77 (m, 2H, CH_2), 1.82–1.89 (m, 2H, CH_2), 1.90–1.99 (m, 2H, CH_2), 2.63–2.67 (m, 2H, CH_2), 2.89–2.93 (m, 2H, CH_2); ^{13}C NMR (CD_3OD) δ 25.30 (CH_2), 28.08 (CH_2), 28.72 (CH_2), 33.15 (H–*C*$_{carborane}$), 33.75 (CH_2), 35.82 (CH_2), 62.57 (N–*C*$_{carborane}$), 196.08 (*C*═N); MS (HR-ESI) $C_8H_{22}B_9N$ $(M+Na)^+$ calcd 252.2561, found: 252.2570.

[¶] 7-(2,4-Dimethoxy)benzylideneammonium-7,9-*nido-m*-carborane (**6**): Compound **3** (100 mg, 0.68 mmol) and 2,4-dimethoxybenzaldehyde (0.2 mL, 1.20 mmol) were dissolved in anhydrous benzene (3 mL) and stirred at room temperature for 6 h. The precipitated solid was collected by filtration and washed with hexanes to give compound **6** in 61% yield. ^{1}H NMR (CD_3CN) δ −1.92 (br s, 1H, bridging H), 1.57 (br s, 1H, *H*–$C_{carborane}$), 3.93 (s, 3H, CH_3), 4.04 (s, 3H, CH_3), 6.67 (d, 1H, ArH, $J = 2.2$ Hz), 6.75 (dd, 1H, ArH, $J = 8.8, 2.2$ Hz), 7.67 (d, 1H, ArH, $J = 8.8$ Hz), 8.45 (s, 1H, C*H*═N), 10.68 (br s, 1H, N*H*); ^{13}C NMR (CD_3CN) δ 33.02 (H–*C*$_{carborane}$), 57.32 (O*C*H$_3$), 57.90 (O*C*H$_3$), 65.10 (N–*C*$_{carborane}$), 99.74 (ArC), 109.30 (ArC), 109.99 (ArC), 139.86 (ArC), 163.86 (*C*═N), 164.88 (ArC), 167.37 (ArC); MS (HR-ESI) $C_{11}H_{22}B_9NO_2$ $(M+Na)^+$ calcd 320.2458, found: 320.2447.

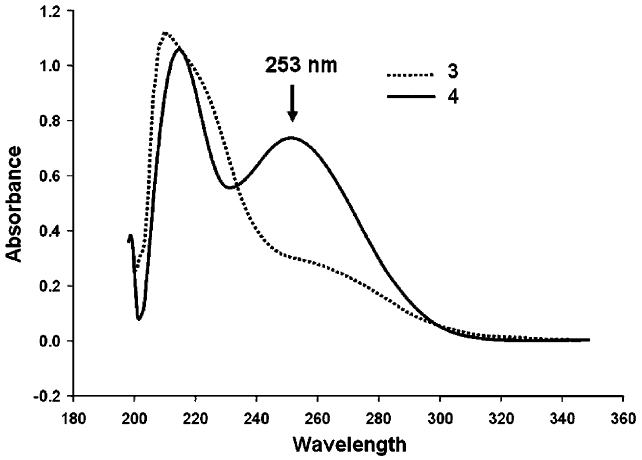

Figure 2. UV absorption spectra of compounds **3** and **4** (10^{-5} M solutions in methanol).

methanol, benzene, and dichloromethane. However, they were easily hydrolyzed under very mild condition (5% aqueous $NaHCO_3$/EtOH, rt, 2 h) to regenerate **3**.

The UV absorption spectra (Fig. 2) of 10^{-5} M solutions of compounds **3** and **4** in methanol showed bands at the 220 nm and 253 nm. Only the 220 nm band is characteristic for the 3D σ-aromatic system of carboranes.[9,10] The band at 253 nm had significant intensity only in the case of **4** whereas it was reduced to merely a shoulder in **3**. A similar UV absorption shift was reported previously for the σ-aromatic *closo p*-carborane cluster when conjugated with π-aromatic benzene.[11]

To the best of our knowledge, however, compound **4** is the first example of stable conjugation of a 3D σ-aromatic system of a *nido* carborane cluster with a non-aromatic iminium group, resulting in a significant alteration in UV absorption. We hypothesize that an electron delocalization from the negatively charged *nido m*-carborane cluster to the iminium double bond in compound **4** is responsible for this bathochromic shift.

Theoretical calculations of compounds **3** and **4** were performed using Gaussian 03[12] running on an Itanium 2 Cluster at Ohio Super Computer Center. Both structures were fully optimized at the B3LYP/6-31G* level. Molecular Orbital (HOMO/LUMO) calculations for **3** and **4** at the same level (Fig. 3) supported the bathochromic shift of **4** observed in the UV experiment. In the case of **4**, alternating-phase orbitals with similar sizes stemming from iminium nitrogen and the *nido* carborane cluster overlapped completely. In particular, the HOMO of **4** showed a pattern of overlapping orbitals similar to that of benzene. In contrast, there is no significant overlap of alternating-phase orbitals between carborane cluster and nitrogen in compound **3**. The energy gap between HOMO and LUMO of compound **4** was 4.98 eV, which is notably smaller than that of compound **3** (5.52 eV).

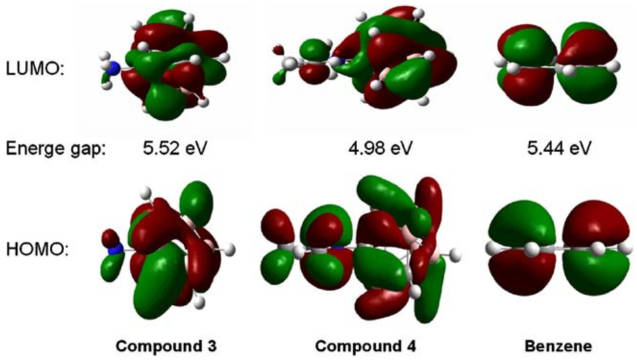

Figure 3. Diagrams of HOMO and LUMO for **3**, **4**, and benzene.

In summary, the zwitterionic ammonium-substituted *nido m*-carborane cluster (**3**) was synthesized. The novel zwitterionic *nido m*-caborane (**3**) exhibited unique chemical properties by reacting with the carbonyl groups of ketones or aldehydes without addition of acid catalyst at room temperature. However, due to the lack of stability of iminium-substituted carboranes under aqueous conditions, we do not anticipate any problems for the use of compound **3** as a boron-carrying moiety in conventional and BNCT drug development. The unique chemical properties of the novel zwitterionic NH_3^+-*nido m*-carborane structure may also lead to a wide range of novel applications in organic chemistry and boron chemistry.

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