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Unexpected Formation of an Azetidine–Carborane Derivative by Dehydration of *N*-(1,12-Dicarba-*closo*-dodecaboran-1-yl)formamide. The First X-ray Structure of a 2,3-Bis(imino)azetidine

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Efforts to dehydrate (1,12-dicarba-*closo*-dodecaboran(12)-1-yl)formamide ($a = 6.685(2)$ Å, $b = 12.877(4)$ Å, $c = 12.547(4)$ Å, $\alpha = \gamma = 90°$, $\beta = 90.724(11)°$, $V = 1080.8(6)$ Å^3, $Z = 4$) resulted in the formation of a series of unexpected products. Addition of the Burgess reagent to the formamide, for example, led to the isolation of the corresponding methyl carbamate ($a = 11.529(8)$ Å, $b = 11.529(8)$ Å, $c = 11.402(12)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1516(2)$ Å^3, $Z = 4$), while treatment with triphosgene, a well-known dehydrating agent, resulted in the formation of a highly unusual 2,3-bis(*p*-carboranylimino)azetidine derivative. This particular compound, in the presence of Re(I), was hydrolyzed to give the corresponding amide, which is the first example of a 2,3-bis(imino)azetidine that has been characterized crystallographically ($a = 38.496(13)$ Å, $b = 11.920(4)$ Å, $c = 27.523(10)$ Å, $\beta = 127.050(5)°$, $V = 10079(6)$ Å^3, $Z = 8$).

Introduction

The coordination chemistry of functionalized carboranes continues to be an intriguing and active area of research.[1] This can, in part, be attributed to the fact that one can selectively functionalize both the CH and BH vertices of the *o*-, *m*-, and *p*-dicarba-*closo*-dodecaborane isomers with a range of donor groups using, for the most part, well-established synthetic methods.

Our group recently reported a new method for the synthesis of isonitrile derivatives of *o*-carborane.[2] In addition to investigating the influence of the carborane moiety on the metal-binding properties of the isonitrile group, we were also interested in using the ligands to prepare metal-based boron neutron capture therapy (BNCT)[3] and boron neutron capture synovectomy (BNCS)[4] agents. BNCT and BNCS are binary therapy techniques for cancer and arthritis, respectively, which require the selective delivery of significant quantities of boron to the target cells to be efficacious.[5] We envisioned using the isonitrile ligands to prepare stable metal complexes containing multiple (3−6) carborane substituents. One of the advantages of this approach, in addition to the elevated boron content, is the ability to replace the central metal atom with a radiometal. This will allow for biodistribution and treatment-planning studies to be carried out using positron emission tomography (PET) and/or single-photon emission computed tomography (SPECT) without changing the overall structure of the compound under investigation. Furthermore, the remaining carborane CH vertices can be readily derivatized with a variety of different biomolecules to facilitate targeting.

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(1) (a) Nabakka, J. M.; Harwell, D. E.; Knobler, C. B.; Hawthorne, M. F. *J. Organomet. Chem.* **1998**, *550*, 423. (b) Lee, T.; Lee, S. W.; Jang, H. G.; Kang, S. O.; Ko, J. *Organometallics* **2001**, *20*, 741. (c) Sterzik, A.; Rys, E.; Blaurock, S.; Hey-Hawkins, E. *Polyhedron* **2001**, *20*, 3007. (d) Paavola, S.; Teixidor, F.; Viñas, C.; Kivekäs, R. *J. Organomet. Chem.* **2002**, *645*, 39. (e) Won, J.-H.; Kim, D.-H.; Kim, B. Y.; Kim, S.-J.; Lee, C.; Cho, S.; Ko, J.; Kang, S. O. *Organometallics* **2002**, *21*, 1443.
(2) Valliant, J. F.; Schaffer, P. *J. Inorg. Biochem.* **2001**, *85*, 43.
(3) (a) Locher, G. L. *Am. J. Roentgenol. Radium Ther.* **1936**, *36*, 1. (b) Soloway, A. H.; Tjarks, W.; Barnum, A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515.
(4) (a) Yanch, J. C.; Shortkroff, S.; Shefer, R. E.; Johnson, S.; Binello, E.; Gierga, D.; Jones, A. G.; Young, G.; Vivieros, C.; Davison, A.; Sledge, C. *Med. Phys.* **1999**, *26*, 364. (b) Watson-Clark, R. A.; Banquerigo, M. L.; Shelly, K.; Hawthorne, M. F.; Brahn, E. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 2531.
(5) Hawthorne, M. F. *Mol. Med. Today* **1998**, April, 174.

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Table 1. Crystallographic Data for Compounds **2**, **3**, and **5**

	2	**3**	**5**
empirical formula	$C_3H_{13}B_{10}NO$	$C_4H_{15}B_{10}NO_2$	$C_{12}H_{46}ON_4B_{40}$
fw	187.24	219.20	696.77
temp, K	173(2)	173(2)	173(2)
wavelength, Å	0.71073	0.71073	0.71073
cryst syst	monoclinic	tetragonal	monoclinic
space group	*P*2(1)/*n*	*P*4(1)	*C*2/*c*
unit cell dimensions	$a = 6.685(2)$ Å	$a = 11.529(8)$ Å	$a = 38.496(13)$ Å
	$b = 12.887(4)$ Å	$b = 11.529(8)$ Å	$b = 11.920(4)$ Å
	$c = 12.547(4)$ Å	$c = 11.402(12)$ Å	$c = 27.523(10)$ Å
	$\alpha = 90°$	$\alpha = 90°$	$\alpha = 90°$
	$\beta = 90.724(11)°$	$\beta = 90°$	$\beta = 127.050(5)°$
	$\gamma = 90°$	$\gamma = 90°$	$\gamma = 90°$
vol, Å^3	1080.8(6)	1516(2)	10079(6)
Z	4	4	8
density(calcd), Mg/m^3	1.151	1.058	1.053
abs coeff, mm^{-1}	0.060	0.060	0.053
F(000)	384	496	3279
cryst size, mm^3	0.1 × 0.15 × 0.3	0.8 × 0.15 × 0.40	0.15 × 0.05 × 0.03
θ range for data collection, deg	2.27−27.47	2.50−24.00	1.33−24.71
index ranges	$-8 \le h \le +8$	$-13 \le h \le +13$	$-41 \le h \le +45$
	$-16 \le k \le +16$	$-12 \le k \le +12$	$-14 \le k \le +14$
	$-16 \le l \le +15$	$-12 \le l \le +13$	$-32 \le l \le +32$
no. of reflns collected	8008	6639	36278
no. of independent reflns	2460 [*R*(int) = 0.0431]	2177 [*R*(int) = 0.0953]	8586 [*R*(int) = 0.1050]
completeness to θ, %	99.2	94.8	100
abs correction	semiempirical	semiempirical	semiempirical
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2
no. of data/restraints/params	2460/0/189	2177/1/209	8586/12/857
goodness of fit on F^2	1.036	0.982	1.025
final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0469	R1 = 0.0755	R1 = 0.0862
	wR2 = 0.1141	wR2 = 0.1741	wR2 = 0.1972
R indices (all data)	R1 = 0.0816	R1 = 0.1333	R1 = 0.1835
	wR2 = 0.1302	wR2 = 0.2066	wR2 = 0.2392
extinction coeff	0.004(3)	0.015(6)	0.00065(14)
largest diff peak and hole, e·Å^{-3}	0.241 and 0.224	0.290 and 0.206	0.378 and 0.214

During the synthesis of the *o*-carborane isonitriles,[2] we were unable to prepare the isonitrile directly off one of the cage carbon atoms. We believe this to be a result of the increased inductive influence and reactivity of the *o*-carborane isomer (with respect to *m*- and *p*-carboranes), which impede the dehydration of (1,2-dicarba-*closo*-dodecaboran(12)-1-yl)formamide and facilitate other more favorable reaction pathways such as cage degradation.[6] Consequently, the only reactions that were successful were those that generated the isonitrile attached to the boron atom at the 3-position or distanced from the cage through an aliphatic spacer group. We were therefore interested in seeing whether the reduced electron-withdrawing properties and robustness of the 1,12-carborane isomer would facilitate the formation of the corresponding *p*-carborane isonitrile directly off one of the carbon vertices.

Experimental Section

Materials and General Procedures. With the exception of *p*-carborane, which was purchased from Katchem Ltd. and used as received, reagents were obtained from Aldrich Chemical Co. TLC was performed using Merck silica gel F-254 on aluminum plates. Solvent systems are reported as v/v mixtures. Compounds were visualized using a 0.1% mixture of $PdCl_2$ in hydrochloric acid (3 M) followed by heating with a heat gun. Merck 60 GF_{254} (7730) on silica gel plates and Silicycle silica gel (70−230 mesh) were used for preparative thin-layer chromatography and flash chromatography, respectively. The NMR spectra were recorded at ambient temperature on a Bruker AV200, 300, or DRX 500 spectrometer as indicated. Chemical shifts (δ) are relative to those of tetramethylsilane as internal standard for ^{1}H NMR and $BF_3{\cdot}OEt_2$ as external reference for $^{11}B\{^1H\}$ NMR. Coupling constants (*J*) are given in hertz. CI refers to chemical ionization mass spectrometry (MS), EI refers to electron impact mass spectrometry, and ES refers to electrospray mass spectrometry, which was performed on a Micromass Quattro Ultima or Quatro LC using samples dissolved in 50:50 CH_3OH-H_2O mixtures. IR spectra were run on a Bio-Rad FTS-40 FT FTIR spectrometer.

Structure Determination by X-ray Crystallography. X-ray crystallographic data were collected from single-crystal samples of **2**, **3**, and **5** mounted onto glass fibers and are given in Table 1. Data were collected using a p4 Bruker diffractometer, equipped with a Bruker SMART 1K charged coupled device (CCD) area detector, using the program SMART,[7] and a rotating anode, using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The crystal-to-detector distance was 4.987 cm, and the data collection was carried out in 512 × 512 pixel mode, utilizing 2 × 2 pixel binning. The initial unit cell parameters were determined by a least-squares fit of the angular settings of the strong reflections, collected by a 12° scan in 40 frames over three different sections of reciprocal space (160 frames in total). Almost a complete sphere of data was collected, to better than 0.8 Å resolution at 173 K. Upon completion of the data collection, the first 40 frames were re-collected to improve the decay correction analyses. Data reduction was carried out using the SAINT program,[8] which applied Lorentz and

(6) Schaeck, J. J.; Kahl, S. B. *Inorg. Chem.* **1999**, *38*, 204.

(7) *SMART*, version 4.05; Siemens Energy and Automotive Analytical Instrumentation: Madison, WI, 1996.

polarization corrections to the three-dimensionally integrated diffraction spots. The program SADABS[9] was utilized for the scaling of diffraction data, the application of a decay correction, and an empirical absorption correction based on redundant reflections. The structure was solved by using the direct-methods procedure in the Bruker SHELXTL program library,[10] and refined by full-matrix least-squares methods on F^2 with anisotropic thermal parameters for all non-hydrogen atoms in all cases.

Synthesis of *N*-(1,12-Dicarba-*closo*-dodecaboran-1-yl)formamide, 2. Formic acid (∼50 mL) was added to 1-amino-1,12-dicarba-*closo*-dodecaborane (1.18 g, 7.41 mmol) and the mixture heated to reflux for 36 h. Upon cooling of the mixture to room temperature, the excess acid was removed by rotary evaporation, leaving an off-white solid. The crude product was taken up in CH_2Cl_2 (50 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 50 mL) and 1 M HCl (2 × 50 mL). The acidic and basic solutions were pooled and separately washed with CH_2Cl_2 (1 × 50 mL). All organic fractions were combined, dried over Na_2SO_4, and filtered, and the solvent was removed by rotary evaporation. The crude product was isolated by silica gel chromatography (hexanes−ether, 1:1), giving pure **2** (1.207 g, 87%). Mp: 193.5−194.5 °C. TLC: R_f 0.70 (5% MeOH in CH_2Cl_2). IR (NaCl, cm^{-1}): ν 3178, 3061, 2607, 1693. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.91 (d, J = 10.9, 1H, CHO), 7.38 (br d, 1H, NH), 3.90−0.50 (br m, BH), 2.66 (br s, 1H, CH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz): δ 162.9, 87.1, 55.2. $^{11}B\{^1H\}$ NMR ($CDCl_3$, 96 MHz): δ −6.0, −9.0. HRMS (FAB, +): *m*/*z* calcd for $C_3H_{13}B_{10}NO$ 190.2008, found 190.2015.

Synthesis of 1-Methylcarbamyl-1,12-dicarba-*closo*-dodecaborane, 3. Fresh Burgess reagent (0.255 g, 1.07 mmol) was added to a solution of the formamide **2** (0.100 g, 0.534 mmol) dissolved in distilled CH_2Cl_2 (20 mL). The reaction was heated to reflux for 40 h whereupon the reaction became orange in color. The mixture was allowed to cool to room temperature and the solvent removed by rotary evaporation. The resulting orange solid was taken up in a minimal amount of light petroleum ether and the product, a colorless solid, isolated by chromatography on silica gel (hexanes−ether, 1:1) (0.084 g, 72%). Mp: 101−102.5 °C. TLC: R_f 0.65 (30% ether in hexanes). IR (NaCl, cm^{-1}): ν 3418, 3057, 2615, 1754. ^1H NMR (acetone-d_6, 500 MHz): δ 7.42 (br s, 1H, NH), 3.90−0.50 (br m, BH), 3.48 (s, 3H, CH_3), 3.32 (br s, 1H, CH). $^{13}C\{^1H\}$ NMR (acetone-d_6, 50 MHz): δ 152.7, 90.0, 56.5, 28.3. $^{11}B\{^1H\}$ NMR (acetone-d_6, 96 MHz): δ −12.0, −12.6, −15.3. HRMS (EI+, TOF): *m*/*z* calcd for $C_4H_{15}B_{10}NO_2$ 219.2033, found 219.2048.

Synthesis of Carborane−Azetidine 4. The formamide **2** (1.156 g, 6.17 mmol) and freshly distilled triethylamine (2.50 g, 3.44 mL, 24.69 mmol) were dissolved in CH_2Cl_2 under dry nitrogen. The solution was cooled to −78 °C and triphosgene (1.76 g, 9.26 mmol) in CH_2Cl_2 (15 mL) added dropwise, which resulted in gas evolution and the formation of a precipitate. The reaction was allowed to warm to 0 °C over 0.5 h, and then to room temperature over 3 h. The reaction was subsequently stirred overnight at ambient temperature whereupon distilled/deionized water (25 mL) was added to quench the reaction. The organic phase was separated and washed with water (3 × 50 mL). All aqueous fractions were pooled and extracted with CH_2Cl_2 (2 × 50 mL). All organic fractions were then pooled, dried over Na_2SO_4, and gravity filtered, and the solvent was evaporated. The mixture was purified by flash silica gel chromatography (100% hexanes), giving the product (0.648 g, 62%) as a colorless solid. Mp: 313.5−314.5 °C dec. TLC: R_f 0.41 (100% light petroleum). IR (NaCl, cm^{-1}): ν 3058, 2619, 2152, 2129, 2021, 1732, 1679, 1644. ^1H NMR (C_6D_6, 500 MHz): δ 3.60−1.10 (br m, BH), 1.91 (br s, CH), 1.84 (br s, CH), 1.58 (br s, CH). $^{13}C\{^1H\}$ NMR (toluene-d_8, 75 MHz): δ 189.9, 162.8, 158.6, 147.0, 145.5, 104.2, 98.7, 97.4, 96.6, 96.4, 95.9, 95.2, 90.0, 88.5; 58.9, 57.6, 57.2, 55.5, 51.0. $^{11}B\{^1H\}$ NMR (acetone-d_6, 160 MHz): δ −12.7, −13.3, −16.6. HRMS (FAB, +): *m*/*z* calcd for $C_{12}H_{44}B_{40}N_4$ 678.7586, found 678.7621.

Synthesis of 1-(1,12-Dicarba-*closo*-dodecaboran-1-yl)-2,3-bis-(1,12-dicarba-*closo*-dodecaboran-1-ylimino)-4-(*N*-1,12-dicarba-*closo*-dodecaboran-1-ylcarboxamido)azetidine, 5. To a suspension of $[NEt_4]_2[ReBr_3(CO)_3]$ (50 mg, 0.065 mmol) in THF (1.3 mL) was added dropwise a solution of $AgPF_6$ (49 mg, 0.195 mmol) in THF (1 mL). The white suspension was exposed to light for 20 min, to facilitate the precipitation of AgBr, whereupon it was filtered under a stream of argon. The residue was rinsed with THF (1 mL) and compound **4** (70 mg, 0.098 mmol) added to the supernatant. The reaction mixture was heated under reflux overnight, affording a clear yellow-green solution. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. The crude product was purified by preparative thin-layer chromatography eluting with a petroleum ether/diethyl ether mixture. The oily product was triturated with ice-cold hexanes, affording a white precipitate, which was collected by decantation. The solid was further purified by flash chromatography (gradient from pure petroleum ether to 90:10 petroleum ether−diethyl ether). After crystallization in CH_2Cl_2, the product was obtained as X-ray-quality crystals (19 mg, 27%). Mp: 328−330 °C. TLC: R_f 0.50 (70:30 petroleum ether−diethyl ether); IR (CH_2Cl_2, cm^{-1}): ν 3687, 3603, 3405, 2617, 1717, 1607, 1502. ^1H NMR (acetone-d_6, 500 MHz): δ 4.58 (s, 1H, NH), 3.60−1.10 (br m, BH), 3.45 (s, CH), 3.40 (s, CH), 3.29 (s, CH), 2.93 (s, CH). $^{13}C\{^1H\}$ NMR (acetone-d_6, 125 MHz): δ 162.7, 152.0, 148.7, 96.8, 95.8, 88.9, 87.4, 58.7, 57.8, 57.3, 53.9. $^{11}B\{^1H\}$ NMR (acetone-d_6, 160 MHz): δ −11.4, −11.8, −14.5, −15.0. HRMS (FAB, +): *m*/*z* calcd for $C_{12}H_{46}ON_4B_{40}$ 696.7726, found 696.7747.

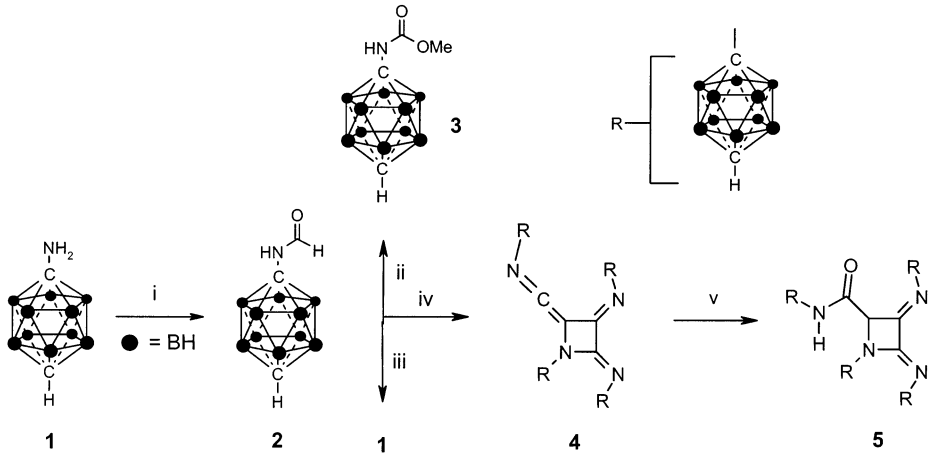
Results and Discussion

Although a number of different strategies exist for the preparation of isonitriles, the dehydration of formamides is a particularly attractive approach because reactions typically can be run under mild conditions in the presence of a variety of different functional groups. Toward this end, we initially synthesized 1-amino-1,12-dicarba-*closo*-dodecaborane following the method developed by Kahl and co-workers.[11] The amine was subsequently converted to the formamide by heating compound **1** in formic acid or by treatment with a mixed anhydride generated in situ from formic acid and acetic anhydride (Scheme 1).

The formamide, which was isolated in excellent yield (87%), showed BH and CO stretches in the IR at 2607 and 1693 cm^{-1}, respectively, while the mass spectrum indicated the expected *m*/*z* value having a B_{10} isotopic distribution. The ^1H NMR and $^{13}C\{^1H\}$ NMR were in agreement with the proposed structure, with the latter spectrum showing three peaks at 162.93, 87.14, and 55.22 ppm, which correspond to the C═O, CH, and substituted carborane carbon vertex,

(8) *SAINT*, version 4.05; Siemens Energy and Automotive Analytical Instrumentation: Madison, WI, 1996.
(9) Sheldrick, G. M. *SADABS* (Siemens Area Detector Absorption Corrections); 1996.
(10) Sheldrick, G. M. *SHELXTL*, release 5.03; Siemens Crystallographic Research Systems: Madison, WI, 1994.
(11) Kahl, S. B.; Kasar, R. A. *J. Am. Chem. Soc.* **1996**, *118*, 1223.

Scheme 1[a]



[a] Reagents and conditions: (i) HCO_2H, heat or HCO_2H, Ac_2O, pyr; (iI) Burgess reagent, CH_2Cl_2, reflux, 40 h, 72%; (iii) $SOCl_2$, NEt_3, −78 °C; (iv) triphosgene, CH_2Cl_2, NEt_3, −78 °C to room temperature, 24 h, 62%; (v) $[NEt_4]_2[Re(CO)_3Br_3]$, $AgPF_6$, THF.

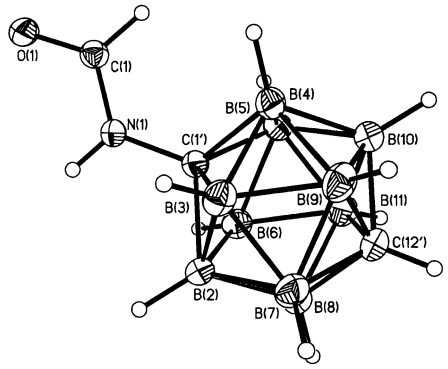


Figure 1. ORTEP representation of compound **2**. Thermal ellipsoids are shown at the 30% probability level. Selected bond lengths (Å) and angles (deg): C(1)−O(1) 1.2311(18), N(1)−C(1) 1.3376(18), N(1)−C(1′) 1.4336(18), C(1)−N(1)−C(1′) 125.67(12), N(1)−C(1)−O(1) 123.27(13).

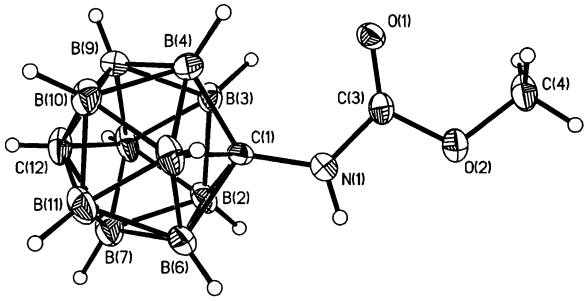


Figure 2. ORTEP representation of compound **3**. Thermal ellipsoids are shown at the 30% probability level. Selected bond lengths (Å) and angles (deg): C(3)−O(1) 1.209(6), C(3)−O(2) 1.361(7), C(4)−O(2) 1.419(7), C(3)−N(1) 1.358(7), N(1)−C(1) 1.423(7), N(1)−C(3)−O(1) 127.4(5), N(1)−C(3)−O(2) 107.8(5), C(1)−N(1)−C(3) 125.4(5).

respectively. The $^{11}B\{^1H\}$ NMR of **2** indicated two peaks at −6.0 and −9.0 ppm, which is consistent with a mono-C-substituted *p*-carborane derivative.

Single crystals of **2** were grown, and the structure was determined crystallographically (Figure 1). The formamide crystallized in a *trans* (*E*) configuration, which is opposite what we observed for 3-*N*-formyl-1,2-dicarba-*closo*-dodecaborane.[2] There was no evidence in the solid state or in solution ($T = 298$ K) for the presence of the *Z*-isomer, which is dissimilar to what was observed for the carbamate groups in Boc-protected *C*-hydrazino-*C*-carboxycarboranes.[12] The C═O bond distance in **2** is 1.2311(18) Å, while the N(1)−C(1) and N(1)−C(1′) distances are 1.3376(18) and 1.4336(18) Å, respectively. The carborane has a distorted icosahedral structure having average C−B and B−B distances of 1.713(3) and 1.774(3) Å, respectively.

The first attempt at dehydrating **2** followed the methodology we used to prepare the *o*-carborane isonitriles.[2] It involved heating the formamide with the Burgess reagent[13] for 2 days (40 h) in dichloromethane. TLC analysis of the reaction mixture indicated only one major product, which was readily isolated by chromatography on silica gel.

X-ray structure determination revealed that the product, which was isolated in good yield (72%), was in fact not the target isonitrile but the corresponding methyl formate **3** (Figure 2). The X-ray structure of **3** indicates the carborane cage contains average B−B distances of 1.770(11) Å, varying between 1.720(12) and 1.810(10) Å. The average C(1)−B bond distance was 1.728(9) Å, ranging from 1.702(9) to 1.759(8) Å, while the average C(12)−B distance was 1.695(9) Å, ranging from 1.670(11) to 1.725(8) Å. The C(3)−O(1) distance was 1.209(6) Å, which is within the range expected for a carbamate.

IR analysis of the product supported the single-crystal X-ray data in that the carbonyl stretch of the carbamate is clearly evident at 1754 cm^{-1}, which is shifted significantly from that of the formamide precursor. The presence of the carbamate is also evident in the $^{13}C\{^1H\}$ NMR spectrum, in which the resonance for the C═O group is present at 152.7 ppm. The ^1H-decoupled ^{11}B NMR spectrum of **3** shows, as would be expected, two main resonances located at −12.0 and −15.3 ppm.

We believe the formation of **3** is the result of methanol, which is produced by decomposition of the Burgess reagent,[14] reacting with the isocyanate **6** (Figure 3).[15] Formation of the

(12) Valliant, J. F.; Sogbein, O. O.; Morel, P.; Schaffer, P.; Guenther, K. J.; Bain, A. D. *Inorg. Chem.* **2002**, *41*, 2731.
(13) Creedon, S. M.; Crowley, H. K.; McCarthy, D. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1015.

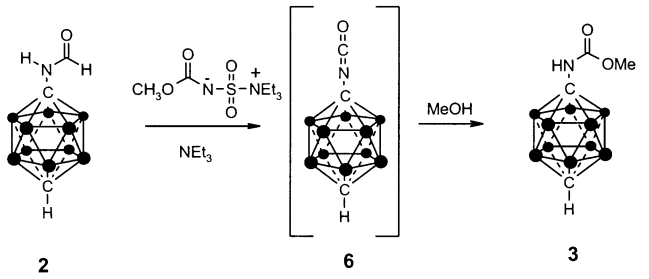


Figure 3. Formation of **3** via the isocyanate **6**.

isocyanate intermediate, which unfortunately could not be isolated chromatographically, was detectable by infrared spectroscopy. Further evidence for the proposed mechanism was gained by adding methanol to the reaction mixture, which led, according to TLC, to rapid consumption of the isocyanate component and formation of compound **3** as the major reaction product. Formation of a carbamate by Burgess reagent mediated dehydration of a formamide is unique to this example and has not, to the best of our knowledge, been previously reported.

After the reactions with the Burgess reagent failed to yield the target isonitrile, we investigated three other dehydration methodologies (Scheme 1). The first method involved treatment of **2** with $POCl_3$, an approach which had been used by Zakharkin et al.[16] for preparing 3-isocyano-1,2-dicarba-*closo*-dodecaborane (3-isonitrile-*o*-carborane). We found, unfortunately, that $POCl_3$ did not react with our formamide to any appreciable extent. Treatment of compound **2** with $SOCl_2$ in the presence of NEt_3, on the other hand, resulted in the loss of the formyl group and formation of the amine **1** in nearly quantitative yield. Reaction of the formamide with triphosgene, following an established procedure,[17] resulted in the formation of a very nonpolar product (as shown by TLC), which was readily isolated as a yellow semisolid in reasonably good yield (62%) by chromatography on silica gel.

The infrared spectrum of the main reaction product exhibited absorptions centered around 2152 cm^{-1}, which correlates with the value expected for the target isonitrile, and 2619 cm^{-1}, which indicates the presence of BH groups. There were, however, additional peaks at 1732, 1679, and 1644 cm^{-1}, which, at the time of analysis, were thought to arise from impurities in the sample (vide infra). The results of mass spectrometry (ESMS) experiments were not immediately discernible as there was no signal that was consistent with the mass of the desired isonitrile. There was, on the other hand, a major peak that corresponded to exactly 4 times the mass of the target compound having a B_{40} isotopic distribution pattern.

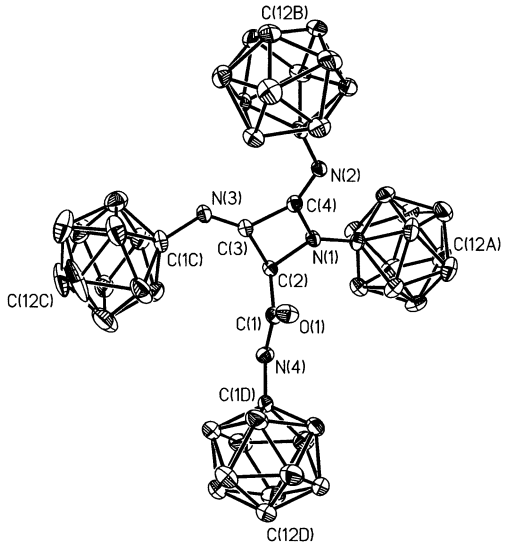


Figure 4. ORTEP representation of compound **5** with thermal ellipsoids shown at the 30% probability level. The hydrogen atoms and solvent of crystallization (THF) have been omitted for clarity. Selected bond lengths (Å) and angles (deg): N(1)−C(2) 1.487(8), C(2)−C(3) 1.566(7), N(1)−C(1A) 1.426(5), C(1)−C(2) 1.561(7), C(3)−N(3) 1.245(7), C(4)−N(2) 1.262(6), C(1)−O(1) 1.211(4), C(2)−N(1)−C(4) 96.7(4), N(1)−C(4)−C(3) 89.3(4), C(4)−C(3)−C(2) 88.6(4), C(3)−C(2)−N(1) 84.7(3), C(3)−N(3)−C(1C) 123.1(5), C(4)−N(2)−C(1B) 125.6(4).

Because of the presence of the isonitrile stretches in the IR, and the fact that there was only one major product visible on the TLC plate, we attempted to trap the isonitrile as a means of establishing whether the target was actually being formed. The purified reaction mixture was treated with $[NEt_4]_2[Re(CO)_3Br_3]$,[18] which is known to form stable $Re(CO)_3L_2Br$ (L = isonitrile) complexes.[19] Upon addition of the ligand, TLC indicated formation of a new product, which was isolated chromatographically. X-ray-quality crystals were grown, and the resulting structure is shown in Figure 4.

To our surprise the X-ray experiments revealed that the product was a racemic mixture of bis(*p*-carboran-1-ylimino)-azetidine derivatives. The imino groups are located adjacent to one another, while a carboranyl amide is pendant from the 4-position of the ring. The carboranes bound to the imino nitrogen atoms are oriented in a propeller-like fashion (carborane B is rotated away from the carborane attached to the azetidine nitrogen), while the carborane attached to the amide (D) is projecting away from the ring to further minimize steric interactions. A molecule of THF, which interacts with the amide group through H-bonding, co-crystallized with each molecule. This is the first example of a 2,3-bis(imino)azetidine that has been characterized crystallographically.

With respect to the azetidine ring, the dihedral angle between the planes defined by N(1)−C(2)−C(4) and C(3)−C(2)−C(4) is around 171(1)°, giving a ring pucker of nearly 9°. This is similar to the 169(1)° dihedral angle found in

(14) Burgess, E. M.; Penton Jr., H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
(15) (a) Wu, Y.; Carrol, P. J.; Kang, S. O.; Quintana, W. *Inorg. Chem.* **1997**, *36*, 4753. (b) Arterburn, J. B.; Wu, Y.; Quintana, W. *Polyhedron* **1996**, *15*, 4355. (c) Kasar, R. A.; Knudsen, G. M.; Kahl, S. B. *Inorg. Chem.* **1999**, *38*, 2936. (d) Scobie, M.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2059.
(16) Zakharkin, L. I.; Kalinin, V. N.; Gedymin, V. V. *Synth. Inorg. Met.-Org. Chem.* **1971**, *1*, 45.
(17) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894.
(18) $[NEt_4]_2[Re(CO)_3Br_3]$ was pretreated with Ag^+ prior to addition of the reaction mixture as a means of facilitating ligand coordination.
(19) Alberto, R.; Schibli, R.; Schubiger, P. A.; Abram, U.; Kaden, T. A. *Polyhedron* **1996**, *15*, 1079.

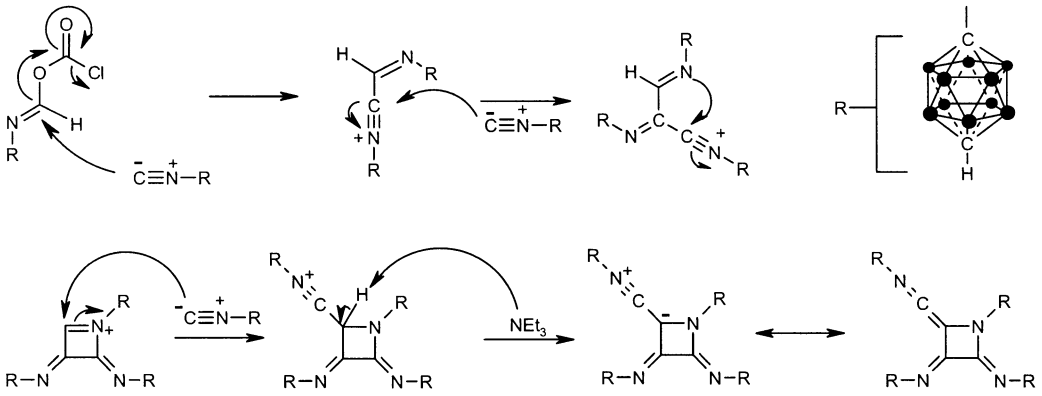


Figure 5. Mechanism for the formation of compound **4**. For the sake of clarity and conciseness, not all possible canonical forms are shown.

L-azetidine-2-carboxylic acid.[20] The dihedral angles in azetidine and azetidinium ions range between 0° and 27° for compounds bearing larger substituents, such as 1,1-dibenzyl-3,3-dimethylazetidinium bromide, approaching planarity.[21] In the case of 4-*tert*-butylimino-3,3-diethoxycarbonyl-1-methyl-2-tosyliminoazetidine, which has two imino groups on either side of the ring nitrogen, the structure was essentially planar.[22] It was reported that in this case the exocylic imino groups reduce the torsional strain compared with ring strain, thereby flattening the azetidine ring. In the case of **5**, it is clear that the azetidine similarly tends toward a planar structure to minimize the interactions between the bulky carborane substituents.

The bond distances and angles reported for **5** are in good agreement with the structure reported for 4-benzylidene-1-*tert*-butyl-2-(*tert*-butylimino)-3-phenylazetidine.[23] The C(2)−C(3) bonds (1.566(7) Å) in the ring are slightly longer than the adjacent C(3)−C(4) bonds (1.524(7) Å). The N(1)−C(4) bond is shorter (1.401(6) Å) than the N1−C(2) bond (1.487(8) Å) possibly due to overlap between the lone pair on the ring nitrogen and the imino group. This is not, however, reflected in the imine bond distances, which are comparable (1.245(7) and 1.262(6) Å). The distances between all nitrogen atoms and the corresponding carborane carbon atoms to which they are attached are nearly identical, and the structures of the carboranes themselves are similar to those of other substituted *p*-carboranes reported in the literature.[24]

Simulation of the highest mass peak observed in the electrospray mass spectrum of a sample of **5** further confirmed the major reaction product was the azetidine derivative. The IR spectrum shows peaks corresponding to the carborane BH (2617 cm^{-1}) and the imine and amide groups (1607 and 1717 cm^{-1}). The $^{13}C\{^1H\}$ spectrum is uncomplicated and shows three peaks shifted downfield which correspond to the amide carbonyl and two imine carbon atoms (162.7, 152.0, and 148.7 ppm). Both the substituted and the unsubstituted carbon atoms of the four carborane cages are also readily identifiable. The ^1H-decoupled ^{11}B NMR spectrum showed four broad overlapping peaks, which provided little additional insight into the solution structure of **5**.

In light of the X-ray structure, the spectral data for compound **4** were reanalyzed to determine whether the formation of **5** was a consequence of a metal-mediated process or whether the azetidine, or some related precursor, was produced during the dehydration reaction.

Mass spectrometry experiments, as mentioned previously, show a high-mass peak at 4 times the mass of the isonitrile, which is consistent with the formation of the tetramer **4**. The aforementioned extraneous IR stretches seen for compound **4** correspond to C═N and C═C groups and are in good agreement with those values reported for related azetidine derivatives.[25] The ^1H and $^{13}C\{^1H\}$ NMR contain, among other signals,[26] multiple resonances corresponding to the different carborane CH groups present in **4**, which suggests, along with the other data, that the formation of the azetidine occurs during dehydration and not after the addition of the metal.

The use of isonitriles to form heterocycles, including azetidines, is well established;[27] however, the formation of **4** under the mild reaction conditions described here is exceptional. Deyrup et al.[28] showed that *N*-arylimines react with *tert*-butyl isocyanide to form 2,3-bis(*tert*-butylimino)-azetidines. Following a similar mechanism, we believe that formation of the target isonitrile is followed by its attack on a reactive chloroformate intermediate (Figure 5). Substitution reactions at vinylic sites are typically "sluggish"; however, in this case the electron-withdrawing "iminocarborane" and

(20) Berman, H. M.; McGandy, E. L.; Burgner, J. W., II; VanEtten, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 6177.
(21) Towns, R. L.; Trefonas, L. M. *J. Am. Chem. Soc.* **1971**, *93*, 1761.
(22) Van Meervelt, L.; L'abbé, G.; King, G. S. D. *Bull. Soc. Chim. Belg.* **1986**, *95*, 97.
(23) Fuks, R.; Baudoux, D.; Piccinni-Leopardi, C.; Declercq, J.-P.; Van Meerssche, M. *J. Org. Chem.* **1988**, *53*, 18.
(24) Yang, X.; Jiang, W.; Knobler, C. B.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1992**, *114*, 9719.
(25) (a) Aumann, R.; Heinen, H. *Chem. Ber.* **1986**, *119*, 2289. (b) Marchand, E.; Morel, G.; Sinbandhit, S. *Eur. J. Org. Chem.* **1999**, 1729.
(26) The $^{13}C\{^1H\}$ NMR spectrum of **4** is complex and seems to indicate that there are two species in solution, which is consistent with the fact that fluxional processes for substituted azetidines are well-known (Katritzky, A. R.; Rees, C. W. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon Press: New York, 1984). Detailed variable-temperature NMR studies are needed to comment further on the observed complexities in the NMR, and are a focus of current work.
(27) Moderhack, D. *Synthesis* **1985**, 1083.
(28) Deyrup, J. A.; Vestling, M. M.; Hagan, W. V.; Yun, H. Y. *Tetrahedron* **1969**, *25*, 1467.

chloroformate groups further activate the position to nucleophilic attack, and the subsequent loss of CO_2 drives the initial reaction to completion. Successive reaction with two isonitrile ligands in addition to ring closure leads to the azetidine **4**. We believe that the reaction of **4** with $[NEt_4]_2[Re(CO)_3Br_3]$, under the specified conditions, simply results in metal-mediated hydrolysis to give the corresponding amide **5**.

For the sake of comparison, we dehydrated formanilide using the same reaction conditions used to prepare **4**. As expected, the major product was the isonitrile and no azetidine derivatives were detected. Consequently, formation of **4** is a result of the unique electronic and/or steric influence of the *p*-carborane group. It is clear that further investigation as to the reason for, and the mechanism behind, the formation of the azetidine, as opposed to the target isonitrile, is warranted.

Concluding Remarks

In conclusion, the dehydration of (1,12-dicarba-*closo*-dodecaboran(12)-1-yl)formamide does not lead directly to isonitriles, as is the case for formanilide, and the structure of the product depends greatly on the nature of the reactants and the reaction conditions. Dehydration of the formamide with the Burgess reagent led to the formation of a carbamate, while reaction with triphosgene resulted in the remarkable condensation of four carborane units to form a 2,3-bis(*p*-carboran-1-ylimino)azetidine, **4**, which is hydrolyzed in the presence of Re(I) to give the corresponding amide **5**.

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Supporting Information Available: Crystallographic data for compounds **2**, **3**, and **5** (tables of crystallographic details, non-hydrogen coordinates, bond distances and angles, anisotropic displacement parameters, and hydrogen coordinates) and spectral data for compounds **3**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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