Functionalization of Polymethylcarboranes. Preparation and Reactivity of 2,3,4,5,6,7,8,9,10,11-Decamethyl-1,12-dicarba-*closo*-dodecaborane(12)-1-carboxylic Acid

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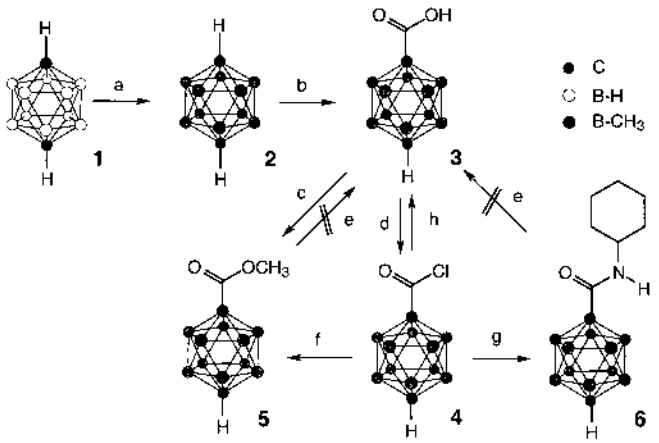
The preparation and reactivity of poly-*B*-methyl-1,12-dicarba-*closo*-dodecaborane (poly-*B*-methyl-*p*-carborane) derivatives are described. 2,3,4,5,6,7,8,9,10,11-Decamethyl-1,12-dicarba-*closo*-dodecaborane(12)-1-carboxylic acid was prepared from 2,3,4,5,6,7,8,9,10,11-decamethyl-1,12-dicarba-*closo*-dodecaborane(12) by lithiation with methyllithium, followed by carboxylation. Conversion of the carboxylic acid into its ester and amide were achieved through its acyl chloride. The ester and the amide could not be hydrolyzed due to severe steric hindrance around the carbonyl group of the molecules owing to the adjacent *B*-methyl groups.

Key words dicarba-*closo*-dodecaborane; carboxylation; Friedel–Crafts reaction; acyl chloride; hydrolysis

Dicarba-*closo*-dodecaboranes (carboranes) are a class of carbon-containing polyhedral boron-cluster compounds.[1] One of their most striking features is the ability of the two carbon atoms and 10 boron atoms to adopt icosahedral geometry, in which the carbon and boron atoms are hexacoordinated. This feature of the icosahedral structure gives rise to unusual properties of such molecules and their carbon and boron derivatives. For example, the stability of the carborane cage has been demonstrated under many reaction conditions, and the hydrophobic character is comparable to that of hydrocarbons. The synthesis of 2,3,4,5,6,7,8,9,10,11-decamethyl-1,12-dicarba-*closo*-dodecaborane(12) (**2**) has been achieved by electrophilic methylation of 1,12-dicarba-*closo*-dodecaborane(12) (**1**) with methyl trifluoromethanesulfonate.[2] The polymethyl carborane **2** provides a unique hydrocarbon surface due to its methyl substituents and is termed a "camouflaged" carborane. Recently, two examples of the functionalization of **2** have been reported, *i.e.*, photochlorination to produce dekakis(dichloromethyl)-1,12-dicarba-*closo*-dodecaborane(12)[3] and the Barton reaction of decamethyl-1,12-dicarba-*closo*-dodecaboranyl(12) nitrite to produce 2-hydroxyimino-1-hydroxymethyl-3,4,5,6,7,8,9,10,11-nonamethyl-1,12-dicarba-*closo*-dodecaboran(12).[4] We have focused on the design, synthesis and biological evaluation of carborane-containing biologically active molecules in order to utilize carboranes as a hydrophobic and spherical pharmacophore,[5] because, ligand-receptor complexation is attributed to a hydrophobic interaction and the fit of overall molecular shapes in addition to hydrogen-bonding character. An understanding of the fundamental reactivity of **2** is required for the use of polymethylcarborane as a component of designed molecules. In this paper, we describe the preparation and reactivity of 2,3,4,5,6,7,8,9,10,11-decamethyl-1,12-dicarba-*closo*-dodecaborane(12)-1-carboxylic acid.

Compound **2** was prepared by reaction of **1** with neat methyl trifluoromethanesulfonate employing a modified method which has been reported.[2,6] It was expected that the acidity of the CH cage vertices of **2** would be reduced compared to the corresponding vertices of **1** by the electron-donating effect of the methyl groups. Only 25—30% deuteration of the CH was observed upon treatment of **2** with *n*-butyllithium followed by quenching with D_2O, and a more forcing condition (10 eq of phenyllithium in benzene heated at reflux, followed by treatment with D_2O) gave [D_2]-**2**.[2] 2,3,4,5,6,7,8,9,10,11-Decamethyl-1,12-dicarba-*closo*-dodecaborane(12)-1-carboxylic acid (**3**) was obtained by lithiation of **2** with methyllithium and subsequent addition to CO_2 (solid) in 76% yield.[7] The dicarboxylic acid, 2,3,4,5,6,7,8,9,10,11-decamethyl-1,12-dicarba-*closo*-dodecaborane(12)-1,12-dicarboxylic acid, was not obtained in this procedure. Figure 1 outlines the reactions of the decamethyl-1,12-dicarba-*closo*-dodecaborane. The reactivity of the carboxyl group of **3** was expected to be greatly reduced by the steric effect of the surrounding five *B*-methyl groups.[8] In fact, acid-catalyzed esterification of **3** in methanol at refluxing temperature for **3** failed to give the methyl ester (**5**), and the starting material **3** (88%) was recovered intact. The methyl ester **5** was obtained by treatment of **3** with diazomethane in an 83% yield. The result indicated that reactivity of the camouflaged carborane distinct from that of *p*-carborane, which reacts with diazomethane on the BH cage vertices to give no methyl ester. On the other hand, compound **3** was converted



a) $CF_3SO_3CH_3$, CF_3SO_3H, 130 °C; b) 1) CH_3Li/THF–Et_2O, 2) CO_2; c) CH_2N_2/Et_2O; d) $SOCl_2$/DMF, 90 °C; e) 1 N KOH/THF, Δ or 6 N HCl/CH_3COOH, Δ; f) CH_3OH, DMAP/pyridine, 70 °C; g) $C_6H_{11}NH_2$, DMPA/pyridine, 50 °C; h) H_2O, DMAP/pyridine, 50 °C.

Fig. 1

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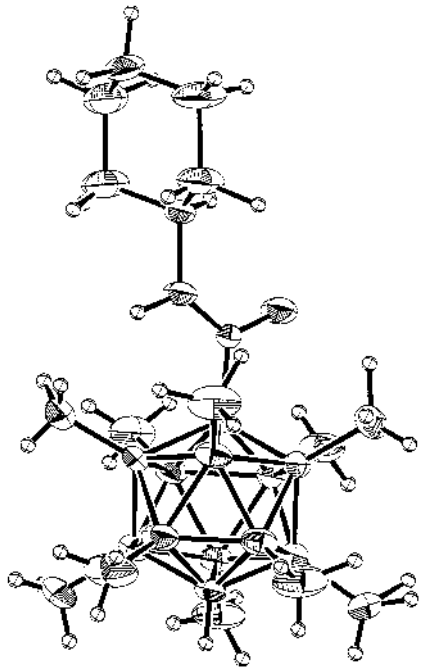

Fig. 2. Crystal Structure of **6** (ORTEP Representation)

to the acyl chloride **4** by treatment with thionyl chloride in 94% yield. The chloride **4** was stable on recrystallization in methanol, and was not hydrolyzed in basic conditions (1 N KOH–THF, 50 °C, 24 h). The chloride **4** was hydrolyzed in pyridine in the presence of water and 4-dimethylaminopyridine (DMAP) to give **3** in 80% yield. The chloride **4** also reacted with methanol or cyclohexylamine in pyridine in the presence of DMAP to give the methyl ester **5** or the amide **6** in high yields. However, the ester **5** and the amide **6** were not hydrolyzed, even under a drastic condition (6 N HCl–CH_3COOH, reflux, 24 h), due to the severe hindrance of the carbonyl group of the molecules by the adjacent *B*-methyl groups. Recrystallization of **6** from methanol afforded single crystals suitable for X-ray crystallographic analysis, and the results are illustrated in Fig 2.[9] The structure of **6** showed a markedly long C1–C=O distance of 1.521 Å and a short amide C–N distance of 1.304 Å as compared with that of the usual aromatic amide (1.484 and 1.345 Å in benzanilide). A similar observation has been reported in the case of the crystalline structure of 2,2′,6,6′-tetramethylbenzanilide, which has bulky substituents around the amide bond.[10]

The results of this study demonstrate the distinction between the reactivity of polymethylcarboranes and that of carboranes, and also demonstrate the utility of polymethylcarboranes, as exemplified by the synthetic intermediates by preparation of 2,3,4,5,6,7,8,9,10,11-decamethyl-1,12-dicarba-*closo*-dodecaborane(12)-1-carbonyl chloride. The present results should be helpful in the design and synthesis of polymethylcarborane-containing biologically active molecules.

Experimental

General Procedures Melting points were obtained on a Yanagimoto micro hot stage without correction. ^{1}H-NMR spectra were recorded with a JEOL JMN-GX-400 spectrometer (400 MHz), with tetramethylsilane (TMS) as an internal standard, and chemical shifts are given in ppm as δ values from TMS. ^{11}B-NMR spectra were recorded with a JEOL JMN-A500 spectrometer (160.35 MHz), with 15% BF_3–etherate in $CDCl_3$ as an external standard, and chemical shifts are given in ppm as δ values from BF_3–etherate. Mass spectra were recorded on a JEOL JMS-D-300 for DI-Mass. Column chromatography was performed on silica gel (Merck 7734 or 9385 (flash chromatography)).

2,3,4,5,6,7,8,9,10,11-Decamethyl-1,12-dicarba-*closo*-dodecaborane(12) (2) A mixture of 1,12-dicarba-*closo*-dodecaborane(12) (**1**, 31.5 mg, 0.22 mmol), methyl trifluoromethanesulfonate (0.25 ml, 2.2 mmol) and trifluoromethanesulfonic acid (0.25 ml, 2.8 mmol) was heated at 130 °C in a sealed tube for 9 h. After cooling, the reaction mixture was added to ice-water and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was purified by silica gel column chromatography (*n*-pentane) to yield **2** as a white solid (56.8 mg, 91.4%). **2**: colorless prisms (MeOH), mp 231—232 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.01 (2H, s, CH), 0.04 (30H, s, BCH_3). ^{11}B-NMR ($CDCl_3$, 160.35 MHz): −9.68 (10B, s, BCH_3). *Anal*. Calcd for $B_{10}C_{12}H_{32}$: C, 50.66; H, 11.34. Found: C, 50.68; H, 11.41.

2,3,4,5,6,7,8,9,10,11-Decamethyl-1,12-dicarba-*closo*-dodecaborane-(12)-1-carboxylic Acid (3) Methyllithium (1.14 M in ether, 42.1 ml, 48.0 mmol) was added dropwise to a solution of **2** (1.36 g, 4.78 mmol) in dry tetrahydrofuran (THF) (100 ml) for 10 min at 0 °C under Ar, and the mixture was stirred at room temperature for 5 h. The reaction mixture was added to dry-ice in THF, followed by the addition of 2 N HCl, and the whole was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was purified by silica gel column chromatography (*n*-hexane : CH_3Cl = 1 : 1, then $CHCl_3$). **2** (312.3 mg, 22.9%) was recovered in the *n*-hexane fraction, and **3** was obtained as a white solid (1.20 g, 76.4%) in the $CHCl_3$ fraction. **3**: colorless prisms (benzene), mp 224—225 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.21 (1H, s, CH), 0.13, 0.07 (each 15H, s, BCH_3). ^{11}B-NMR ($CDCl_3$, 160.35 MHz): −7.98 (5B, s, BCH_3), −9.49 (5B, s, BCH_3). IR (KBr): 2930, 2890, 2800, 1712, 1425, 1385, 1319, 1248, 1183, 1110, 1040, 1000, 918, 840, 730 cm^{-1}. *Anal*. Calcd for $B_{10}C_{13}H_{32}O_2$: C, 47.53; H,9.82. Found: C, 47.33; H, 9.59.

2,3,4,5,6,7,8,9,10,11-Decamethyl-1,12-dicarba-*closo*-dodecaborane-(12)-1-carbonyl Chloride (4) A solution of **3** (60.1 mg, 0.18 mmol), thionyl chloride (6 ml) and *N*,*N*-dimethylformamide (0.06 ml) was heated at 90 °C under Ar for 5 h. The solvent and excess thionyl chloride were removed under a vacuum. Water was added to the residue, and the whole was extracted with AcOEt. The organic layer was washed with brine, then dried over $MgSO_4$. After evaporation, the residue was purified by silica gel column chromatography (*n*-hexane) to afford **4** as a white solid (59.5 mg, 93.7%). **4**: Colorless prisms (MeOH), mp 183—184 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.29 (1H, s, CH), 0.22, 0.10 (each 15H, s, BCH_3). ^{11}B-NMR ($CDCl_3$, 160.35 MHz): −7.64 (5B, s, BCH_3), −9.32 (5B, s, BCH_3). IR (KBr): 2920, 2880, 2800, 1775, 1429, 1320, 1183, 1130, 1040, 1000, 918, 810 cm^{-1}. *Anal*. Calcd for $B_{10}C_{13}H_{31}ClO$: C, 45.00; H, 9.01. Found: C, 45.00; H, 8.78.

Methyl 2,3,4,5,6,7,8,9,10,11-decamethyl-1,12-dicarba-*closo*-dodecaborane(12)-1-carboxylate (5)

Procedure A: A solution of CH_2N_2 in Et_2O was added dropwise to a solution of **3** (59.4 mg, 0.18 mmol) in Et_2O at 0 °C under Ar until the solution color changed to yellow, and the mixture was stirred at room temperature for 2 h. After evaporation, the crude product was recrystallized from MeOH to afford **5** as colorless leaflets (51.3 mg, 82.9%). **5**: mp 147—148 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 3.55 (3H, s, $COOCH_3$), 2.18 (1H, s, CH), 0.11, 0.07 (each 15H, s, BCH_3). ^{11}B-NMR ($CDCl_3$, 160.35 MHz): −8.04 (5B, s, BCH_3), −9.57 (5B, s, BCH_3). IR (KBr): 3400, 2920, 2890, 2800, 1730, 1429, 1315, 1250, 1190, 1110, 1085, 1000, 970, 918, 780 cm^{-1}. *Anal*. Calcd for $B_{10}C_{14}H_{34}O_2$: C, 49.09; H, 10.01. Found: C, 48.89; H, 10.05.

Procedure B: A solution of **4** (30.5 mg, 0.088 mmol), dry MeOH (1 ml) and DMAP (16.1 mg, 0.132 mmol) in dry pyridine (2 ml) was heated at 70 °C under Ar for 1 h. Then, 2 N HCl was added, and the reaction mixture was extracted with AcOEt. The organic layer was washed successively with water, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation, the residue was purified by silica gel column chromatography (*n*-hexane then CH_2Cl_2: *n*-hexane = 1 : 1) to afford **5** as a white solid (24.6 mg, 81.7%).

***N*-Cyclohexyl-2,3,4,5,6,7,8,9,10,11-decamethyl-1,12-dicarba-*closo*-dodecaborane(12)-1-carboxamide (6)** A solution of **4** (99.6 mg, 0.287 mmol), cyclohexylamine (0.05 ml, 0.430 mmol) and DMAP (52.8 mg, 0.432 mmol) in dry pyridine (3 ml) was heated at 50 °C under Ar atmosphere for 30 min. 2 N HCl was added to the reaction mixture, then extracted with AcOEt. The organic layer was washed successively with water, sat. $NaHCO_3$ aq. and brine, and dried over $MgSO_4$. After evaporation, the residue was pu-

rified by silica gel column chromatography (CH_2Cl_2 : *n*-hexane = 1 : 4 then 1 : 1) to afford **6** as a white solid (111.9 mg, 95.2%). **6**: colorless prisms (MeOH), mp 204—205 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 5.12 (1H, br s, NH), 3.60 (1H, m), 2.17 (1H, s, CH), 1.79 (2H, m), 1.64 (2H, m), 1.55 (1H, m), 1.30 (2H, m), 1.17 (1H, m), 1.04 (2H, m), 0.17, 0.07 (each 15H, s, BCH_3). ^{11}B-NMR ($CDCl_3$, 160.35 MHz): −8.45 (5B, s, BCH_3), −9.39 (5B, s, BCH_3). IR (KBr): 3450, 3000, 2900, 2880, 2830, 1675, 1510, 1445, 1316, 1268, 1250, 1230, 1189, 1110, 1068, 1000, 918, 886 cm^{-1}. *Anal*. Calcd for $B_{10}C_{19}H_{43}NO$: C, 55.71; H, 10.58; N, 3.42. Found: C, 55.47; H, 10.77; N, 3.34.

References and Notes

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6) Attempts to prepare 3,4,5,6,7,8,9,10,11,12-decamethyl-1,2-dicarba-*closo*-dodecaborane(12) (*o*-carborane) or 2,3,4,5,6,8,9,10,11,12-decamethyl-1,7-dicarba-*closo*-dodecaborane(12) (*m*-carborane) by the present procedure were unsuccessful.
7) When **2** was treated with methyllithium followed by quenching with D_2O, deuteration of CH was not observed.
8) A facile decarboxylation of 1,2-dicarba-*closo*-dodecaborane-1-carboxylic acid due to a leaving ability of 1,2-dicarba-*closo*-dodecaborane has been reported: Nakamura H., Aoyagi, K., Yamamoto, Y., *J. Org. Chem*., **62**, 780—781 (1997). However, the compound **3** was stable under a diluted alkaline condition.
9) Crystallographic data for **6**: $B_{10}C_{19}H_{43}NO$, M.W. = 409.65, monoclonic, space group $P\ 2_1/n$, a = 9.6938 (3), b = 19.9628 (7), c = 3.6540 Å, β = 97.893 (2)°, V = 2617.2 (1) Å^3, Z = 4, $\rho_{calcd.}$ = 1.040 g/cm^3. Data were collected on a Bruker SMART CCD diffractometer, $Mo_{K\alpha}$ radiation (λ = 0.71073), μ = 0.56 cm^{-1}, 22519 reflections (total), 6841 reflections (unique), R = 0.055, R_w = 0.063 for 2090 independent reflections with $I > 3\sigma(I)$. Selected bond length: B1–C range 1.714—1.743 average 1.735, B12–C range 1.692—1.697 average 1.694, B–B range 1.754—1.804 average 1.779, C1–C12 cross cage distance 3.007 Å.
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