Inorg. Chem. **2007**, *46*, 3966–3970

Facile and Efficient Synthesis of *C*-Hydroxycarboranes and *C,C′*-Dihydroxycarboranes

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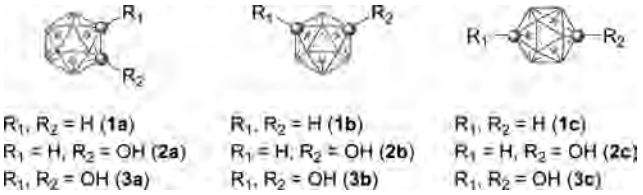
Received October 23, 2006

C-Hydroxylated carboranes, carboranols, have interesting properties resulting from their hydroxyl protons being highly acidic because of the electron-deficient nature of the carborane cage. We described here an efficient synthesis of *C*-hydroxycarboranes **2** and *C,C′*-dihydroxycarboranes **3** by the reaction of carboranyl lithium and trimethylborate, followed by oxidation with hydrogen peroxide in the presence of acetic acid, to afford the corresponding *o*-, *m*-, and *p*-hydroxycarboranes **2** and *o*-, *m*-, and *p*-dihydroxycarboranes **3** selectively in high yields through a one-pot procedure. The *m*- and *p*-carborane isomers of **2** and **3** were obtained in especially good yields (**2b**, 85%; **2c**, 85%; **3b**, 95%; **3c**, 96%). DFT calculations were performed on the dihydroxycarboranes **3** to compare the geometrical features of the isomers at the same level of theory and to characterize their electronic and NMR spectroscopic (^{13}C chemical shift) properties.

Introduction

Carboranes (dicarba-*closo*-dodecaboranes)[1] (**1**) are a class of carbon-containing boron cluster compounds that exhibit remarkable thermal and chemical stability (Chart 1). There are three isomers, ortho, meta, and para, depending on the position of two carbon atoms, and all of them have aromatic properties. Thus, these compounds are often labeled as "three-dimensional benzene". Carboranes are versatile synthons, which have found many applications in the fields of catalysts,[2] polymers,[3] material sciences,[4] and supramolecular chemistry.[5] In medicinal chemistry, carboranes have been applied in boron neutron capture therapy (BNCT)[6] and boron neutron capture synovectomy (BNCS),[7] and they have also been used as a hydrophobic pharmacophore of drugs.[8] Therefore, the development of new and more efficient methods for the preparation of functionalized carboranes is of considerable interest. In particular, *C*-hydroxylated car-

Chart 1. Structures of Carboranes **1**, *C*-hydroxycarboranes **2**, and *C,C′*-dihydroxycarboranes **3**



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10.1021/ic062025q CCC: $37.00
Published on Web 04/13/2007

boranes, carboranols (**2**) and (**3**), have received much attention in recent years since they are expected to display interesting properties related to their hydroxyl protons, which are highly acidic because of the electron-deficient nature of the carborane cage: the pK_a values reported for the ortho (**2a**), meta (**2b**), and para (**2c**) *C*-hydroxyl isomers are 5.33, 8.39, and 9.03, respectively.[9] The pK_a of the ortho isomer is similar to that of benzoic acid (pK_a = 4.25),[10] and those of the meta and para isomers are similar to that of phenol (pK_a = 10.0).[10] Therefore, carboranols are considered to have great potential value as synthons, reagents, or functional triggers in various fields.

As mentioned above, the *C,C′*-dihydroxycarboranes **3** are of as much interest as the *C*-hydroxycarboranes **2**, but no synthetic method for **3** has yet been reported. It is unexpectedly difficult to perform effective transformation of **1** into **2**. Oxidation of carbon atoms of carboranes with benzoyl peroxide is a well-known general method for the preparation of *C*-hydroxycarboranes.[11] However, when *C*-hydroxycarboranes are prepared by oxidation of the corresponding lithiocarboranes with benzoyl peroxide, a 2-fold molar excess of carborane is required because half of the carborane is lost by conversion to 1-benzoylcarborane as a byproduct. An improved synthesis of all three *C*-hydroxycarboranes in moderate yields was reported by Michl and co-workers in 1997.[9] However, the preparation of bis(trimethylsilyl)-peroxide as an oxidant for their method is troublesome, and there is no advantage over *C*-hydroxylation with benzoyl peroxide in terms of the yields of **2b** and **2c**. Another method for the preparation of *C*-hydroxycarboranes, that is, oxidation of the lithiocarboranes with oxygen, afforded *C*-hydroxycarboranes in low yields.[12] Morin and co-workers have reported an attractive method for the oxidation of the carbon atom in *C*-diethoxymethyl-*p*-carborane through a stepwise procedure that involves isolation of *C*-carboranylboronic acid and hydrolysis of the acetyl ester group, but the generality of this method has not been established yet.[13] Building on their approach, we have developed an efficient and selective one-pot synthesis of **2** and **3**.

Experimental Section

General Considerations. Melting points were determined with a Yanaco micro melting point apparatus without correction. ^{1}H NMR, ^{13}C NMR, and ^{10}B NMR spectra were recorded with JEOL JNM-EX-270, JNM-LA-400, and JNM-LA-600 spectrometers. Chemical shifts for ^{1}H NMR spectra were referenced to tetramethylsilane (0.0 ppm) as an internal standard. Chemical shifts for ^{13}C NMR spectra were referenced to residual ^{13}C present in deuterated solvents. Chemical shift values for ^{11}B spectra were referenced relative to external BF_3·OEt (0.0 ppm, with negative values upfield). The chemical shifts are reported in parts per million (δ scale), and all coupling constants (J) values are given in hertz (Hz). The splitting patterns are designated as follows: s (singlet), m (multiplet), and br (broad). Mass spectra were recorded on a JEOL JMS-DX-303 spectrometer. Elemental analyses were performed by a Perkin-Elmer 2400 CHN spectrometer.

Typical Experimental Procedure for Monohydroxylation of Carboranes. A solution of 1.59 M *n*-BuLi in *n*-hexane (1.4 mL, 2.18 mmol) was added to a solution of a carborane (300 mg, 2.08 mmol) in 3 mL of dry ether at 0 °C under an Ar atmosphere, and the mixture was stirred at room temperature for 1 h. After it was cooled to −30 °C, neat trimethyl borate (0.28 mL, 2.50 mmol) was added in one portion. The mixture was warmed to 0 °C over 1 h; then 1 mL of 30% H_2O_2 and 1 mL of acetic acid were added. The reaction mixture was stirred at room temperature for 20 h, and 4 mL of saturated $NaHSO_3$ aqueous solution and 6 mL of 10% NaOH solution were added dropwise. The stirring was continued at room temperature for 1 h, and the solution was extracted with ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel with 1:8 AcOEt/*n*-hexane to give the corresponding *C*-hydroxycarborane as a colorless solid.

1-Hydroxy-1,2-dicarba-*closo*-dodecaborane (2a). Yield: 76%. Colorless needles (*n*-hexane/ether). mp: 112.0−114.0 °C. ^{1}H NMR (395.8 MHz, $CDCl_3$): δ 1.20−3.30 (brm, 10H), 3.96 (brs, 1H), 5.50 (brs, 1H D_2O exchangeable). ^{13}C NMR (99.5 MHz, $CDCl_3$): δ 62.83, 98.34. ^{11}B NMR (126.9 MHz, $CDCl_3$): δ −14.52 (2B), −12.14 (7B), −3.81(1B). MS (EI): *m*/*z* 159 (M^+ − 1, 100%). HRMS Calcd for $C_2H_{12}B_{10}O$: 160.1891. Found: 160.1925.

1-Hydroxy-1,7-dicarba-*closo*-dodecaborane (2b). Yield: 85%. Colorless prisms (*n*-hexane/ether). mp: 110.5−112.5 °C. ^{1}H NMR (395.8 MHz, $CDCl_3$): δ 1.2−3.8 (brm, 10H), 2.84 (s, 1H), 3.57 (s, 1H D_2O exchangeable). ^{13}C NMR (99.5 MHz, $CDCl_3$): δ 51.55, 101.27. ^{11}B NMR (126.9 MHz, $CDCl_3$): δ −15.80 (5B), −13.09 (2B), −11.26 (2B), −4.58 (1B). MS (EI): *m*/*z* 159 (M^+ − 1, 100%). HRMS Calcd for $C_2H_{12}B_{10}O$: 160.1891. Found: 160.1893.

1-Hydroxy-1,12-dicarba-*closo*-dodecaborane (2c). Yield: 85%. Colorless needles (*n*-hexane/ether). mp: 124.5−126.0 °C. ^{1}H NMR (395.8 MHz, $CDCl_3$): δ 1.3−3.3 (brm, 10H), 2.44 (s, 1H), 3.19 (s, 1H D_2O exchangeable). ^{13}C NMR (99.5 MHz, $CDCl_3$): δ 48.08, 108.31. ^{11}B NMR (126.9 MHz, $CDCl_3$): δ −17.21 (5B), −13.0 (5B). MS (EI): *m*/*z* 160 (M^+, 100%). HRMS Calcd for $C_2H_{12}B_{10}O$: 160.1891. Found: 160.1878.

Typical Experimental Procedure for Dihydroxylation of Carboranes. A solution of 1.52 M *n*-BuLi in *n*-hexane (2.9 mL, 4.37 mmol) was added to a solution of a carborane (300 mg, 2.08 mmol) in 3 mL of dry ether at 0 °C under an Ar atmosphere, and the mixture was stirred at room temperature for 1 h. After the mixture was cooled to −30 °C, neat trimethyl borate (0.58 mL, 5.20 mmol) was added in one portion. The mixture was warmed to 0 °C over 1 h; then 2 mL of 30% H_2O_2 and 2 mL of acetic acid were added. The reaction mixture was stirred at room temperature for 20 h, and 6 mL of saturated $NaHSO_3$ aqueous solution and 9 mL of 10% NaOH solution were added dropwise. The stirring was continued at room temperature for 1 h; then the mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel with 1:5 AcOEt/*n*-hexane to AcOEt to give the corresponding *C,C′*-dihydroxycarborane as a colorless solid.

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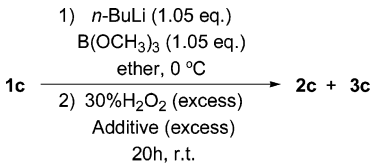
Table 1. Effects of Additives on the Transformation of *p*-Carborane **1c** to Hydroxy-*p*-carborane **2c**



		yield (%)[a]	
entry	additive	**2c**	**3c**
1	none	2	
2	AcOH	82	trace
3	Ac_2O	77	4
4	CF_3CO_2H	78	trace
5	$(CF_3CO)_2O$	73	trace
6	aq 10% HCl	10	

[a] Isolated yield.

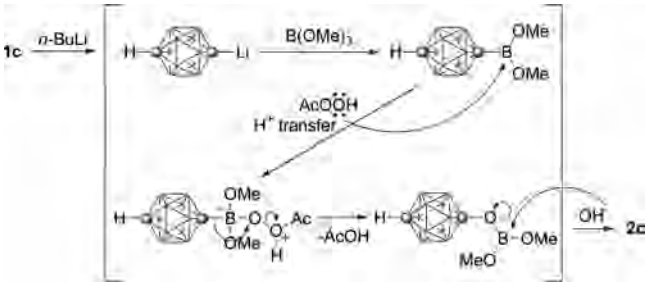
1,2-Dihydroxy-1,2-dicarba-*closo*-dodecaborane (3a). Extraction with AcOEt as described above afforded a crude mixture of **2a** and **3a**. The residue was purified by column chromatography on silica gel with 1:8 AcOEt/*n*-hexane to give **2a** as a colorless solid (37% yield) and subsequently with 1:5 AcOEt/*n*-hexane to give **3a** as a colorless solid (60% yield). Colorless needles (*n*-hexane/CH_2Cl_2). mp: 86.0−88.0 °C. ^{1}H NMR (395.8 MHz, DMSO-d_6): δ 0.8−4.0 (brm, 10H), 10.93 (s, 2H D_2O exchangeable). ^{13}C NMR (99.5 MHz, DMSO-d_6): δ 105.94. ^{11}B NMR (126.9 MHz, DMSO-d_6): δ −17.80 (2B), −13.44 (6B), −10.30 (2B). MS (EI): *m*/*z* 176 (M^+, 100%). Anal. Calcd for $C_2H_{12}B_{10}O_2$: C, 13.63; H, 6.86. Found: C, 13.36; H, 7.09.

1,7-Dihydroxy-1,7-dicarba-*closo*-dodecaborane (3b). Yield: 95%. Colorless needles (*n*-hexane/ether). mp: 134.0−136.0 °C. ^{1}H NMR (395.8 MHz, DMSO-d_6): δ 1.0−3.2 (brm, 10H), 8.82 (s, 2H D_2O exchangeable). ^{13}C NMR (99.5 MHz, DMSO-d_6): δ 99.75. ^{11}B NMR (126.9 MHz, DMSO-d_6): δ −16.49 (2B), −13.52 (8B). MS (EI): *m*/*z* 176 (M^+, 100%). Anal. Calcd for $C_2H_{12}B_{10}O_2$: C, 13.63; H, 6.86. Found: C, 13.75; H, 6.95.

1,12-Dihydroxy-1,12-dicarba-*closo*-dodecaborane (3c). Yield: 96%. Colorless cubes (*n*-hexane/ether). mp: 140.0−142.0 °C. ^{1}H NMR (395.8 MHz, DMSO-d_6): δ 1.5−3.2 (brm, 10H), 8.10 (s, 2H D_2O exchangeable). ^{13}C NMR (99.5 MHz, DMSO-d_6): δ 100.58. ^{11}B NMR (126.9 MHz, DMSO-d_6): δ −14.24 (10B). MS (EI): *m*/*z* 176 (M^+, 100%). Anal. Calcd for $C_2H_{12}B_{10}O_2$: C, 13.63; H, 6.86. Found: C, 13.67; H, 6.94.

Computational Details. Density functional theory (DFT) calculations were performed with the Gaussian 03 software package.[14] The hybrid functional of Perdew, Burke, and Ernzerhov (PBE1PBE)[15] was employed in combination with the DGauss double-ζ valence polarization (DGDZVP) all-electron basis set.[16] Atomic charges were computed using the natural population analysis method of Weinhold and co-workers.[17] Chemical shifts for ^{13}C nuclei were computed with the gauge-independent atomic orbital (GIAO) method,[18] in combination with the 6-311+G(2d, p) basis set of Mc Lean and Chandler;[19] at this level of theory the absolute value of the ^{13}C chemical shift of TMS corresponds to 187.8 ppm. Pre- and postprocessing operations were carried out with the aid of GaussView[20] and Molden[21] graphic user interfaces.

Chart 2. Suggested Mechanism of One-Pot C-Hydroxylation of *p*-Carborane



Results and Discussion

We first examined the C-hydroxylation of *p*-carborane **1c**, which is the most stable isomer in various organic reagents and under various conditions, in a one-pot reaction. Compound **1c** was treated with *n*-BuLi (1.05 equiv) in ether at 0 °C to give the *C*-lithio-*p*-carborane. Successive treatment with trimethylborate (1.05 equiv) at 0 °C gave carboranyl boron esters *in situ*. An excess of H_2O_2 and an excess of additive were added to the reaction mixture, followed by hydroxylation of the boron ester (formed by transcarboranylation) with 10% NaOH aqueous solution, to afford hydroxy-*p*-carborane **2c**. In the absence of any additive, the yield of **2c** was only 2% (Table 1). Nevertheless, it is noteworthy that **2c** was generated through an oxidative rearrangement involving H_2O_2. We next attempted to activate H_2O_2 by using various additives. Table 1 summarizes the effects of various additives on the synthesis of **2c**. Acetic acid was the most effective, and **2c** was obtained in an 82% yield (entry 2). There was no marked difference among the yields of **2c** when other additives were used, but acids gave better results than anhydrides (entries 2−5). The additive is considered to activate H_2O_2 by forming the peracetic acid *in situ*.[22] When 10% HCl aqueous solution was used, **2c** was obtained in a 10% yield (entry 6). It seems that the 10%

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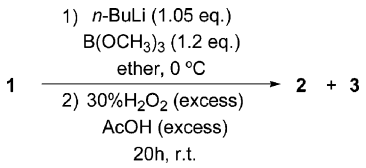
Table 2. Yields of *C*-Hydroxycarboranes **2** from Carboranes **1** under the Optimized Conditions



entry	starting material	yield (%) of **2**[a]	yield (%) of **3**[a]
1	**1a**	77 (**2a**)	(**3a**)
2	**1b**	85 (**2b**)	trace (**3b**)
3	**1c**	85 (**2c**)	trace (**3c**)

[a] Isolated yield.

HCl aqueous solution also serves to accelerate hydrolysis of the boronate produced by oxidative rearrangement. However, it was less effective than the 10% aqueous NaOH solution for hydroxylation of boronate. A plausible mechanism of the one-pot C-hydroxylation reaction is shown in Chart 2.[23]

C-Hydroxylation of the *o*- and *m*-carboranes, **1a** and **1b**, was also examined under these conditions, and the corresponding carboranols, **2a** and **2b**, were obtained in 76 and 77% yields, respectively. During optimization studies, we found that when the amount of trimethyl borate was changed from 1.05 to 1.2 equiv, the yields were improved; **2a**, **2b** and **2c** were obtained in 77, 85, and 85% yields, respectively (Table 2 and typical procedure in the experimental section). Unlike the C-alkylation of carboranes to afford two products, that is, C-monosubstituted and C,C′-disubstituted carboranes, the C-hydroxylation under the above conditions proceeded with high selectively, providing the corresponding C-monohydroxycarboranes in high yield.

Next, the selective synthesis of *C,C′*-dihydroxycarboranes **3** was examined by using twice-equimolar *n*-BuLi and trimethylborate under the conditions used for the C-hydroxylation of the carboranes. It is well-known that dilithiocarboranes can be prepared by the reaction of carboranes **1** and 2 equiv of *n*-BuLi.[24] We expected that the dilithiocarboranes would be readily transformed to the corresponding diboronates, which would be successively oxidized to **3** in one pot. Indeed, when carboranes **1b** and **1c** were treated with 2.2 equiv of *n*-BuLi and 2.2 equiv of trimethylborate, before the addition of 30% H_2O_2 and acetic acid, they readily produced the corresponding dihydroxycarboranes, **3b** and **3c**, in 79 and 81% yields, respectively. However, dihydroxy-*o*-carborane **3a** was isolated in only a 23% yield, and the hydroxycarboranes **2a**, **2b**, and **2c** were also isolated as byproducts of the reactions in 68, 12, and 8% yields, respectively. Therefore, we optimized the conditions for the C,C′-dihydroxylation of carboranes in the same manner as before (Table 3). The yield of **3a** was greatly improved to 60%, and that of **2a** was reduced to 37%. Further, the yields of the byproducts **2b** and **2c** fell to 4%, and the desired

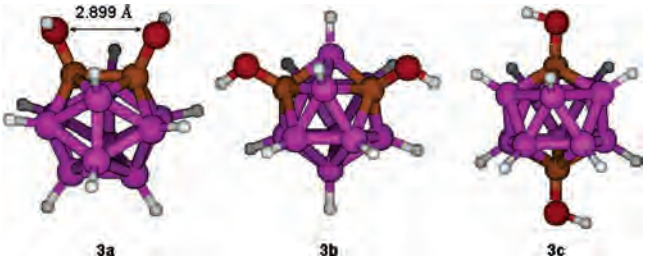
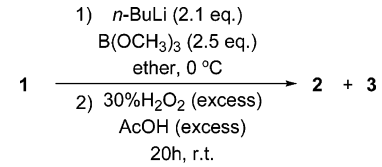


Figure 1. DFT-optimized geometries of dihydroxycarboranes.

Table 3. One-Pot Transformation of Carboranes **1** to *C,C′*-Dihydroxycarboranes **3** under the Optimized Conditions



entry	starting material	yield (%) of **2**[a]	yield (%) of **3**[a]
1	**1a**	37 (**2a**)	60 (**3a**)
2	**1b**	4 (**2b**)	95 (**3b**)
3	**1c**	4 (**2c**)	96 (**3c**)

[a] Isolated yield

Table 4. Computed Properties of **3a**−**c**

	3a	**3b**	**3c**
ΔE (kcal mol^{-1})	12.9	2.5	0.0
H−L gap (eV)	8.4	8.6	8.2
dipole (debye)	3.7	0.1	0.0
^{13}C (ppm)	104.7	102.6	103.6
d_{CO} (Å)	1.360	1.378	1.379
d_{CC} (Å)	1.727	2.624	3.100

products **3b** and **3c** were obtained in excellent yields of 95 and 96%, respectively. We attribute the moderate yield of **3a** to steric hindrance in the formation of the *o*-carborane diboronate.

Computational Characterization of *C,C′*-Dihydroxycarboranes (3a−c). To gain further insights into the properties of the *C,C′*-dihydroxycarboranes **3a**−**c**, we performed a series of DFT calculations. Compounds **3a** and **3c** have already been theoretically investigated by Oliva et al.[25] and Hnyk et al.,[26] respectively, whereas **3b** has not been studied computationally. We therefore performed calculations for all three isomers at the same level of theory to allow valid comparisons to be made. The geometries of **3a**−**c** optimized at the PBE1PBE/DGDZVP level of theory are shown in Figure 1, while Table 4 summarizes the relative energy, HOMO−LUMO energy gap, dipole moment, ^{13}C chemical shift, and selected atom−atom distances. The oxygen atoms of *o*-dihydroxycarborane **3a** are separated by a distance of 2.899 Å, and the O−C−C angle is 115.5°. This spatial arrangement of the negatively charged hydroxyl groups (the natural charge of the oxygen atom corresponds to −0.73 au) contributes to the dipole moment of 3.7 D

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(Table 4). For symmetry-related reasons, the dipole moment of **3c** is zero, while that of **3b** is very small (0.1 D). The results of natural population analysis of **3a**−**c** indicate that the distribution of natural charges among the boron atoms is not uniform. For instance, in the skeletons depicted in Figure 1, the four B atoms located at the bottom part of **3a** are negatively charged, while only two B atoms at the bottom part of **3b** are negatively charged. On the other hand, none of the B atoms of **3c** bears a negative charge. This result, which is a consequence of the relative positions of the C−OH moieties within the three clusters, suggests that differences in the reactivity of the B atoms of these *C,C′*-dihydroxycarboranes can be expected.

As shown in Table 4, **3a** is the least stable of the three isomers, having electronic energies 10.4 and 12.9 kcal mol^{-1} higher than those of **3b** and **3c**, respectively. From these theoretical results, we can conclude that the rank order of stability in this isomeric series is **3c** > **3b** > **3a**. The computed HOMO−LUMO energy gap varies only slightly among the three isomers, ranging from 8.2 (**3c**) to 8.6 eV (**3b**). Finally, we computed the chemical shifts of the ^{13}C atoms of **3a**−**c** using the GIAO-PBE1PBE/6-311+G(2d, p) method. As shown in Table 4, the computed values of δ differ by only 2−3 ppm from the corresponding experimental values (see Experimental Section), and the relative chemical shift ordering δ(**3a**) > δ(**3c**) > δ(**3b**) is correctly reproduced. This result provides further support for the identity of the species synthesized in the present study.

Conclusions

In conclusion, we have developed a simple and highly efficient synthetic method for the preparation of *C*-hydroxycarboranes **2** and *C,C′*-dihydroxycarboranes **3** through a one-pot procedure. This method affords much better yields (more than 77%) than the previously reported methods for the synthesis of **2**. Dihydroxycarboranes **3** were obtained with high selectivity in excellent yields (>95%), except for dihydroxy-*o*-carborane **3a**. The identity of the dihydroxycarboranes **3a**−**c** was confirmed by means of DFT calculations of the geometrical features and electronic properties. Dihydroxy-*o*-carborane **3a** is characterized by a much larger dipole moment than those of **3b** and **3c**, and the rank order of stability was estimated to be **3c** > **3b** > **3a**. Further experimental studies, particularly X-ray crystal structure analyses and pK_a measurements on the *C,C*'-dihydroxycarboranes **3**, are in progress.

Acknowledgment. This work was supported by Grant-in-Aid for Scientific Research (B) (No. 16390032) and Grant-in-Aid for Young Scientists (B) (No. 18790089) from the Ministry of Education, Culture, Sports, Sciences and Technology, Japan. F.P. thanks the COE project "Giant Molecules and Complex Systems" of Tohoku University for financial support.

IC062025Q