Rapid Cage Degradation of 1-Formyl- and 1-Alkyloxycarbonyl-Substituted 1,2-Dicarba-*closo*-dodecaboranes by Water or Methanol in Polar Organic Solvents

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Introduction

The number of syntheses incorporating 1,2-dicarba-, 1,7-dicarba-, or 1,12-dicarba-*closo*-dodecaboranes (*ortho*-, *meta*-, or *para*-carboranes, respectively) into small organic molecules such as amino acids, peptides, and porphyrins has increased in recent years.[1] Their high lipophilicity and spherical shape have made carboranes of interest in drug design and their high percent by weight boron have made them of particular interest for boron neutron capture therapy for cancer.[1] Part of their appeal is their relatively high chemical stability, being among the most stable of boron cluster compounds particularly to acids, oxidizing agents, and reducing agents. They are, however, known for instability to basic conditions. We report herein on the instability of certain commonly encountered *ortho*-carborane cage compounds to essentially neutral, nonbasic conditions which cause the formation of the corresponding *nido*-carborane cage compounds.

The conversion of unsubstituted and alkyl substituted closo *ortho*-carboranes and *meta*-carboranes to their respective dicarbaundecaborane (nido) analogues by alkoxide[2] and amine bases[3] has been widely studied. The reaction of several C- and B-brominated 1,2-dicarba-*closo*-dodecaboranes with a variety of Lewis bases has also been described.[4] Room-temperature cage opening of 1-methyl-2-cyano-*o*-carborane[5] and 1,2-dichloro-*o*-carborane[6] in methanol has also been reported. The mechanism of degradation is thought to involve an initial nucleophilic attack upon the 3 or 6 boron atom, which are the most electropositive boron atoms in the icosahedron. A second nucleophilic attack results in loss of a borohydride species from the icosahedron leaving a negatively charged open-faced nido cage.[2,3] In the presence of hydroxylic species, the boron hydride is consumed to liberate H_2. It was also shown that the rate of the reaction depended upon both the type of base used and the electron donating or withdrawing properties of cage substituents.[3]

The carbon−carbon bond between the carborane cage and the carbonyl group of α-formyl, α-keto, and α-alkyloxycarbonyl substituted *ortho*-carboranes is reported to cleave under the influence of hydroxide and alkoxide ion,[7,8] but to smoothly progress to the corresponding *nido*-carboranes under the influence of amine bases.[5] However, reports on conversion of such *closo*-carboranes to *nido*-carboranes under nonbasic conditions appear to be lacking in the literature.

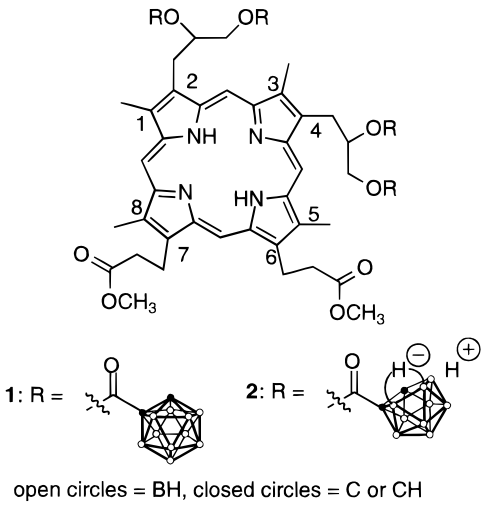

Figure 1. The *closo*- and *nido*-carboranyl porphyrin inhibitors of HIV-1 protease.

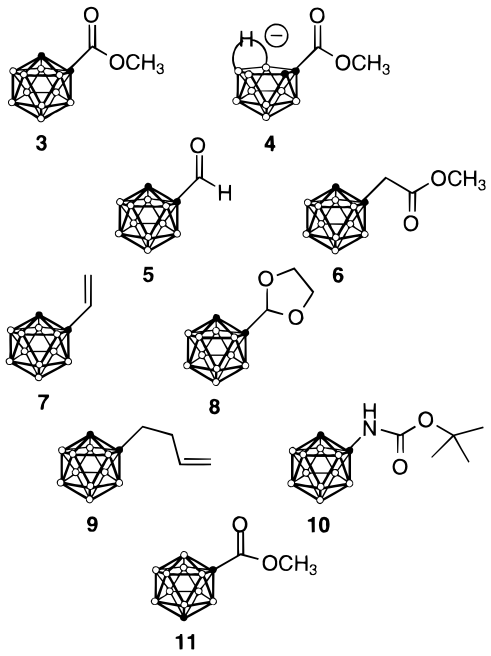

Figure 2. Model carboranes with and without α-carbonyl functions.

Experimental Section

The synthesis of compounds **1** and **2** (Figure 1) will be reported elsewhere. Compounds **3**, **6**, and **11** (Figure 2) were synthesized by literature methods from the corresponding acid chlorides and methanol.[9] Vinylcarborane **7** and butenylcarborane **9** were purchased from Dexsil Corp. (Hamden, CT). Compounds **5**, **8**, and **10** were gifts of Dr. Ramesh

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(1) Hawthorne, M. F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 950.
(2) Hawthorne, M. F.; Young, D. C.; Garrett, P. M.; Owen, D. A.; Schwerin, S. G.; Tebbe, F. N.; Wegner, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 862.
(3) Zakharkin, L. I.; Kirillova, V. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1975**, 2484.
(4) Plesek, J.; Hanslík, T.; Hanousek, F.; Hermánek, S. *Collect. Czech. Chem. Commun.* **1972**, *37*, 3403.
(5) Zakharkin, L. I.; Kirillova, V. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1975**, 1076.
(6) Stanko, V. I.; Anorova, G. A.; Klimova, T. P. *J. Gen. Chem. USSR* **1969**, *39*, 1045.
(7) Stanko, V. I.; Klimova, T. V. *J. Gen. Chem. USSR* **1977**, *47*, 1844.
(8) Stanko, V. I.; Klimova, A. I.; Chapovskii, Y. A.; Klimova, T. P. *J. Gen. Chem. USSR* **1966**, *36*, 1773.
(9) Grimes, R. N. *Carboranes*; Academic Press: New York, 1970.

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Table 1. ^{13}C Chemical Shifts (in ppm) for **1** and **2** in the Indicated Solvent

tentative resonance assignment	**1** $CDCl_3$	"**1**" DMSO-d_6	**2** acetone-d_6
1,3,5,8-methyls	11.7−11.9	11.9−12.1	12.5
6,7-$CH_2\underline{C}H_2CO_2CH_3$	21.8	21.2	22.0
6,7-$\underline{C}H_2CH_2CO_2CH_3$	27.0	27.1	under solvent
2,4-$\underline{C}H_2CH(OCOR)CH_2(OCOR)$	36.8	35.6	35.8
6,7-$\underline{C}H_2CH_2CO_2\underline{C}H_3$	51.8	51.4	51.6
carborane $\underline{C}$-H	56.9	42.5	42.9
carborane $\underline{C}$-R	66.9	54.6−55.2	55.3−56.0
2,4-$CH_2C\underline{H}(OCOR)CH_2(OCOR)$	68.3	64.3	65.0
2,4-$CH_2CH(OCOR)\underline{C}H_2(OCOR)$	under solvent	72.6	73.5
2,4-$CH_2\underline{C}H(OCOR)CH_2(O\underline{C}OR)$	161.0	170.8, 171.1	171.7, 172.4
6,7-$CH_2CH_2\underline{C}O_2CH_3$	173.4	172.5	173.0

Kasar. All other reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used without further purification. TLC was performed on E. Merck silica gel 60 F_{254}. Carboranes were visualized on TLC by dipping in a 0.5% w/v $PdCl_2$ in 10% concd HCl/acetone solution followed by heating which gave black spots on a yellow background (works with *ortho*-carboranes but not all *meta*-carboranes). ^1H NMR spectra were recorded at 300 MHz with TMS as internal standard. ^{13}C NMR spectra were recorded at 75.5 MHz with solvent as internal standard. For the NMR experiments the indicated compound was added directly to the NMR tube and then dissolved in situ in the indicated anhydrous solvent. A single drop of D_2O or CD_3OD was added to those NMR experiments requiring "wet" conditions.

Results and Discussion

Compound **1** was synthesized in research to expand on the SAR of boronated porphyrin inhibitors of HIV-1 protease.[10] In the course of characterizing **1** by ^{13}C NMR, one of the carbon resonances was apparently obscured by the $CDCl_3$ solvent, so the spectrum was acquired again in DMSO-d_6. Attempts to later recover compound **1** from DMSO-d_6 via an extractive work up indicated the presence of a porphyrin with significant aqueous solubility and radically different TLC mobility. The ^{13}C NMR spectra of **1** in $CDCl_3$ and DMSO-d_6 were compared to the ^{13}C NMR spectrum of *nido*-carboranyl porphyrin **2** in acetone-d_6. **2** had been generated independently via piperidine/pyridine (1:1) treatment of **1** followed by acid work up and isolation of the fully protonated *nido*-carborane free acid (as opposed to the usual ammonium, tetraalkylammonium, or alkali metal salt). Table 1 lists the chemical shifts of the porphyrin side chains of **1** and **2** in the three solvents and gives tentative assignments based upon APT experiments and comparison with the spectra of other boronated and unboronated porphyrins. Most of the side chain chemical shifts are nearly identical over the range of solvents used. However, the resonances corresponding to the carborane cage C−H and C−C of **1** are shifted substantially upfield in going from $CDCl_3$ to DMSO-d_6 and the values in DMSO-d_6 are very close to those seen for **2** in acetone-d_6. Based upon the ^{13}C NMR, TLC, and chemical behavior evidence, it was clear that *closo*-carborane **1** was converted to *nido*-carborane **2** in DMSO-d_6.

This reaction was further investigated using model carborane **3**. As it happens, a new vial of DMSO-d_6 was opened in which **3** was dissolved and then examined by ^1H NMR. To our surprise no change was observed even after 18 h. It was realized that the newly opened DMSO-d_6 was probably much drier than the DMSO-d_6 used with **1**. When a drop of D_2O was added, all of **3** was converted to *nido*-carborane **4** within 30−35 min. A build-up of pressure in the NMR tube, consistent with hydrogen evolution, was also noted, though this gas was not specifically identified. The ^1H NMR chemical shift of the carborane C−H of **3** moved substantially upfield, while the upfield movement of the chemical shift for $-OCH_3$ was more modest (Table 2). Similar shifts were seen in the ^{13}C NMR (except for the carbonyl carbon, which moved downfield in a shift also seen in the conversion of **1** to **2** by piperidine/pyridine). When CD_3OD was added to **3** dissolved in DMSO-d_6, a similar rapid reaction occurred giving the same ^1H NMR spectrum. However, when **3** was dissolved directly in neat CD_3OD, no reaction was observed even over 24 h at room temperature. Lack of aqueous solubility of **3** prevented a similar experiment in D_2O. These observations demonstrate that neither a hydroxylic solvent alone nor an aprotic polar solvent alone is sufficient to cause the degradation.

Table 2. ^1H and ^{13}C NMR Chemical Shifts (in ppm) for Compound **3**

atom	DMSO-d_6	DMSO-d_6 + D_2O
carborane C$\underline{H}$	5.51	2.32
$RCO_2C\underline{H}_3$	3.84	3.48
$RCO_2\underline{C}H_3$	55.8	52.3
carborane $\underline{C}$H	59.4	42.9
carborane $\underline{C}$R	69.3	55.5
$R\underline{C}O_2CH_3$	160.2	172.3

The effect of solvent on the reaction was investigated further by TLC monitoring of the disappearance of **3** dissolved in various polar solvents containing 5% water. It was found that reaction in wet hexamethylphosphoramide was at least as rapid as reaction in DMSO. Wet *N*,*N*-dimethylformamide and *N*-methylpyrrolidinone were about three times slower than DMSO, taking about 1.5 h for complete disappearance of **3**. On the other hand, acetonitrile, THF, acetone, and dioxane were very much slower, having an apparent reaction rate measured in days.

It was suspected that the degradation reaction would be limited to *ortho*-carboranes bearing an electron withdrawing group α to the cage. As expected, 1-formyl-*o*-carborane **5** was rapidly degraded in wet DMSO as judged by TLC. Separation of the ester carbonyl group from the cage system by even one methylene unit was sufficient to render **6** immune to the degradation as judged by ^1H NMR over 24 h. Likewise, *ortho*-carboranes **7**−**9** were degraded very slowly if at all under wet DMSO conditions over 24 h as judged by TLC. Compound **10** might have been expected to undergo the reaction because of the direct attachment of the electronegative nitrogen to the carborane cage but was no more reactive than carboranes **7**−**9**. The *meta*-carboranyl ester **11** also failed to react in DMSO-d_6/D_2O over 24 h as judged by ^1H NMR.

Conclusion

The serendipitous observation of this degradation reaction in the characterization of **1** explained anomalous results in the

(10) DeCamp, D. L.; Babé, L. M.; Salto, R.; Lucich, J. L.; Koo, M.-S.; Kahl, S. B.; Craik, C. S. *J. Med. Chem.* **1992**, *35*, 3426.

investigation of the inhibition of HIV-1 protease by a number of boronated compounds which had been routinely dissolved in nonanhydrous DMSO for use in the protease activity assay. It also paradoxically provided an alternative means of intentionally generating certain *nido*-carborane compounds from the corresponding closo compounds in cases where the compounds are hydroxide and amine base sensitive. A more detailed account of the preparation of compounds **1** and **2** and other boronated inhibitors of HIV-1 protease is in preparation.

It seems reasonable to conclude that the observed reaction is highly dependent on the electron withdrawing nature of the α-substituent, either through an inductive mechanism or through an ability to delocalize the negative charge generated in the transition state from a closo to a nido cage. The inherently greater stability of a *meta*-carborane cage limits the observed reaction to the ortho series at least at room temperature. The reaction is likewise dependent on the ability of the solvent to stabilize the process of nucleophilic attack by water or methanol on boron, a stabilization ability apparently not possessed by methanol alone. These results suggest caution in the handling of carborane compounds, particularly with respect to exposure to polar organic solvents, whether during synthetic transformations, in dilutions for biological studies, or simply during the acquisition of an NMR spectrum in DMSO-d_6.

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